universität wien

DIPLOMARBEIT / DIPLOMA THESIS

Titel der Diplomarbeit / Title of the Diploma Thesis

„Development of a pharmaceutical care tool to guide community pharmacy interventions in osteoporosis“

verfasst von / submitted by

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angestrebter akademischer Grad / in partial fulfilment of the requirements for the degree of

Magister der Pharmazie (Mag.pharm.)

Wien, 2019 / Vienna, 2019

Studienkennzahl lt. Studienblatt / degree programme code as it appears on the student record sheet:	A 449
Studienrichtung lt. Studienblatt / degree programme as it appears on the student record sheet:	Diplomstudium Pharmazie
Betreut von / Supervisor:	ao. Univ.-Prof. Mag. Dr. Oskar Hoffmann
Mitbetreut von / Co-Supervisor:	

Acknowledgements

I know that at this point, most people express their gratitude to their supervisors, supporters, parents, loved ones, friends and the ones that made them finish their thesis. But I think it is just fair to dedicate this section to one specific person only: Steve Hudson. Thank you for everything we shared. May you rest in peace with F. Zappa et al. 2010 onwards...

German Abstract

Development of a pharmaceutical care tool to guide community pharmacy intervention in osteoporosis

Einleitung

Osteoporose ist die häufigste metabolische Knochenerkrankung, die mit erhöhter Morbidität, Mortalität und hohen Gesundheitskosten einhergeht. Osteoporose ist vor allem ein altersbedingtes Phänomen, das sowohl Frauen als auch Männern betrifft. Die patientenorientierte Pharmazie ist ein relativ junger Ansatz in der Osteoporosetherapie und ihre Bedeutung in diesem Gebiet muss noch bewertet werden. Das „Medication Assessment Tool“ für Osteoporose (MAT_{osteo}) zur Einhaltung der aktuellen Richtlinienempfehlungen, wurde in dieser Arbeit aktualisiert und wurde in ein neu entwickeltes „Pharmaceutical Care Model“ (PCM) integriert.

Methoden

Im Rahmen einer Literaturrecherche wurden aktuelle Änderungen der Richtlinienempfehlungen festgestellt und klinische Risikofaktoren für Osteoporose identifiziert. Das aktuelle MAT_{osteo} wurde im Hinblick auf Anwendbarkeit und Einhaltung der aktuellen Richtlinienempfehlungen bewertet. Nach der Integration der neuesten schottischen und internationalen Richtlinien in MAT_{osteo} wurden die Daten von 217 Patienten neu bewertet. Ein PCM zur Behandlung und Prävention von Osteoporose in wurde von ExpertInnen auf dem Gebiet der Osteoporose validiert.

Ergebnisse

Die Überarbeitung von MAT_{osteo} führte zu einer Reduktion der Kriterien von 28 auf 21. Das aktualisierte MAT_{osteo} wurde in ein neu erstelltes PCM integriert, welches von Pharmazeuten als valide Hinsichtlich der Anwendbarkeit im Großraum Glasgow bewertet wurde. Die erneute Anwendung der Patientendaten auf MAT_{osteo} ergab eine Einhaltung der aktuellen Richtlinienempfehlungen von 71,6 % und eine Anwendungsfähigkeit der Kriterien von 47,0 % für beide Patientenkollektive kombiniert.

Diskussion

Die Anpassung von MATosteo an aktualisierte Richtlinien führte zu einer allgemeinen Steigerung der Anwendbarkeit und Einhaltung der Richtlinienempfehlungen. Der Einsatz von MAT_{osteo} in einer Kollaboration von öffentlichen Apotheken und AllgemeinmedizinerInnen sollte hinsichtlich der praktischen Anwendung im Regelbetrieb überprüft werden.

Abstract

Development of a pharmaceutical care tool to guide community pharmacy intervention in osteoporosis

Introduction

Osteoporosis is the most common metabolic bone disease, associated with excess morbidity, mortality and health care costs. Osteoporosis is predominantly an age-related phenomenon in both women and men and its management is therefore a vital topic, especially for Europe's aging society. Pharmaceutical care is a rather recent development in the field of osteoporosis and its impact on this field is yet to be determined. The medication assessment tool for osteoporosis (MAT_{osteo}) is a valuable resource to assess the adherence to actual guideline recommendations.

Methods

A literature review was conducted to detect current changes in guideline recommendations and to identify clinical risk factors for osteoporosis. The current MAT_{osteo} was assessed in terms of applicability and adherence in the light of actual guideline recommendations. After the implementation of the latest Scottish and international guideline advancements into MAT_{osteo}, data of 217 eligible patients was reassessed. A model of pharmaceutical care for the treatment and the prevention of osteoporosis in a community pharmacy – general practitioner setting was created and evaluated by experts in the field of osteoporosis.

Results

The revision of MAT_{osteo} resulted in the reduction from 28 to 21 criteria for osteoporotic and osteopenic patients. The revised MAT_{osteo} was integrated in a model of pharmaceutical care, which was found to be valid in a community pharmacy – general practitioner setting. Reapplication of patient data to MAT_{osteo} showed a total adherence to current guideline recommendations of 71.6% and an overall applicability of 47.0%.

Discussion

The adaption of MAT_{osteo} to updated guidelines resulted in an overall increase of both applicability and adherence. The use of MAT_{osteo} in a community pharmacy – general practitioner was validated, but yet has to be evaluated in terms of usability in this specific setting.

Abbreviations

5-HT	5-Hydroxytryptamine
AED	Antiepileptic drug
BMC	Bone mineral content
BMD	Bone Mineral Density
BMI	Body mass index
BNF	British national formularium
BP	Bisphosphonate
BTM	Bone turnover marker
CI	Confidence interval
CRF	Clinical risk factor
CSF	Colony Stimulating Factor
CTX-I	C-telopeptide of type I collagen
CYP450	Cytochrome P450
DADS	Direct Access Densitometry Service
DEXA	dual-energy X-ray absorptiometry
DMPA	depot medroxyprogesterone acetate
ER	Estrogen receptor
FORE	Foundation for osteoporosis research and education
GC	Glucocorticoid
GP	general practitioner
HIV	Human immunodeficiency virus
HRT	Hormone replacement therapy
IDQ	Insufficient Data to address the qualifying statement
IDS	Insufficient data of the standard
IDS	Insufficient Data to address the standard statement
IGF	Insulin like growth factor
IL	Interleukin

MAT	Medication Assessment tool
MRI	Magnetic resonance imaging
NA	Not applicable
NHANES	National health and nutrition examination survey
NHS	National Health Service
NICE	National institute for clinical excellence
No(J)	No (justified)
No(U)	No (unjustified)
NOS	National osteoporosis foundation
OPG	Osteoprotegerin
PC	Pharmaceutical Care
PINP	N-terminal propeptide of type I procollagen
PCM	Pharmaceutical care model
PMR	Patient Medication Record
PMW	Postmenopausal woman
PPAR	peroxisome proliferator activated receptor
PTH	Parathyroid Hormone
QCT	Quantitative computed tomography
QOS	Quality outcomes framework
QUS	Quantitative ultrasound
RANK	Receptor Activator of NF-κB
RANKL	Receptor Activator of NF-κB Ligand
RR	Risk ratio
SD	Standard deviation
SERM	Selective estrogen receptor modulator
SES	Socioeconomic status
SIGN	Scottish intercollegiate guidelines network
SOF	Study of osteoporotic fractures

SR	Strontium ranelate
SSRI	Selective serotonin reuptake inhibitor
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TGF-β	Transforming growth factor-β
TNF	Tumor Necrosis Factor
VF	Vertebral fracture
WHI	Women's health initiative
WHO	World Health Organisation

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1. Introduction

1.1. Definition of Osteoporosis

The World Health Organization (WHO) defines osteoporosis as "a disease characterised by low bone mass and micro architectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk" (Cummings and Melton, 2002). Osteoporosis often remains undetected and is thus not treated appropriately, especially in men (Geusens and Dinant, 2007). The primary and most evident consequence of the condition is the fragility fracture, which is associated with pain, disability, increased morbidity and mortality. The incidence of osteoporosis is three times higher in women than in men, partly due to lower peak bone mass acquisition and postmenopausal oestrogen decrease (Compston, 2001; WHO, 2003). From a clinical point of view osteoporosis is defined by a bone mineral density (BMD) of 2.5 standard deviations (SD) below the young adult average (WHO, 2003). Osteoporosis is the most common metabolic bone disease. By considering the underlying cause, the condition can be further categorised into primary and secondary osteoporosis. Whereas primary osteoporosis is generally related to the imbalance in remodelling associated with the natural aging processes, secondary causes also occur in younger individuals as a result of a prevalent medical condition such as rheumatoid arthritis, ankylosing spondylitis, osteogenesis imperfecta, osteotoxic medication (e.g. corticosteroids), organ transplantation, diabetes mellitus type I & II, HIV infection and its treatment. Regarding hip fractures, secondary causes are more significant in men than in women (Cummings and Melton, 2002).

1.2. Bone Biology, Physiology and Pathophysiology of Osteoporosis

Fragility fractures, the primary outcome of osteoporosis, are easily detected by X-ray films; the underlying pathogenesis though is complex and multifactorial (Rosen, 2000). Besides BMD, bone macro- and microarchitecture, matrix and mineral composition, degree of mineralisation and mineral size, micro damage and bone turnover are considered as determinants of bone strength (Curtis, et al., 2015; Rosen, 2000). These features can all be subject to pathogenic influences leading to decreased resistance against mechanical stress. A number of local and systemic factors are known to interact with bone modelling and remodelling. Under ideal conditions, the same amount of bone is present at the remodelling site after a remodelling cycle. From intrauterine life until early

adulthood, formation generally exceeds resorption and peak bone mass is acquired. When an imbalance in bone turnover occurs in favour of resorption, bone is lost (Curtis, et al., 2015; Rosen, 2000). Although the cause of osteoporosis is multifactorial, oestrogen deficiency is considered as one of the strongest determinants for bone loss and fracture susceptibility in both men and women. This circumstance leads to an acceleration of bone loss in women after the menopause, which explains the major focus on postmenopausal osteoporosis (Seeman, 2002).

The understanding of bone biology and physiology is critical for the identification of risk factors and treatment options of osteoporosis. The following will give a brief overview of physiological mechanisms of bone. The bone organ system is responsible for mechanical, metabolic and protective functions. Bone allows muscular activity and thus, movement of the body. Further, bone facilitates balanced calcium and phosphate blood levels and protection of bone marrow and vital organs. The bone system additionally plays a major role in haematopoiesis. Bone tissue consists of an inorganic (mineral) phase and an organic phase with proportions of 50 to 70 % and 20 to 40 %, respectively. The inorganic phase mainly consists of calcium hydroxyapatite, a natural form of calcium phosphate (Clarke, 2008). The major constituent of the organic phase is type I collagen and various non-collagenous proteins and is completed by a low proportion of bone cells (2 % by volume) (Morgan, et al., 2013). Together, these components build the mineralised collagen fibril, the building block of bone tissue. Water bound to collagen or free, represents the remaining proportion (Griffith and Genant, 2008).

The system comprised of the components named above, is a dynamic tissue that undergoes a permanent modelling and remodelling process, accomplished by osteoclast and osteoblast cell lineages. After peak bone mass is attained in early adulthood, the balance between bone formation and bone resorption is increasingly shifted to the latter one, resulting in a constant decrease in bone mineral density and the bone's resistance to mechanical stress in general (Farr and Khosla, 2015). Osteoblasts, primarily being responsible for bone formation, utilize the production of bone matrix (osteoid) and regulate its mineralization. Osteoblasts and their precursors also regulate the osteoclasts' growth and impact on remodelling, employing the mediators RANKL (Receptor Activator of NF-κB Ligand) and osteoprotegerin (Farr and Khosla, 2015; Martin and Seeman, 2008). Osteoprotegerin is a soluble member of the tumor necrosis factor (TNF) alpha super family that binds receptor activator of nuclear kappa-B (RANK) and thus interferes with osteoclast development and activity. Osteoclasts are considered as the cellular counterpart of osteoblasts. They are multinucleated cells derived from haemopoietic

precursors and are generally associated with bone resorption, especially throughout the remodelling process. Formation and activity of osteoclasts is regulated by a number of cytokines and mediators facilitating their effects, amongst others through RANKL, osteoprotegerin (OPG), several interleukins (IL), colony-stimulating factor (CSF), 1,25-dihydroxyvitamin D and calcitonin. At sites where bone matrix is exposed, osteoclasts secrete proteolytic enzymes and protons at the bone remodelling compartment. This results in the hydrolisation of collagen type 1 and dissolving of bone mineral, yielding the formation of resorption pits. After the apoptosis of osteoclasts, the resorption pits are colonized by osteoblasts to rebuild bone. These two bone cells work at the remodelling site in a sequential manner, until after approximately four to six months, the remodelling cycle is completed. Both the maintenance of bone stability and mineral homoeostasis are the two major functions of the remodelling process. Osteocytes, the third cell line regarded as bone cells, are able to conduct mechanic stimuli into the centre of the bone, another stimulus for bone formation (Clarke, 2008).

1.3. Epidemiology of Osteoporosis

Fragility fractures, the clinical endpoint of osteoporosis, are associated with increased morbidity, mortality and healthcare costs. When the limit of elastic and plastic deformation of the bone is exceeded, fractures occur (Seeman, 2002). Although any bone can be subject to bone loss, sites most likely to be affected by osteoporotic fractures are the vertebrae, proximal femur and distal forearm. Hip fractures are considered to be the most severe osteoporotic fractures, as they are associated with high mortality and morbidity rates; up to 20 % of patients die within the first year after obtaining a hip fracture and two thirds never recover entirely (Cummings and Melton, 2002; WHO, 2003). Although 90 % of hip fractures are caused by falls, the coexistence of several factors including low bone mass and low body mass index (BMI) contributes to these high numbers (Cummings and Melton, 2002).

Osteoporosis affects both women and men; however, differences in sex and ethnicity have been reported. In a subpopulation of the Rotterdam Study the fracture incidence for non-vertebral fractures in women aged 55 years or older was calculated to be 2.3 (95 % CI 2.0-2.7) times higher than in same aged men (Schuit, et al., 2004). In a population-based study comprising 26,891 subjects, the 10 year lifetime and absolute fracture risk was calculated for men and women. In this study, men were shown to present a greater number of all non-vertebral fractures before the age of 45 but not after. The estimated

lifetime risks for fractures of all locations were higher in women than in men. At the age of 50 years the estimated lifetime risk for osteoporotic fractures was 24.8 % (95 % CI 21.3-28.3) for men and 55.0 % (95 % CI, 51.4-58.5) for women (Ahmed, et al., 2009).

1.3.1. Morbidity & Mortality

Data available from the General Practice Research Database in the UK shows, that the lifetime risk of sustaining an osteoporotic fracture at the age of 50 years in women and men is 53.2 % and 21.7 %, respectively. All osteoporotic fractures are associated with increased morbidity and mortality. Vertebral and hip fractures though appear to bear the most severe consequences. Nearly 8 % of men and 3 % of women above the age of 50 die during hospitalisation due to hip fractures. During the first year after a hip fracture, mortality increases up to 36 % in men and 21 % in women (Holroyd, et al., 2008). In a study comprising 2,847 patients, survival rates during the first year were 78 % for hip fractures, 72 % for fractures of the spine, 87 % for shoulder fractures, and 94 % for fractures of the forearm. At five years after the fracture, a survival rate of 41 % for hip fractures and only 28 % for vertebral fractures was reported in the study. Mortality was highest within the first year in both, men and women at a similar level (Johnell, et al., 2004).

BMD variations and differences in the incidence of osteoporotic fractures have been shown to be associated with ethnic background in a large observational study (n = 197,848). In the study conducted by Barret-Connor et al., BMD values and fracture risk were compared between African American, Hispanic, Native American, Asian and white women. In all age groups, black women had the highest and Asian women the lowest BMD values. After adjusting for body weight, significant differences could only be found between black women and the remaining ethnic groups. Corresponding to these findings fracture risk was found to be lowest for the female black population. Despite low BMD values, Asian women showed the lowest fracture risk (RR = 0.32; 95 % CI, 0.15-0.66). This discrepancy is regarded to be due to structural and material properties of the bone, hip geometry and other musculoskeletal factors. White (Caucasian) women, the reference group, presented the highest fracture risk (RR = 1.0) followed by Hispanics (RR = 0.95; 95 CI, 0.76-1.20), Native Americans (RR = 0.87; 95 % CI, 0.57-1.32) and black women (RR = 0.52, 95 % CI, 0.38-0.70). The authors of the study conclude that ethnic differences in BMD are strongly influenced by weight and that this fact should be taken into account when comparing data (Barrett-Connor, et al., 2005).

1.4. Bone mineral density

BMD or bone mineral content (BMC) is the amount of mineralized bone present at a certain site measured in grams for BMC and g/cm^2 or g/cm^3 for BMD or volumetric BMD, respectively. A more specific term for the result of the measurement is “apparent bone mineral density”, since densitometry measurement techniques also measure non-osseous tissue (Griffith and Genant, 2008). Low BMD is associated with increased mortality; it is elevated by 20 % with each SD decrease in BMD (Browner, et al., 1991). BMD loss, in particular at the femoral neck, is as well as the occurrence of osteoporotic fractures, age-related and is therefore often used as a surrogate for fracture risk and can be used as a strong predictor for fracture probability (Cummings and Melton, 2002). The national osteoporosis foundation (NOF) recommends the use of the national health and nutrition examination survey (NHANES) reference in women aged 20-29 for BMD measurement (Kanis, 2002). Although BMD is a strong predictor for fracture probability, the use of BMD alone for identifying osteoporotic patients is considered to be inaccurate, because microarchitectural deteriorations of the bone are not taken into account (Holroyd, et al., 2008).

1.5. Risk Factors

Several factors are associated with an increased risk of sustaining an osteoporotic fracture. Risk factors can be categorized as dependent or independent of BMD, although it is not always clear to which extent independency exists. Increasing age, low BMI, high bone turnover, the use of corticosteroids, a parental hip fracture, chronic alcohol abuse, smoking, prior fractures and rheumatoid arthritis are considered to be at least partly BMD-independent. Further categorization into factors according to their amount of contribution to fracture risk in major and minor risk factors is common, in particular in guidelines to identify patients eligible for BMD testing. It has been shown that a combination of BMD and certain clinical risk factors are more effective in identifying osteoporotic patients, than BMD measurement alone. According to Brown and Josse low BMD, prior fragility fractures, age and family history of osteoporosis are the key risk factors for osteoporotic fractures. Other clinical risk factors (CRF) were reported not to be independent of the circumstances named above (Brown, et al., 2002). Recently published guidelines suggest to start treatment in elderly women presenting indicators for low BMD or significant clinical risk factors without osteoporosis confirmed by BMD measurement if the clinician

considers a dual-energy X-ray absorptiometry (DEXA) scan unfeasible or inappropriate (Holroyd, et al., 2008; NICE, 2008).

1.5.1. Age

As mentioned above, bone loss is an age-related condition. Peak bone mass is obtained in the third life decade in both men and women. Until the fifth decade of life, BMD remains stable and increases constantly both in women and in men. Whereas the progression of bone loss is rather linear, the incidence of fractures, in particular hip fractures, increases exponentially with age (Holroyd, et al., 2008).

1.5.2. Family History of Osteoporotic Fractures

A family history of osteoporotic fractures is often considered for assessing a patients' risk of osteoporotic fractures. A meta-analysis pooling data from 34,928 men and women from seven prospectively studied cohorts presented a statistically significant contribution of parental fractures to a patient's fracture risk. Especially a maternal history of hip fractures is associated with high risk ratios and was found to be higher in men (RR = 2.18, 95 % CI = 1.25-3.80) than in women (RR = 1.29, 95 % CI = 0.98-1.69) (Kanis, et al., 2004). According to the Scottish Intercollegiate Guidelines Network (SIGN) guidelines, a family history of kyphosis should also be taken into account for risk assessment (SIGN, 2003).

1.5.3. Prior fractures

It was shown in large prospective studies, that patients with previous osteoporotic fractures have a 50-100 % higher risk of sustaining another fracture of a different type. This effect is in part attributed to changes in the microarchitecture and accelerated bone loss after fracture or immobilisation (Klotzbuecher, et al., 2000).

1.5.4. Sex Hormone Deprivation

The decrease in sex hormones during the menopause is a major factor that pertains to the pathogenesis of osteoporosis. A decrease in sex hormones, especially oestrogen, increase apoptosis of osteoclasts, as a result of increased TGF-β levels and reduced NFκB-mediated expression. Conditions associated with low sex hormone levels are in general associated with increased bone loss (Compston, 2001).

1.5.5. Body Mass Index

A BMI below a certain threshold represents a strong predictor of fracture risk independent of BMD. Inconsistencies in findings exist concerning the actual threshold. Guideline recommendations for this threshold range from 19 kg/m^2 to 22 kg/m^2 (NICE, 2010) (Brown, et al., 2002).

1.5.6. Falls

Falls are not an indicator for low BMD but are a risk factor for fractures. In a study conducted by Scuffham et al. 647,721 accident and emergency attendances and 204,424 admissions to the hospital associated with falling were reported for patients aged over 60 in the UK. The highest proportion (78 %) of those admitted to hospital, were aged 75 years or older (Scuffham, 2003). Falls are considered to be responsible for about 90 % of all hip fractures. Again, there are certain factors that contribute to the risk of falling: Muscle weakness, in particular weakness in lower extremities and poor grip strength. Also other intrinsic factors like gait and balance deficits, visual impairments and arthritis are considered as strong predictors for falls.

The use of certain medication, in particular psychotropic medication, class 1a antiarrhythmics, digoxin and diuretics were reported to have a significant influence on the incidence of falls (Guideline for the prevention of falls in older persons. American Geriatrics Society, 2001). Of the agents affecting the central nervous system, benzodiazepines, antidepressants and anticonvulsants are associated with increased risk of falling in community-dwelling older women. In women on benzodiazepines, the incidence of falling at least once was reported to be 34 % higher than in non-users. This was shown to be significant for both long- and short-acting benzodiazepines (Ensrud, et

al., 2002). The cause for this raise in fall incidence is considered to be related to dizziness and body sway. Again, these side effects are dose-dependent and are likely to be less harmful in patients receiving benzodiazepine-like agents (*Z-drugs* e.g. zopiclone) due to their shorter half-lives (Allain, et al., 2003). Women using SSRIs were 2.6 times more likely to fall at least once compared to non-users. Anticonvulsant medication was reported to be strongly linked to the patients' history of falling; no significant increase in falls was found in women on anticonvulsant medication without a fall history (Ensrud, et al., 2002).

1.5.7. Smoking

Smoking is known to account for a clinically significant number of fractures. It is associated with a decrease in BMD and a partly BMD-independent increase of osteoporotic fractures. In contrast to rather transient influences like depot medroxyprogesterone acetate (DMPA) use, smoking is likely to contribute to fracture risk in a cumulative manner and is not entirely reversible. Especially at the hip, the fracture risk is significantly increased in women and men by 31 % and 40 %, respectively. The overall risk of fracture was found to be 5 % in women and 11 % in men. The effect of smoking on bone health is multifactorial. The underlying mechanisms are at least in part related to other risk factors for osteoporosis. In particular, smoking-induced weight decrease corresponds to the correlation of BMI on bone loss. Also a decrease in sex hormone levels and influences on other mediators are associated with increased bone loss and fracture risk (Ward and Klesges, 2001). Also, the inhibitory effect of nicotine on new bone formation, decreased 25(OH)D, osteocalcin levels and the adverse effect of cigarette smoke on parathyroid hormone and alkaline phosphatise have been proposed as possible mechanisms (Nieves, 2008).

1.5.8. Diabetes

Vestergaard examined the incidence of fracture rates among patients with diabetes mellitus in a meta-analysis. Especially type 1 diabetes (T1DM) was associated with a higher risk (RR = 6.94); this subtype was also associated with decreased BMD. On the contrary, individuals with type 2 diabetes mellitus (T2DM) presented higher BMD. BMI increases are correlated with increased BMD and can therefore explain this phenomenon, since T2DM is associated with increased bodyweight. In contrast to these findings, higher fracture rates occur also in T2DM patients (RR = 1.38) (Vestergaard, 2007).

1.5.9. Chronic Alcohol Consumption

Chronic alcoholism is another condition that is related to higher fracture rates. Partly, these effects are due to direct toxic effects of alcohol on osteoblasts (Kanis, et al., 2005). In addition, chronic alcohol consumption can induce male hypogonadism by having toxic effects on the testis. The associated calcium and vitamin D deficiency and an unhealthy lifestyle further contribute to increased fracture risk (Adler, 2006). A study investigating data of 16,971 men and women drawn from three different cohorts revealed that the increased fracture risk is only in part attributed to decreased BMD. The authors also identified an amount of two or more units of alcohol daily as a threshold for increased risk of fracture. The risk of hip fracture increased by seven percent with each additional unit of alcohol consumed. Overall, the incidence of hip-fractures that could be associated with high intake of alcohol was seven percent for men and two percent for women (Kanis, et al., 2005). Further, the risk of falls is increased by excessive alcohol intake (Black and Rosen, 2016).

1.5.10. Socioeconomic Status (SES)

A systematic review conducted in 2009, identified patient's socioeconomic factors associated with altered BMD. The study found BMD levels of individuals with a higher level of education to be significantly higher. High quality data was not available for a patient's income and occupation. Further research adjusted for confounders that applies more sensitive measures is needed to clarify the association between SES and BMD (Brennan, et al., 2011).

1.5.11. Medication Associated with Osteoporosis

Many targets for therapeutic drugs of various diseases also play a major role in bone homoeostasis and can therefore cause bone loss as an adverse event. This accounts especially for systemic factors like parathyroid hormone (PTH), growth factors, glucocorticoids, thyroid hormones and sex hormones. Thus, it is of great importance to consider not only a patient's current medication but also the past medical history to evaluate a patient's personal risk for osteoporotic fractures. The following section is focusing on pharmaceutical substances where evidence suggests a direct or indirect association with osteoporosis, fractures and falls.

1.5.11.1. Glucocorticoids

Glucocorticoids (GC) are considered to affect calcium homeostasis, sex hormone levels and inhibit bone formation and their application therefore results in increased fracture risk (Tannirandorn and Epstein, 2000). The impact of glucocorticoid use increases with dose and duration of the exposure; a dose of 2.5 mg of systemic glucocorticoids per day (prednisone or equivalent) for more than three months already increases fracture risk. GC use is associated with loss of BMD, especially in the first view months. Also, non BMD-related contributions of GCs to fracture risk are being discussed. Thus, patients on corticosteroid therapy with low BMD are even at higher risk than patients with low BMD only. These findings and the high prescription rates of GCs highlight the value of taking long-term GC use into account when assessing a patient's fracture risk (Brown, et al., 2002).

1.5.11.2. Antidepressants

Selective serotonin reuptake inhibitors (SSRI), are commonly used in the treatment of depression. Several influences of serotonin (5-HT) on the regulation pathways of bone formation have become evident (Warden, et al., 2005). A study comprising of 93,676 postmenopausal women enrolled in the women's health initiative observational study, found an increased fracture risk at any site and especially at the vertebra to be associated with antidepressant use; no decrease in BMD was reported in this study (Spangler, et al., 2008). Another study, using a smaller but more representative sample reported a twofold increased risk of sustaining osteoporotic fractures in postmenopausal women receiving SSRIs and additionally, a decrease in BMD was measured (Richards, et al., 2007).

1.5.11.3. Anti-Ulcer Agents

Another group of drugs being discussed to cause secondary hyperparathyroidism and therefore increased fracture risk are proton pump inhibitors. Lack of acid in upper gastrointestinal bowel and the resulting unavailability of food-calcium leads to an increase in PTH induced skeletal turnover (Wright, et al., 2008). The overall risk of obtaining a fracture in general and the risk of hip-fractures is increased after exposure to proton pump inhibitors for 7 and 5 years, respectively. No increase in fracture risk was reported in exposure time shorter than this (Targownik, et al., 2008).

1.5.11.4. Antiepileptic Drugs

The use of antiepileptic drugs (AEDs) was reported to raise the risk of hip fractures by 29 % over a period of 5 years in women aged 65 or older (Ensrud, et al., 2004). Especially phenytoin, carbamazepine and phenobarbital interact with cytochrome P450 CYP450 metabolism of vitamin D resulting in low plasma levels. The resulting increase in PTH levels again leads to increased bone resorption and increased fracture risk. This mechanism is considered to account for the use of the agents named above as they are hepatic enzyme inducers. In contrast, this model is inappropriate for drugs not associated with vitamin D catabolism; for valproate,drug-induced renal dysfunction is regarded as cause for increased bone loss. Also other causes for elevated PTH levels, like direct interference with intestinal calcium absorption, are being discussed for anticonvulsant agents (Drezner, 2004).

1.5.11.5. Antidiabetics

Thiazolidinediones are regarded as insulin sensitizers as they increase insulin sensitivity by activating peroxisome proliferator activated receptor (PPAR)-γ, a nuclear receptor that regulates differentiation of adipocytes (Grey, 2009). Activation of these receptors by rosiglitazone and pioglitazone promotes adipocyte formation on the expense of osteoblast differentiation from pluripotent precursors. In addition to this direct effect of Thiazolidinediones, the increased production of adipocytokines might have negative effects on bone formation. Also PPAR-γ agonist promoted decrease of insulin and IGF-1 levels are considered to have a negative impact on bone (Grey, 2008; Grey, 2009). A meta-analysis conducted in 2008 states that the risk of fractures for women treated with thiazolidinediones is twofold increased (Loke, et al., 2009).

1.5.11.6. Anti-retroviral Medication

Results of recently conducted studies indicate that HIV-associated bone loss and increased fracture risk are rather linked to the infection itself than to the use of medicines for the management of the condition (Fausto, et al., 2006). HIV positive patients already have CRFs for osteoporosis that are related to the infection like weight loss, immobilisation and altered thyroid hormone levels associated with fragility fractures and

bone loss (Landonio, et al., 2004). However the available data suggests considering HIV infection as a risk factor for osteoporosis assessment regardless of their treatment.

1.5.11.7. Heparin

The data available for the treatment of heparin is limited in terms of patient numbers and possible confounders. The results of these studies indicate that the treatment with heparin is associated with lower BMD and higher fracture risk. These effects were indirectly correlated with molecular weight of the agents, presenting the highest fracture risk for unfractionated heparin, and the lowest risk for fondaparinux, a synthetic pentasaccharide (Rajgopal, et al., 2008). The binding of heparin to OPG is considered as the underlying mechanism; the lack of the inhibitory impact of OPG results in enhanced osteoclast activity and subsequent bone resorption (Irie, et al., 2007).

1.5.11.8. Systemic Contraceptive Agents

Depot medroxyprogesterone acetate (DMPA) is a progestin-based injectable contraceptive agent, administered on a three-monthly basis (Scholes, et al., 2005). The contraceptive activity is considered to be based on the suppression of pituitary gonadotropin release resulting in anovulation and alteration of the endometrium accompanied by reduced oestrogen production and secretion (Shaarawy, et al., 2006). The oestrogen deficiency was reported to be associated with slight BMD decreases at the hip and the vertebra but not at the whole body, with annual changes in BMD of -1.81%, -0.97 % and 0.73 % in DMPA users and -0.19 %, 1.32 % and 0.88 % in the control group, respectively. Also changes were found to be greater in new users of than in women already on DMPA with -6.09 % compared to -2.04 % after two years respectively. These effects were reported to be reversible after discontinuation of contraceptive treatment (Scholes, et al., 2005). Participants of a scientific meeting on this specific topic concluded that, the use of DMPA does not imply pharmacologic intervention in healthy individuals. However, in patients presenting additional clinical risk factors the need for such interventions should be assessed (Guilbert, et al., 2009).

1.5.11.9. Anticancer therapeutics

Anticancer therapeutics, which reduce sex hormone levels, are associated with higher fracture rates in both women and men. Aromatase inhibitors are used in early-stage breast cancer in patients with hormone receptor positive tumours. Anastrozole is a competitive antagonist of the enzyme aromatase, an enzyme that converts testosterone to oestrogen. The resulting decreases in oestrogen levels are associated with increased fracture risk, during the treatment period only (ATAC Trialists' Group, 2005). Androgen deprivation therapy is also associated with accelerated bone loss and osteoporotic fractures in men in a dose-dependent manner (Liu, et al., 2008).

1.6. Diagnosis of Osteoporosis

For the purpose of identifying osteoporosis, a patient's bone mineral density is measured given that BMD is the best surrogate marker for bone strength (Griffith and Genant, 2008). Technically, the diagnosis is based on the deviation of a patient's BMD from the mean young adult. The current standard technique to diagnose osteoporosis is dual energy X-ray absorptiometry (DXA or DEXA) (WHO, 2003). Besides BMD measurement, the incidence of osteoporotic fractures also implies a diagnosis of osteoporosis. In addition, techniques focusing on direct assessment of bone, certain compounds have been identified in blood or urine that indicate bone resorption or formation (SIGN, 2003).

1.6.1. DEXA-Scan

DEXA or DXA is a non-invasive, projectional imaging technique based on the relative absorption of the tissue of X-ray beams (Griffith and Genant, 2008). Results from BMD measurements are presented as T-scores and Z-scores; both represent a value that refers to a number of standard deviations (SDs) below or above the value of a specific segment of population. Whereas the T score is related to the young adult mean (20-29 years), the Z score is the number of SDs above or below the mean of the same aged population. For patients under 20 years a Z-score adjusted for gender and ethnicity should be used. The sites predominantly used in DXA scanning are the lumbar spine, proximal humerus. For diagnostic purposes the most reliable results are obtained from BMD measurement at the proximal femur. This site is less likely to be influenced by concomitant age-related circumstances that affect BMD values like arthritis or arthrosis

(Lynn, et al., 2005). Although this technique is regarded as the gold standard for the diagnosis of osteoporosis, it does not take bone quality and a patient's propensity to fall into account (Hoiberg, et al., 2016).

1.6.2. Quantitative Computed Tomography (QCT)

Quantitative computed tomography (QCT) is a technique which creates three-dimensional images of the investigated site and allows to measure a patient's volumetric BMD and geometry of the regarding bone. In QCT, X-ray beams are directed to the site of interest and are rotated around the bone, which allows for 3D-images to be reconstructed. The technique is beneficial for assessing clinically significant sites such as spine and hip and allows to distinguish between cortical and cancellous bone (Hunt and Donnelly, 2016). Despite these benefits, QCT shows lower reproducibility, patient's receive significantly higher doses of radiation compared to DXA and the method is less standardized than other techniques (Sheu and Diamond, 2016).

1.6.3. Magnetic Resonance Imaging (MRI)

MRI is another imaging technique that allows to determine fracture risk and to monitor osteoporosis treatment. MRI is predominantly applied to peripheral sites such as radius, tibia and calcaneum and assesses the trabecular microarchitecture by determining trabecular water content. Recent advancements allow for measurement of the proximal femur, which is of greater clinical importance to predict a patient's fracture risk and monitor osteoporosis treatment. Although this non-ionizing technique shows promising results for osteoporosis screening, its use in a clinical setting is limited by the high costs of devices and yet the low resolution of trabeculae (Hunt and Donnelly, 2016).

1.6.4. Quantitative Ultrasound (QUS)

Quantitative Ultrasound (QUS), another nonionizing method, measures the stiffness of the assessed bone as a surrogate for BMD (Sheu and Diamond, 2016). The technique was shown to predict fracture risk and confirm low BMD levels determined by DXA-scan. It is suggested to be used as a surrogate for DXA in areas with low radiographic coverage or as pre-screening tool to categorise patients into low- and high-risk groups for sustaining

osteoporotic fractures, amongst others due to the method's low costs and the portability of the measuring devices (Hoiberg, et al., 2016).

1.6.5. Biochemical Markers

Biochemical markers, in specific bone turnover markers (BTM) have been investigated as an additional resource to monitor the management of osteoporosis, but only N-terminal propeptide of type I procollagen (PINP), a marker for bone formation and C-telopeptide of type I collagen (CTX-I), a marker for bone resorption are recommended for the use in a clinical setting. Despite the benefits of these measurements, of not being invasive and the cost-effectiveness, BTMs are not recommended for the diagnosis of osteoporosis alone so far (Eastell and Szulc, 2017).

1.7. Fracture Risk Assessment

National and international guidelines recommend the consideration of clinical risk factors for the prevention and management of osteoporosis. Several studies have been conducted during the last years to identify CRFs to predict fracture risk or low BMD and to create algorithms for risk assessment of the condition (Lynn, Lau et al. 2005).
In February 2008, a tool has become available to predict the 10-year probability of sustaining an osteoporotic fracture, providing an international algorithm for the use in men and women (Kanis, et al., 2008).

In the following, a selection of available fracture risk assessment tools will be presented and their suitability of integrating such methods in a model of pharmaceutical care will be discussed.

1.7.1. FRAX®

FRAX® is a multivariate model, developed by the WHO collaborating centre of metabolic bone disease at the University of Sheffield that provides the 10-year probability of hip or major osteoporotic fractures as output information. Clinical spine, hip, forearm or shoulder fractures are regarded as major osteoporotic fractures. It addresses men and women aged 40 years or older not receiving medication for the prevention and treatment of

osteoporosis. A major objective of the risk assessment tool is to compensate insufficient sensitivity of BMD measurement to identify patients at high risk of sustaining osteoporotic fractures. The purpose of FRAX® is not to replace bone mineral density measurement but to include the aspect of CRFs into osteoporosis management decisions. Potential CRFs were obtained from a series of meta-analyses previously conducted. Baseline and follow up data of nine population-based cohort studies were used to identify relevant predictors and their contribution to fracture risk. Relationships between these factors were validated in 11 independent population-based cohorts exceeding one million patient years to validate algorithms (Kanis, et al., 2008).

BMD measurement results reported as T-score of the hip (optional), a set of clinical risk factors, age and sex are taken into account to predict the fracture probability. The tool provides four algorithms to predict the fracture probability for men and women aged 40 years or older with or without measured BMD (Fardellone, 2008). CRFs used in the tool are: femoral neck BMD, low BMI, history of osteoporotic fractures, history of oral corticosteroid therapy, parental history of hip-fractures, alcohol intake (3 or more units a day), smoking, and rheumatoid arthritis. In addition, more causes for secondary osteoporosis, in particular untreated hypogonadism, inflammatory bowel disease, prolonged immobility, organ transplantation, type I diabetes and thyroid disorders are implemented in the tool. The independence of these CRFs of BMD remains unclear. Therefore, they are not counted as an independent risk factor. When rheumatoid arthritis is chosen as ‘yes’ or a T-score is entered, other causes for secondary osteoporosis are not taken into account for probability calculation. For the United States also ethnicity is considered in the algorithm. Falls are not included in the tool, but have been reported to be integrated into the age contributor (Ettinger, 2008). The CRFs used in the online-questionnaire contribute to the outcome in an incremental manner; each predictor computes as a certain variable depending on the combination of predictors (Kanis, et al., 2008). FRAX® is also available for mobile devices like mobile phones and tablets, which allows the application of the tool, if a computer with an active internet connection is not available (Kanis, et al., 2011).

1.7.2. FORE Fracture Risk Calculator

The FORE Fracture Risk Calculator is another tool that provides an algorithm for fracture risk prediction. It resembles the current version of FRAX® in terms of clinical risk factors and prediction algorithm. The web-based application, provided by the foundation for

osteoporosis research and education (FORE) estimates the 10-year fracture risk for men and postmenopausal women aged from 45 to 85 years not receiving medication for osteoporosis treatment. Results are presented as percentages of 10-year risk of obtaining a hip fracture or a fracture at one of the following sites: hip, wrist, upper humerus, spine (clinically apparent). Fracture risk is graphically presented and categorized as low, moderate or high risk (Ettinger, 2008).

1.7.3. Other Fracture Risk Assessment Tools and Algorithms

A study conducted by Judith et al. aimed to create, implement and evaluate a service for the prevention (and management) of osteoporosis. The service included conducting a risk assessment questionnaire, BMD testing (for the BMD group), risk categorisation and a strategy to inform the participants, to make recommendations for prevention of the condition and to refer high-risk patients to a GP. The effect of providing BMD measurement at the pharmacy on the participants' adherence to referral or given advice was tested in the study. Risk predictors used in the questionnaire were categorized in modifiable and non-modifiable risk factors. In addition the participant's satisfaction with the service was evaluated. The final study population consisted of a BMD group (n= 113; finally used for assessment) and a non-BMD group (n= 80; finally used for assessment), receiving the service with or without a peripheral DXA-scan, respectively. A telephone survey, including 172 participants was conducted three months and six months after distribution of the service (Crockett, et al., 2008).

The study showed low adherence regarding referral uptake. Three out of 22 GP-referred participants took up the referral. Also a considerable difference in identifying those at risk was reported in the two groups 10.0 % at risk in the non-BMD group and 2.7 % in the BMD group (Crockett, et al., 2008).

In a follow-up study, a secondary data analysis was conducted to refine the questionnaire and assess the influence of BMD testing in risk categorisation of osteoporosis by community pharmacists. A significant difference in categorising participants as low or moderate/high risk has been reported between pharmacists and the research group. Also statistically significant differences have been shown for the identification of patients at risk when BMD results were considered and when the risk was identified based on risk factors alone. Multiple linear regression was used to identify a set of clinical factors that can predict BMD scores. A simple algorithm was derived from the findings comprising the

predictive factors age, weight, cessation of periods for 12 month or more, and hormone replacement therapy. These components were reported to be the strongest predictors for BMD (Poh, et al., 2008).

A cross-sectional study conducted by Scholtissen et al. focused on the development of an algorithm for predicting osteoporosis in men. Two Models, including the predictors: age, BMI and a family history of osteoporotic fractures are provided. Model II additionally includes a biomarker for bone resorption, in particular CTX-1 blood levels (Scholtissen, et al., 2009).

The women's health initiative (WHI) hip fracture risk calculator available on http://hipcalculator.fhcrc.org calculates the 5-year probability of sustaining a hip fracture for women based on general health status, ethnicity, physical activity, smoking, family history of osteoporotic fractures after the age of 40, current use of corticosteroids, diabetes, age and BMI. Eleven risk predictors were identified using data of the observational component including 93,676 women of the multi-ethnic longitudinal study. The algorithm was validated using data of the clinical trial component of the WHI (Robbins, et al., 2007).

Data from the Study of Osteoporotic fractures (SOF) was used to create a simple algorithm for osteoporosis risk assessment, based on the predictors age, BMD T-score, fracture after the age of 50, family history of osteoporosis, weight less than 125 pounds (57 kg), smoking, and use of arms to stand up from a chair. These risk factors, obtained by logistic regression analysis of 20 potential risk factors were reported to be consistent with the NOF guidelines. A total of 7782 women aged 65 years or older were included in the study to create the FRACTURE index in order to predict fracture risk for hip, vertebral and non-vertebral fractures. The index was validated using data from the EPIDOS (n=7575) fracture study (Black, et al., 2001). This model has been used besides the index created by Doherty et al (Doherty, et al., 2001) in systematic reviews to calculate fracture risk for the untreated population to allow calculation of relative and absolute risk reduction in the intervention population (Wells, et al., 2008b).

1.8. Management of Osteoporosis

1.8.1. Pharmacological Treatment

The primary aim of osteoporosis treatment is the reduction of fractures and associated increase of morbidity and mortality. Pharmacological fracture risk reduction can be achieved by reducing the demineralization of bone (antiresorptives) on the one side and enhancing bone formation on the other side (osteoanabolics). Treatment options slightly differ regarding the cause of osteoporosis (postmenopausal osteoporosis, glucocorticoid induced osteoporosis or other secondary causes).

1.8.1.1. Calcium and Vitamin D

Calcium is the “medication” being used for the longest time for the treatment of osteoporosis. The evidence base for the use of calcium and vitamin D shows discordant results for the efficacy of calcium. A meta-analysis conducted by Tang et al comprising 29 randomised trials (n = 63879) reports a risk reduction of 12 % (risk ratio 0.88, 95% CI 0.83–0.95; p = 0.0004) regarding all types of fractures in 17 trials (n = 52625). In trials using BMD as outcome (17 trials, n = 41419) bone loss was reduced by 0.54 % at the hip and by 1.19 % at the spine. In studies showing greater compliance a significant risk reduction of 24 % has been shown for any type of fracture. Also a dosage higher than 1200 mg of calcium was reported to be more effective than dosage below 1200 mg (Tang, et al., 2007).

1.8.1.2. Bisphosphonates

Bisphosphonates (BP) are regarded as the mainstay in first-line treatment of osteoporosis. The anti-fracture efficacy and the safety of these agents have become evident in several large randomised controlled trials (RCT). BPs are stable analogues of pyrophosphate containing a carbon atom between two phosphate units with high affinity to calcium hydroxyapatite crystals. The resulting P-C-P bond is not metabolized and guarantees in vivo activity for many years. The potency of the various BPs is determined by the side chain attached to the central carbon atom. After the ingestion of amino-bisphosphonates (alendronate, risedronate, ibandronate and zoledronic acid) by osteoclasts the farnesyl diphosphate synthase, a key enzyme of the mevalonate pathway is inhibited, leading to low attachment to the bone and in higher doses, to apoptosis in these cells (Reid, 2008).

The bioavailability of BPs is poor with percentages of absorption ranging from 0.3 to 6 percent of the orally administered drug and in addition, absorption is likely to be declined by concomitant food and medication intake such as vitamins with mineral supplements, calcium supplements, laxatives containing magnesium, or antacids containing calcium or aluminium (NICE, 2008). In order to raise absorption and avoid upper gastrointestinal symptoms, BPs must be washed down with a large glass of water on an empty stomach with a subsequent food-avoidance of 30 minutes, or in the middle of a 4 hour feast (SIGN, 2003). In addition to these partly avoidable adverse events, there is evidence of bisphosphonate use resulting in other serious adverse events especially osteonecrosis of the jaw. Primary endpoints used in most trials are vertebral fractures as they are less likely to be influenced by "extrinsic factors". Also increased BMD values and biochemical markers are used as endpoints to provide comparability of available agents (especially in bridging studies) (Adami, 2007).

1.8.1.2.1. Alendronate

Alendronate is recommended as first-line treatment for primary and secondary prevention of osteoporosis in postmenopausal women (Harris, et al., 2009). A systematic review of eleven trials (n = 12,068) including results of the FIT-study amongst others, showed a significant reduction for daily oral administration of 10 mg alendronate in postmenopausal women. A relative risk reduction of 45 % (RR = 0.55, 95% CI = 0.45-0.67) was reported for vertebral fractures. This effect was reported to be statistically significant for both primary and secondary prevention. A significant relative risk reduction for secondary prevention only was found for non-vertebral, hip and wrist fractures of 23 % (RR = 0.77, 95% CI = 0.64-0.92), 53 % (RR = 0.47, 95% CI = 0.26-0.85) and 50 % (RR = 0.50, 95% CI = 0.34-0.73), respectively (Wells, et al., 2008b). The results for fracture risk reduction in the review are based on risk calculations for the untreated population using the "Fracture Index" (Black, et al., 2001) and the model by Doherty et al. (Doherty, et al., 2001).

1.8.1.2.2. Risedronate

Risedronate is a third generation nitrogen containing BP. The standard dose regimen for this agent is 5 mg/day and 35 mg/week for oral administration in postmenopausal women for primary prevention (5mg/day only) and for vertebral and hip fracture reduction (BNF 2008). A systematic review of the Cochrane database in 2008 including 14,049 women report a significant relative risk reduction for vertebral fractures of 39 % (RR = 0.61, 95% CI = 0.50-0.76). For non-vertebral and hip fractures a significant relative risk reduction of 20% (RR= 0.80, 95% CI = 0.72-0.90) and 26 % (RR = 0.74, 95% CI = 0.59-0.94), respectively. These results refer to secondary prevention only. For primary prevention no statistically significant fracture risk reduction was reported (Wells, et al., 2008a).

1.8.1.2.3. Etidronate

A systematic review conducted by the ScHARR in 2008 reported a risk ratio of 0.51 for vertebral fractures; the evidence was classified as moderate. Also a risk reduction for no vertebral fractures was shown in the review (RR = 0.72, 95% C I= 0.29-1.80). No risk reduction for hip fractures and peripheral fractures could be revealed in the analysis. The evidence level for non-vertebral, hip and peripheral fractures was ranked as low and very low respectively. The analysis embraced 11 out of 33 originally reviewed studies that used a cyclical intermittent regimen comparable to the BNF regimen for etridronate of 400mg/day for 14 days followed by calcium carbonate (500mg/day elemental calcium) for 76 days (NICE, 2008).

1.8.1.2.4. Ibandronate

In the Oral Ibandronate Osteoporosis Vertebral Fracture Trial in North America and Europe (BONE) a randomized, double-blind, placebo-controlled, parallel-group study comprising 2946 postmenopausal women, a relative risk reduction of 62% (P=0.0001) for daily oral ibandronate and 50% (P=0.0006) for intermittent oral ibandronate regarding morphometric vertebral fractures. In the VIBE study 7345 monthly ibandronate and 56,837 weekly BP patients were observed in the primary analysis of the population. In this head-to-head study no statistically significant difference between the weekly BP group and the monthly ibandronate group was reported for the reduction of hip, vertebral or any clinical fracture. However, an adjusted relative risk of 0.36 (95% CI= 0.18-0.75, p=0.006) was

reported for vertebral fractures in patients receiving 150mg monthly oral ibandronate (Harris, et al., 2009) The use of 150mg ibandronate for monthly oral administration was reported to be most effective in the Monthly Oral iBandronate in LadiEs study (MOBILE) study. This dosage regimen is more effective in terms of BMD gains and reduction of adverse reactions than the 2.5 mg (Reginster, et al., 2006) In addition it was shown in the BALTO II study that a majority of women prefers the monthly ibandronate regimen over weekly alendronate (Hadji, et al., 2008).

1.8.1.2.5. Zoledronic Acid

In the UK, zoledronic acid is licensed for the treatment of postmenopausal osteoporosis. A dose of 5 mg is administered by intravenous infusion once a year. A significant reduction of fracture risk and bone turnover markers and an increase in BMD was shown in a double-blind placebo-controlled trial including 7,765 patients undergoing randomisation. Adverse events were significantly higher in the zoledronic acid group. Besides transient post-dose symptoms a significant increase in arterial fibrillation was detected in patients receiving zoledronic acid (Black, et al., 2007). In addition there is evidence that zoledronic acid can prevent bone loss in postmenopausal women on cancer treatment (Hershman, et al., 2008). Regarding the complexity of rules for the oral administration of BPs (leading to low compliance) and the low absorption of oral bisphosphonates, the use of a yearly regimen can improve the benefit of osteoporosis treatment for the patient.

1.8.1.2.6. Strontium ranelate

Strontium ranelate, the divalent strontium salt of ranelic acid, has both anabolic and antiresorptive effects on the bone. The SOTI trial showed a relative risk reduction of 49% (RR= 0.51, 95% confidence interval, CI= 0.36-0.74, P≤0.001) regarding new vertebral fractures in patients receiving 2g strontium ranelate per day compared to placebo in the first year. The benefit for a period of three years was 41% (RR = 0,51 95% CI = 0.48-0.73, p < 0.001) compared to placebo. In this trial no statistically significant risk reduction for peripheral fractures was found (Meunier, et al., 2004).

The TROPOS study showed a risk reduction for sustaining a non-vertebral fracture of 16% (RR= 0.84, 95% CI= 0.702-0.995, p =0.04) during a period of three years. The risk

reduction regarding major fragility fractures was reduced by 19 % during the study period (Reginster, et al., 2005).

1.8.1.3. Selective Estrogene Receptor Modulators (SERM)

Selective estrogen receptor modulators show different effects on organs depending on the estrogen receptor subtype expressed in the tissue. SERMs act as agonists on estrogene receptors in bone (ER_{β}) and have antagonistic effects on the female reproductive tract (ER_{α}), which provides an ideal “drug profile” for the treatment of postmenopausal osteoporosis (Nelson, et al., 2013).

National guidelines recommend the use of raloxifene, as second-line therapy option for secondary prevention of osteoporosis in postmenopausal women (NICE, 2008). The efficacy of raloxifene was shown in the Multiple Outcome of Raloxifene Evaluation (MORE) trial. A decrease in vertebral fractures classified by the authors as moderate or severe of 61 % in women without prevalent vertebral fractures (RR= 0.39, 95% CI = 0.17-0.69) and 37 % in women with prevalent vertebral fractures (RR= 0.63, 95% CI = 0.49-0.83) was reported after three years. Differences between the 60 mg/day and the 120 mg/day were found not do be statistically significant in respect of vertebral fracture risk reduction (Siris, et al., 2002). A reanalysis of patient data of osteopenic and osteoporotic patients, without a vertebral fracture at baseline showed a relative risk of 0.53 (95% CI, 0.32-0.88) and 0.31 (95% CI = 0.06-0.71) for osteopenia and osteoporosis patients treated with 60 mg raloxifene respectively (Kanis, et al., 2003).

1.8.1.4. Teriparatide

Teriparatide is an osteoanabolic agent approved for the treatment of osteoporosis since 2002 and consists of a fragment of the human parathyroid hormone (PTH 1-34) (Bhattacharyya, et al., 2019). The anabolic effect is accomplished by increased stimulation of osteoblast activity (Dempster, et al., 2012). The administration of teriparatide improves cortical geometry and the architecture of trabeculae. (Body, et al., 2002). In the UK, teriparatide is an alternative treatment option for severe cases of osteoporosis in postmenopausal women with at least one fracture and with a contraindication or an intolerance to bisphosphonates and strontium ranelate (NICE, 2008). A RCT comparing the effects of teriparatide to placebo in 1637 women with

osteoporosis, found a relative risk for fractures of 0.35 (95% CI= 0.22-0.55) and 0.31 (95% CI= 0.19-0.50) in patients receiving 20 µg and 40 µg of teriparatide, respectively. The increase in spinal BMD was found to be 9 % and 13 % in the patient groups receiving 20 µg and 40 µg of teriparatide, respectively, compared to placebo (Neer, et al., 2001). A randomised controlled trial, comparing the efficacy of once-daily, subcutaneous injection of teriparatide to oral alendronate administration, demonstrated the superiority of teriparatide concerning BMD increase and the reduction of non-vertebral fractures over alendronate (Body, et al., 2002).

1.8.1.5. Abaloparatide

Abaloparatide is a recently introduced, synthetic analogue of the endocrine PTH-related protein (PTHrP) and is the second agent in the class of osteoanabolic drugs. Abaloparatide binds to the type 1 PTH receptor (PTH1R), which is a G-protein coupled receptor and a target for the endogenous ligands PTH and PTHrP. Amongst other effects, PTHrP regulates bone remodelling in adults. Abaloparatide has similar anabolic effects as teriparatide, but it's administration is associated with less incidences of hypercalcaemia, less resorption and an earlier onset of protection against fracture (Bhattacharyya, et al., 2019). An RCT found a significant reduction of new vertebral fractures, similar to teriparatide. Additionally, BMD was significantly increased at the total hip, femoral neck and lumbar spine (Miller, et al., 2016). In the extension of this trial it was shown, that antiresorptive therapy for 24-month following 18-month treatment with abaloparatide could further decrease fracture risk and increase BMD compared to abaloparatide alone (Bone, et al., 2018).

1.8.1.6. Calcitonin

A recent multicentre study conducted to evaluate the efficacy of oral calcitonin, an antiresorptive peptide hormone, used in the treatment of osteoporosis, came to the conclusion that the agent is ineffective in preventing osteoporotic fractures. (Henriksen, et al., 2016). Additionally, recent guidelines do not recommend the use of calcitonin for the treatment of osteoporosis, because it was withdrawn from the marked for this indication due to an increased risk of cancer (SIGN, 2015).

1.8.1.7. Denosumab

Denosumab is a monoclonal antibody, which interferes with osteoclast differentiation and function by binding RANKL. It was reported to be effective in increasing BMD and reducing bone turnover markers similarly to first-line therapy agents in postmenopausal women (McClung, et al., 2006). In the UK, denosumab is recommended by national guidelines for the secondary prevention of osteoporosis in postmenopausal women presenting a contraindication or an intolerance to the standard treatment (i.e. antiresorptives), or who present a disability to comply with the special administration instructions given for these agents (NICE, 2010).

1.9. NHS Scotland

1.9.1. DADS

The Direct Access Densitometry Service (DADS) is a program, established in 1998 to refer patients at risk of sustaining an osteoporotic fracture to a DXA scan in *Greater Glasgow*. It is a scheme that provides collaboration between GPs and GGHB DEXA providers. According to the model's criteria, a patient who has one or more of the following criteria is referred to a DXA scan by their GP (NHS Scotland 2010). A patient database called GISMO (Glasgow Integrated System for Management of Osteoporosis) was created especially to administrate data of osteoporotic patients (Pell, 2002).

1.9.2. QOF

The Quality Outcomes Framework (QOF) is a voluntary feature of the General Medical Services (GMS) contract for general practices across the UK. It is a quality assurance system that rewards practices with points and payments according to their quality of practice using a range of evidence-based indicators. QOF contracts are available for a series of chronic diseases. Also osteoporosis is suggested to be included in the QOF, but this has not been implemented to date (Langdown and Peckham, 2013).

1.9.3. READ Codes

Read codes are combinations of letters and digits to label a certain medical condition or pharmacological treatment in patient data storage systems. For diseases that are included in the QOF system, READ codes that are relevant to the disease and associated co-morbidities are listed (de Lusignan, 2005).

1.10. Medication Assessment Tool: MAT_{osteo}

The medication assessment tool (MAT), originally created by JJ McAnaw is a tool to measure the adherence to guideline recommendations. The algorithm of the tool consists of a qualifying statement in the numerator and a standard statement in the denominator. The qualifying statement determines whether a criterion is applicable to a patient or not. If a criterion can be applied to a patient, it is examined whether the standard, predominantly regarding treatment options or dosage regimes, is met. If the standard is met (recorded as "YES" in the MAT) in all patients the criterion applies to, the adherence is 100 %. If there is a justification for not meeting the standard (e.g. contraindications to the recommended drug), "No justified" is chosen. "No(J)" computes equal to "YES" and therefore does not decrease the percentage of adherence. When the standard is not met, either "No unjustified" (No(U)) or "Insufficient data on the standard" ("IDS") is recorded. IDS is for instance chosen if patient data is poorly recorded or a part of the information is missing. Both unjustified non-adherence and insufficient data on the standard, result in a decline in adherence of the regarding criterion (Hakonsen, et al., 2006).

Figure 1. Formula for the calculation of applicability

$$Applicability = \frac{\sum Yes, No(U), IDS}{n} \; x \; 100$$

Figure 2. Formula for the calculation of adherence

$$Adherence = \frac{\sum Yes}{\sum Yes, No(U), IDS} \; x \; 100$$

The arrangement of the original MAT was adapted for the use in a range of indications. In the MAT_{osteo} was created by Aish Al-Harti to measure the adherence for primary and secondary prevention of osteoporosis and osteopenia. The model was modified by E Past resulting in a total number of 28 criteria. In a subsequent study the tool was adapted by J Schlais for the use in osteoporotic patients only.

2. Aims and Objectives

The aim of this study was the development and validation of a pharmaceutical care model to provide community pharmacists and clinicians with a means to deliver primary and secondary prevention of osteoporosis to eligible patients. The pharmaceutical care tool was scheduled to comprise an updated version of MAT_{osteo} in combination with a fracture risk assessment tool and was designed to run alongside with the NHS's falls prevention programme. A major objective was to develop a plan to adjust the delivery of pharmaceutical care to the individual patient's care issues. The current MAT_{osteo}, was modified and adjusted to new guidelines. It was tested on two GP's patient databases collected by J. Schlais in 2008 and validated by experts, specialised on osteoporosis in the field of pharmaceutical care.

3. Methods

3.1. Literature Review

A literature review was conducted to assess the current evidence base and to identify recent changes in guideline recommendations. Also valid inclusion criteria for osteoporosis primary and secondary prevention screening strategies were identified. The investigator consulted the online resources embase, medline and pubmed to obtain the eligible data. References were obtained by accessing these online resources through the intranet of University of Strathclyde and a VPN-tunnel to the University of Vienna. Further selected journals including Bone, Journal of Densitometry, J. Bone miner. and Osteoporosis International were consulted to obtain actual and relevant changes for guideline recommendations. The Scottish NHS website was accessed in order to gain knowledge about the implementation of national and local health initiatives in recent years. In addition, the NICE website was consulted to check the availability of new guideline recommendations.

3.2. Implementation of new Guideline Recommendations

The new guideline recommendations that were identified during the literature review - NICE technical appraisal 160 and 161 for the primary and secondary prevention of osteoporotic fractures - were compared with the recommendations in the previous version of MAT_{osteo} created by E. Past. Each of the changes, modifications and rephrasing were discussed with the research group and implemented in an iterative manner.

3.3. Database Protocols

Database protocols were previously created by J. Schlais to facilitate the automated application of MAT_{osteo} during data handling in Microsoft Access®. The protocols instruct the investigator to design Microsoft Access® queries, a database search function, in order to apply each criterion of the MAT. In consistency with the MAT, each protocol consists of a denominator and a numerator which corresponds to the MAT's qualifying statement and the standard statement, respectively. In this study the protocols were adjusted according to the changes carried out in MAT_{osteo}. A literature search was conducted to find missing READ codes for criteria that were processed manually in the previous study conducted by

J. Schlais. Further, the meaning of critical READ codes was added to the database protocol and to the corresponding queries, to increase both applicability and adherence. The database protocols can be found in the Appendix section below.

3.4. Data Collection

Patient data collected in a study conducted by J. Schlais was reanalysed in the present study. Data from 217 patients with a diagnosis of osteoporosis or osteopenia collected from two GP practices in Clydebank and Paisley was assessed. Patient's data-sets were downloaded from GPASS® into Microsoft Excel® sheet in several visits to the GP practices by Schlais in 2008. The patient data in this study was obtained from the original Microsoft Excel® tables compiled by Schlais and was imported into Microsoft Access®. In this study, patients with a diagnosis of osteopenia were included from the original dataset to meet the newly implemented criteria, which follow the actualised guideline recommendations.

3.5. Data Analysis

In order to apply the database queries adapted before, patient tables were created for osteoporosis and osteopenia patients in practice A (Clydebank) and for osteoporosis patients only in practice B (Paisley). Patient data was categorised into tables for diagnostic status and demographic information, DEXA-scans, past and current medication, medical history and fractures. Each patient had a unique patient number, assigned in the GPASS® system which was used as unique primary key. This patient-key allowed to link patient data contained in the individual tables to each other unambiguously in Microsoft Access®. For each of the imported tables, a query designed to detect duplicates was created to find patient data that was ambiguous in terms of diagnosis. Patients that presented a diagnosis for both conditions were categorised in either osteopenia or osteoporosis patients according to the most recent date of the recorded diagnosis. Subsequently, the duplicates were eliminated in a semi-automated manner from the eligible tables in Microsoft Access® and Microsoft Excel®.

3.6. Access Query Design

For each criterion at least two queries were created in Microsoft Access®, which correspond to each of the steps illustrated in the database protocols below. In principal one query was created to identify patients that meet the qualifying statement and at least one to identify those adhering. The majority of criteria required the design of more than two queries. Once the investigator became acquainted with the database software, the number of queries for each criterion could be reduced by editing and combining already existing queries. In order to increase the number of criteria processed automatically, in addition to READ codes also medical terms (e.g. osteoporosis, osteopenia) were included in the search form. Although this was likely to create abundant query results, this was done prospectively to decrease the number of false negative results for the qualifying and adherence outcomes. For patients that yielded double entries in the corresponding queries, a function was used in Microsoft Access®, which allowed displaying only one line of the corresponding patient record. After all necessary queries were created and combined for each criterion, the hereby created lists were exported to Microsoft Excel® to review the patient data and calculate the output variables listed in table 1 below.

Table 1. Output variables of MAT_{osteo}

Variable	Description
NA	Not applicable
Yes	Standard is adhered to in eligible patients
No(J)	No, justified
No(U)	No, unjustified
IDS	Insufficient data to address the standard statement
IDQ	Insufficient data to address the qualifying statement

3.7. Design of the Pharmaceutical Care Model

The osteoporosis screening and audit model was created in an iterative manner. The aim of the design was to provide a model of pharmaceutical care which combines a valid fracture risk assessment method, an up-to-date assessment tool to measure guideline adherence in patients at risk and give specific prevention advice to all patients invited to participate in the scheme. Each of the stages included in the model, was adjusted to be applicable in a Scottish community pharmacy-GP collaboration setting. The stages of the PC Model were planned to be categorised in two phases: a screening phase and a diagnosis and treatment phase. A standardised questionnaire, to be filled in by the patient in assistance with a pharmacist involved in the prevention model, was created to lead the experts conducting the model's steps through each stage. During the development and validation process of the model, the questionnaire was rephrased to meet the patients' understanding of the questions.

3.8. Validation of the Pharmaceutical Care Model

The model was validated in expert interviews in semi-structured interviews. Overall five interviews with six pharmacists involved in former osteoporosis prevention schemes were conducted in the greater Glasgow and Clyde area. The pilot interview was conducted at the "Falls Home", an institution run by NHS-Scotland in Glasgow. The interviews were scheduled to take 40 minutes, of which 20 minutes the experts were given to get familiar with the model's components and 20 minutes to state their opinion about the benefit for the patient and the obstacles in implementing such a scheme in a community pharmacy GP collaboration setting. After each interview the results were reported to the research group with the aim of eliminating obstacles that were brought up in the interviews. The remaining four interviews were conducted at community pharmacies. The interviews were transcribed and for each stage in the model obstacles and benefits were identified and listed chronologically, which is to be found in the result section of this study.

4. Results

4.1.1. Statistical analysis of previous projects' results

Before the design and validation of the current version of MAT_{osteo}, p-values of chi and fisher test were calculated to identify criteria, which have proven to be impractical in previous studies conducted by E. Past and J. Schlais. Although the original MAT_{osteo} consists of 28 criteria, only 26 criteria were compared, owing to the fact that J. Schlais excluded the two criteria assessing patients with a diagnose of osteopenia. This analysis provided in part the basis for modifications of the previous version of MAT_{osteo}.

Table 2. Statistical analysis and comparison of criteria of prior studies

Criterion		Applicability		Adherence		p value chi	p value fisher
		Study E	Study J	Study E	Study J		
1	Patient with fracture aged ≥60 has a recorded DEXA scan result	35	114	94.3	59.6	0.0003	0.0001
2	PMW, or men >50, with ≥2 minor CRFs has a DEXA scan	31	19	96.8	61.5	0.0086	0.0059
3	PMW, or men >50, with ≥1 major CRF	54	21	92.6	47.6	0.0001	0.0001
4	BMD is measured at least at two sites by DEXA scan	53	90	92.5	91.1	0.7799	1.0000
5	Osteoporosis patient with prescription of calcium ± vitamin D	48	180	91.7	81.7	0.1473	0.1229
6	Patient with prescription of calcium on 500 – 1500 mg/day	53	150	100	98.7	0.9714	1.0000
7	Prescription of vitamin D in vitamin D deficiency or patient ≥65	42	150	92.9	76.0	0.0164	0.0290
8	Patient with prescription of vitamin D on 400 – 800IU/day	51	136	98.0	97.8	0.9178	1.0000
9	Patient with CIs on 1000-1200 mg calcium plus 800IU vitamin D/day	0	11	0	100	-	1.0000
10	Bisphosphonate prescribed simultaneously with calcium ± vit D	45	133	95.6	83.5	0.0717	0.0440
11	Patient given recommendations about prevention of further bone	57	194	61.4	25.3	0.0001	0.0001

Criterion		Applicability		Adherence		p value chi	p value fisher
		Study E	Study J	Study E	Study J		
12	Prescription of bisphosphonates in osteoporosis as first-line therapy	42	189	83.3	68.3	0.0533	0.0398
13	Patient on bisphosphonate without reason to avoid bisphosphonates	45	116	82.2	100	0.0001	0.0001
14	Patient with prescription of bisphosphonates is on standard dose	45	131	82.2	83.2	0.8796	1.0000
15	Patient given instructions for bisphosphonate use	45	130	40	0.8	0.0001	0.0001
16	Bisphosphonate therapy started with alendronate or risedronate	47	178	97.9	77.0	0.0025	0.0005
17	PMW not on alendronate is prescribed risedronate	12	32	41.7	6.3	0.0165	0.0110
18	Prescribed alendronate or risedronate in women age ≥80 ± fractures	5	64	80	67.2	0.9252	1.0000
19	Prescription of etidronate in PMW with ≥2 vertebral fractures	1	3	100	0	0.0505	0.2500
20	Patient on long-term GC therapy	5	9	100	55.6	0.2516	0.2208
21	Prescription of raloxifene in PMW with reason to avoid	4	19	0	0	-	1.0000
22	Patient prescribed raloxifene on 60 mg/day	0	0	0	0	-	-
23	Prescription of teriparatide in PMW aged ≥65 with osteoporosis	1	0	0	0	-	1.0000
24	Dose and application of teriparatide	0	0	0	0	-	-
25	Prescription of calcitonin in PMW with osteoporosis	6	21	0	0	-	1.0000
26	Dose and application of calcitonin	0	0	0	0	-	-
	Overall	739	2084	84.6	68.3		

4.2. Changes and modifications of MAT_{osteo}

The previous version of MAT_{osteo} created by E. Past consisted of 28 criteria, assessing primary and secondary prevention interventions of osteoporosis and osteopenia. The revision of the MAT, resulted in a new version consisting of 21 criteria. For the study conducted by J. Schlais, criteria assessing patients with a diagnosis of osteopenia were excluded resulting in a MAT that consisted of 26 criteria. The majority of the changes in the current version (MAT_{osteo} Luf [final]) were made to implement the new guidelines NICE TA 160 and 161 published in 2008 for the primary and secondary prevention of osteoporotic fractures respectively, which replace the NICE technical appraisal 87 released in 2005. This resulted in the inclusion of the new treatment option strontium ranelate for primary and secondary prevention of fractures. Another consequence was the creation of stricter inclusion criteria, in order to receive alternative treatment options to bisphosphonates. All modifications to MAT_{osteo} that were made during the revision process are listed in table 3 together with their corresponding justification.

After the statistical analysis and the review of data produced in previous studies, criteria for which data is not likely to be available due to documentation difficulties at the GP, were excluded. The regarding criteria focusing on risk factors, instructions for the correct administration and specific prevention advice given by the GP. All criteria concerning the dosage regimen were merged to one major dosage regimen criterion to raise the applicability and hence the power of the results and to increase the usability of the assessment tool. In addition changes in wording were made to either meet the new guideline recommendations or to avoid ambiguous qualifying or standard statements. For example the wording in criterion 11 was changed from “…no recorded reason…” to “…no reason on record.”

In Table 3 a comparison of both the previous and the revised version of MAT_{osteo} and summarises all modifications that were made to MAT_{osteo} during the revision process are displayed. In total, five criteria were excluded, either because the guidelines have changed or the criterion has proven to be unpractical during assessment. Four criteria were merged to increase the applicability of the regarding criteria, resulting in an overall dose regimen criterion. Six criteria were rephrased, owing to changes in guideline recommendations. Finally, one criterion was created to take the new treatment option strontium ranelate into account.

Table 3. Changes and modifications of criteria of MAT_{osteo}

MAT_{osteo} E Past & J Schlais	MAT_{osteo} Revised	Comments
Criterion 1 **A patient aged ≥ 60 with at least one of the following:** **☐ vertebral fracture** **☐ non-vertebral fracture** has a recorded DEXA scan result to confirm or exclude osteoporosis/osteopenia. [Justification for not referring to DEXA scan: Patient ≥ 60 years and ≥ 2 vertebral fractures imply a diagnosis of osteoporosis]	**Criterion 1** **A patient receiving osteoporosis treatment** has been assessed by DEXA scan [Justification for not referring to a DEXA Scan Patient ≥ 60 years and ≥ 2 vertebral fractures imply a diagnosis of osteoporosis or a postmenopausal woman ≥ 75 years and two or more independent clinical risk factors for fracture or indicators of low BMD] Independent clinical risk factors are: ☐parental history of hip fracture, ☐alcohol intake of 4 or more units per day ☐rheumatoid arthritis Indicators for low BMD are: ☐ low body mass index (defined as less than 22 kg/m^2) ☐ ankylosing spondylitis ☐ Crohn's disease ☐ conditions that result in prolonged immobility ☐ untreated premature menopause	The criterion was reworded to apply to primary and secondary prevention patients in regards of NICE 2008 for primary and secondary prevention of osteoporosis. The Justification for non-adherence was added according to NICE 2008 ['…the diagnosis may be assumed in women aged 75 years or older if the responsible clinician considers a DXA scan to be clinically inappropriate or unfeasible. …'] (NICE, 2008)

Criterion 2 **A postmenopausal woman, or a man aged > 50, with at least two minor clinical risk factors (CRFs, see below)** has been assessed by DEXA scan. [Minor CRFs are: ☐ rheumatoid arthritis ☐ past/present hyperthyroidism ☐ chronic anticonvulsant therapy ☐ low dietary calcium intake ☐ current smoker (> 10 cigarettes per day) ☐ excessive alcohol intake (> 10 units per week) ☐ weight < 57 kg ☐ weight loss > 10 % by age of 25 ☐ chronic heparin therapy]	Excluded	Criteria dealing with assessment of fracture risk and a resulting need for a DEXA scan were excluded; risk factor assessment is a major component of the Osteoporosis Screening and Audit Model. This was done because this criterion would have to be applied to all male patients > 50 years and all postmenopausal women at a GP; this would result in scanning a large amount of patient data (approximately 1800 patients per GP; based on the average list size of approximately 5300 patients).
Criterion 3 **A postmenopausal woman, or a man aged > 50, with at least one major clinical risk factor (CRFs, see below)** has been assessed by DEXA scan. [Major CRFs are: ☐ vertebral compression fracture ☐ fragility fracture after age 40 ☐ family history of osteoporotic fracture ☐ osteopenia apparent on X-ray ☐ BMI ≤ 19 ☐ systemic glucocorticoid therapy ≥ 3 months duration ☐ early menopause (age < 45) ☐ ovariectomy ☐ hypogonadism ☐ malabsorption syndrome ☐ primary hyperparathyroidism ☐ chronic inflammatory bowel disease ☐ propensity to fall ☐ conditions associated with prolonged immobility]	Excluded	See criterion 2

Criterion 4 **Measurement of the BMD by DEXA scan** is performed at least at the two specific sites – namely, anteroposterior spine and hip	**Criterion 2** **Measurement of the BMD by DEXA scan** is performed at least at the two specific sites – namely, anteroposterior spine and hip.	No changes
Criterion 5 **A patient with a recorded diagnosis of osteoporosis** is prescribed supplementary calcium (± vitamin D). **[Justification for non-prescribing calcium and vitamin D:** There is a record that the patient has an adequate dietary intake of calcium and no vitamin D deficiency.]	**Criterion 3** **A patient with a recorded diagnosis of osteoporosis** is prescribed supplementary calcium (± vitamin D). **[Justification for non-prescribing calcium and vitamin D:** There is a record that the patient has an adequate dietary intake of calcium and no vitamin D deficiency.]	No changes
Criterion 6 **A patient with a recorded diagnosis of osteoPENIA** is prescribed supplementary calcium (± vitamin D) for the prevention of osteoporosis. [Justification for non-prescribing calcium and vitamin D: There is a record that the patient has an adequate dietary intake of calcium and no vitamin D deficiency.]	**Criterion 4** **A patient with a recorded diagnosis of osteoPENIA** is prescribed supplementary calcium (± vitamin D) for the prevention of osteoporosis. [Justification for non-prescribing calcium and vitamin D: There is a record that the patient has an adequate dietary intake of calcium and no vitamin D deficiency.]	No changes
Criterion 7 **A patient prescribed supplementary calcium** is prescribed a daily dose of 500 – 1500 mg calcium.	**Criterion 7** **A patient prescribed supplementary calcium** is prescribed a daily dose of 500 – 1500 mg calcium.	No changes
Criterion 8 **A patient with confirmed vitamin D deficiency or aged ≥ 65** is prescribed vitamin D.	**Criterion 5** **A patient with confirmed vitamin D deficiency or aged ≥ 65** is prescribed vitamin D.	No changes
Criterion 9 **A patient prescribed vitamin D** is prescribed a daily dose of 10 – 20 µg (400 - 800 IU) vitamin D.	**Criterion 8** **A patient prescribed vitamin D** is prescribed a daily dose of 10 – 20 µg (400 - 800 IU) vitamin D.	No changes
Criterion 10 **A patient with a contraindication (see below) to all of the following: bisphosphonates, raloxifene AND calcitonin** is prescribed 1000 – 1200 mg calcium plus 800 IU vitamin D per day.	**Criterion 6** **A patient with a contraindication (see below) to all of the following: bisphosphonates, raloxifene, strontium ranelate AND calcitonin** is prescribed 1000 – 1200 mg calcium plus 800 IU vitamin D	It was decided by the study group to keep this criterion, despite the fact that calcium and vitamin D supplementation and the corresponding dose regimens are assessed in

[Contraindications to bisphosphonates are: ☐ oesophageal strictures or achalasia ☐ inability to remain upright for > 30 min after ingestion ☐ hypocalcaemia ☐ osteomalacia (etidronate) ☐ moderate renal impairment (CrCl < 35 mL/min) ☐ pregnancy and breast feeding] [Contraindications to raloxifene are: ☐ past/present venous thromboembolic events ☐ hepatic impairment ☐ cholestasis ☐ severe renal impairment (CrCl < 10 mL/min) ☐ endometrial cancer ☐ uterine bleeding ☐ pregnancy and breast feeding] [Contraindications to calcitonin are: ☐ hypocalcaemia ☐ hypersensitivity]	per day. [Contraindications to bisphosphonates are: ☐ oesophageal strictures or achalasia ☐ inability to remain upright for > 30 min after ingestion ☐ hypocalcaemia ☐ osteomalacia (etidronate) ☐ moderate renal impairment (CrCl < 35 mL/min) ☐ pregnancy and breast feeding] [Contraindications to raloxifene are: ☐ past/present venous thromboembolic events ☐ hepatic impairment ☐ cholestasis ☐ severe renal impairment (CrCl < 10 mL/min) ☐ endometrial cancer ☐ uterine bleeding ☐ pregnancy and breast feeding] [Contraindications to strontium ranelate are: ☐ pregnancy and breast feeding ☐ hypersensitivity] [Contraindications to calcitonin are: ☐ hypocalcaemia ☐ hypersensitivity]	criteria 3 and 7. This criterion represents a scenario with more specific rules in the standard than the rules in the criteria prior to this. Contraindications to strontium ranelate were added, according to BNF and eMC. This change was implemented despite the fact that strontium ranelate is not discussed in SIGN 2003, the primary source of this criterion. Strontium ranelate is according to NICE 2008 a treatment option equal to raloxifene and would be prescribed preferred to treatment with calcium and vitamin D only and was therefore added to the criterion.

Criterion 11 **A patient who is prescribed a bisphosphonate (alendronate, risedronate or etidronate), raloxifene or calcitonin** is prescribed supplementary calcium with or without vitamin D. [Justification for non-prescribing calcium and vitamin D: There is a record that the patient has an adequate dietary intake of calcium and no vitamin D deficiency.]	**Criterion 9** **A patient with osteoporosis and NOT prescribed any of the following: bisphosphonates, raloxifene, strontium ranelate or calcitonin** is prescribed ≥1000mg calcium plus 800 IU vitamin D per day	A diagnosis of osteoporosis or osteopenia is a prerequisite for the treatment of these conditions (NICE, 2008). The guidelines recommend calcium and vitamin D supplementation for osteoporotic and osteopenic patients. The criterion was reworded to meet the requirements of latest guideline recommendations and treatment options.
Criterion 12 **A patient who is diagnosed with osteopenia or osteoporosis** has been given recommendations about non-pharmacological interventions to prevent further bone loss. [Non-pharmacological interventions are: ☐ **regular low impact weight bearing exercise** ☐ **high intensity strength training** ☐ **smoking cessation** ☐ **reduction of alcohol consumption to < 10 units/week** ☐ calcium rich diet with an aimed intake of > 1000 mg/d]	Excluded	This criterion was excluded due to lack of reliable documentation at the GP-practice and the resulting falsified adherence. Non pharmacological interventions are a component of the Osteoporosis Screening and Audit Model; the corresponding step is named 'Check

		patient's understanding of prevention advice and treatment administration instructions'
Criterion 13 **A patient with a recorded diagnosis of osteoporosis** is prescribed an oral bisphosphonate as first-line therapy. Recorded reasons for non-conformance (justification): _____	**Criterion 10** **A patient with a recorded diagnosis of osteoporosis** is prescribed an oral bisphosphonate as first-line therapy. Recorded reasons for non-conformance (justification): _____	
Criterion 14 **A patient with a recorded diagnosis of osteoPENIA** is prescribed an oral bisphosphonate as first-line therapy. Recorded reasons for non-conformance (justification): _____	**Criterion 11** **A patient with a recorded diagnosis of osteoPENIA** is prescribed an oral bisphosphonate as first-line therapy. Recorded reasons for non-conformance (justification): _____	
Criterion 15 **A patient who is prescribed a bisphosphonate** has no recorded reason to avoid bisphosphonates. [Reasons to avoid bisphosphonates are: ☐ contraindication to bisphosphonates (see 10) ☐ inability to comply with the instructions for use of bisphosphonates (see 17) ☐ unsatisfactory response to bisphosphonates o another fracture occurs o decrease in BMD despite adherence to treatment ☐ intolerance to bisphosphonates o oesophageal ulceration o erosion or stricture o severe lower GI symptoms]	**Criterion 12** **A patient who is prescribed a bisphosphonate** has no reason on record to avoid bisphosphonates. [Reasons to avoid bisphosphonates are: ☐ contraindication to bisphosphonates - oesophageal strictures or achalasia - inability to remain upright for > 30 min after ingestion - hypocalcaemia - osteomalacia (etidronate) - moderate renal impairment (CrCl < 35 mL/min) - pregnancy and breast feeding ☐ inability to comply with the instructions for use of bisphosphonates - ingestion on an empty stomach - washing the medication down with 250 ml water - avoidance of food for 30 min - avoidance of lying flat within 30 min of ingestion ☐ unsatisfactory response to bisphosphonates - another fracture occurs - decrease in BMD despite adherence to treatment ☐ intolerance to bisphosphonates - oesophageal ulceration - erosion or stricture - severe lower GI symptoms]	The sections 'inability to comply with the instructions for use of bisphosphonates' and 'contraindications to bisphosphonates' were integrated in this criterion, as this is the first criterion involving these rules. Subsequent criteria that also apply to these rules refer to this criterion. The wording was rephrased to be more

precise from 'no recorded reason' to 'no reason on record'.

Criterion 16
A patient treated with a bisphosphonate
is prescribed a standard dose regimen.

❑ **Prevention (in osteopenia)**	❑ **Treatment (of osteoporosis)**
Postmenopausal Osteoporosis	
❑ Alendronic acid	
□ 5 mg daily PO	□ 10 mg daily or 70 mg once weekly PO
❑ Disodium etidronate	
□ 400 mg for 14 days PO; 1,25 g calcium carbonate for 76 days PO	□ 400 mg for 14 days PO, 1,25 g calcium carbonate for 76 days PO
❑ Ibandronic acid (not in guidelines)	
	□ 150 mg once a month PO or 3 mg every 3 months IV
❑ Risedronate sodium	
□ 5 mg daily PO	□ 5 mg daily PO or 35 mg weekly PO
Osteoporosis in men	
❑ Alendronic acid	
	□ 10 mg daily PO
Glucocorticoid-induced Osteoporosis	
❑ Alendronic acid	
□ 5 mg daily PO	□ 5 mg daily PO
❑ Disodium etidronate	
□ 400 mg for 14 days PO, 1,25 g calcium carbonate for 76 days PO	□ 400 mg for 14 days PO, 1,25 g calcium carbonate for 76 days PO
❑ Risedronate sodium	
□ 5 mg daily PO	

Criterion 13
A patient receiving treatment for osteoporosis/ osteopenia
is prescribed a standard dose regimen.

❑ **Prevention (in osteopenia)**	❑ **Treatment (of osteoporosis)**
Postmenopausal Osteoporosis	
❑ Alendronic acid	
□ 5 mg daily PO	□ 10 mg daily or 70 mg once weekly PO
❑ Disodium etidronate	
□ 400 mg for 14 days PO; 1,25 g calcium carbonate for 76 days PO	□ 400 mg for 14 days PO, 1,25 g calcium carbonate for 76 days PO
❑ Risedronate sodium	
□ 5 mg daily PO	□ 5 mg daily PO or 35 mg weekly PO
❑ Calcitonin	
	□ 200 units daily intranasally
❑ Raloxifene	
(□ 60 mg daily PO)	□ 60 mg daily PO
❑ Strontium ranelate	
	□ 2 g daily PO
❑ Teriparatide	
	□ 20 micrograms daily, for a maximum duration of treatment of 18 months
Osteoporosis in men	
❑ Alendronic acid	
	□ 10 mg daily PO
Glucocorticoid-induced Osteoporosis	
❑ Alendronic acid	
□ 5 mg daily PO	□ 5 mg daily PO
❑ Disodium etidronate	
□ 400 mg for 14 days PO, 1,25 g calcium carbonate for 76 days PO	□ 400 mg for 14 days PO, 1,25 g calcium carbonate for 76 days PO
❑ Risedronate sodium	
□ 5 mg daily PO	
❑ Teriparatide	
	□ 20 micrograms daily, for a maximum duration of treatment of 18 months

The dose regimens of alternative options to bisphosphonates were added to this criterion to raise the applicability of the regarding criteria. The criterion now assesses the adherence to dose regimens for all treatment options for osteoporosis and osteopenia covered by the guidelines used in the tool. This modification is anticipated to result in decreased specificity but increased applicability.

Ibandronic acid was excluded; currently none of the guidelines recommend the use of this agent for the treatment of osteoporosis or osteopenia. This was done to increase simplicity of

	the tool. The investigator suggests, reintegrating this agent, when corresponding guidelines will be implemented in this tool.

Criterion 17 **A patient who is prescribed a bisphosphonate** has been given special instructions for the use of this medication. [Special instructions are: ☐ ingestion on an empty stomach ☐ washing the medication down with 250 ml water ☐ avoidance of food for 30 min ☐ avoidance of lying flat within 30 min of ingestion]	Excluded	This criterion was excluded in the current version of the tool. The research group concluded that the information is not likely to be recorded in the patient data storage system. The assessment of a patient's understanding on the use of their medication is more likely to be achieved in a face to face interview and was therefore included as an element of the pharmaceutical care model.
Criterion 18 **A patient when started on bisphosphonate therapy** was initiated on alendronate or risedronate.	**Criterion 14** **A patient when started on bisphosphonate therapy** was initiated on alendronate.	According to NICE 2008 patients should be started on alendronate; the term 'a patient' in the previous MAT also includes male patients in the qualifier; only alendronate is recommended for the treatment of osteoporosis in men. Therefore it was decided to exclude 'risedronate' from this criterion. This would also apply to men and additionally according to NICE 2008 alendronate is more effective and less expensive than any other treatment options appraised.
Criterion 19 **A postmenopausal woman diagnosed with osteoporosis/osteopenia and not treated with alendronate** is prescribed risedronate.	**Criterion 15** **A postmenopausal woman diagnosed with osteoporosis/osteopenia and not treated with alendronate** is prescribed risedronate	No changes
Criterion 20 **A patient who is a frail, elderly woman aged ≥ 80 diagnosed with osteoporosis with or**	Excluded	It was decided to exclude this criterion because the rules implemented in criteria

without previous osteoporotic fractures is prescribed alendronate or risedronate.		12 and 13 take account of this specific circumstance. In addition the words frail and elderly are not practicable when applying database protocol.
Criterion 21 **A postmenopausal woman with ≥ 2 vertebral fractures and NOT treated with alendronate or risedronate** is prescribed intermittent cyclical etidronate for the reduction of vertebral fracture risk.	**Criterion 16** **A postmenopausal woman with ≥ 2 vertebral fractures and NOT treated with alendronate or risedronate** is prescribed intermittent cyclical etidronate.	Sign 2003 recommends the use of etidronate in this specific case, because there is evidence of etidronate preventing further vertebral fractures. The term for the reduction of vertebral fracture risk was excluded since this is not likely to be recorded.
Criterion 22 **A patient who is on long-term glucocorticoid therapy (≥ 7.5 mg prednisolone or equivalents for ≥ 3 months)** is prescribed a bisphosphonate.	**Criterion 17** **A patient who is on long-term glucocorticoid therapy (≥ 7.5 mg prednisolone or equivalents for ≥ 3 months)** is prescribed a bisphosphonate.	No changes
No corresponding criterion	**Criterion 18** **A postmenopausal woman diagnosed with osteoporosis without osteoporotic fractures who has an identifiable reason for not being prescribed a bisphosphonate** is prescribed strontium ranelate. [Reasons for non-use of bisphosphonates are Contraindications to bisphosphonates ❑ contraindication to bisphosphonates (see 11) ❑ inability to comply with the recommendations for use of bisphosphonates (see 11) ❑ intolerance to bisphosphonates]	This new criterion corresponds to NICE 2008 recommendations for primary prevention (no osteoporotic fractures but a diagnosis of osteoporosis). The term “unsatisfactory response to bisphosphonates” in the qualifying statement was removed from this criterion because there is no corresponding recommendation in NICE 2008, the guideline that this criterion originates from. It was decided to exclude the requirement in the qualifying

		statement described by the term 'AND who has a combination of T-Score, age and number of independent clinical risk factors as indicated in the table below' although this is required according to NICE 2008. These rules correspond to the cost utility analysis conducted for the guideline and were not included because assessing this specific aspect is not the aim of the tool
Criterion 23 A postmenopausal woman diagnosed with osteoporosis or osteopenia who has an identifiable reason for not being prescribed a bisphosphonate (see below) is prescribed raloxifene. [Reasons for non-use of bisphosphonate are: ☐ contraindication to bisphosphonates (see 10) ☐ inability to comply with the recommendations for use of bisphosphonates (see 17) ☐ unsatisfactory response to bisphosphonates (see 15) ☐ intolerance to bisphosphonates (see 15)]	**Criterion 19** **A postmenopausal woman diagnosed with osteoporosis with one or more osteoporotic fractures (secondary prevention) who has an identifiable reason for not being prescribed a bisphosphonate** is prescribed strontium ranelate or raloxifene. [Reasons for non-use of bisphosphonates are Contraindications to bisphosphonates ❑ contraindication to bisphosphonates (see 11) ❑ inability to comply with the recommendations for use of bisphosphonates (see 11) ❑ intolerance to bisphosphonates (see 11)]	For specifications of contraindication, inability to comply and intolerance it is referred to criterion 11. The reason "unsatisfactory response to bisphosphonates" was removed from this criterion because there is no corresponding rule in NICE 2008, from which this criterion is originally derived. It was decided to exclude the requirement in the qualifying statement described by the term 'AND who has a combination of T-Score, age and number of independent clinical risk factors as indicated in the table below' although this is required in NICE 2008. These rules correspond to the cost utility analysis conducted for the guideline and were not included because this specific aspect is not to be assessed by the tool.

Criterion 24 **A postmenopausal woman diagnosed with osteoporosis or osteopenia and treated with raloxifene** is prescribed a daily dose of 60 mg raloxifene.	Integrated in criterion 12.	The investigator decided to integrate this recommendation into the criterion 12 dealing with bisphosphonate dose regimens to raise the applicability of the dose regimen criteria. This results in a general criterion for dose regimen assessment. It has to be examined whether this can raise the overall applicability of the tool.
Criterion 25 **A postmenopausal woman diagnosed with osteoporosis aged ≥ 65 who has either** **☐ an unsatisfactory response to bisphosphonates (see 15)** **☐ an intolerance to bisphosphonates (see 15)** **and at least one of the following:** **☐ an extremely low BMD (T-score ≤ - 4)** **☐ a very low BMD (T-score ≤ - 3) plus ≥ 2 fragility fractures** **PLUS at least one of the following age-independent risk factors (see below)** is prescribed teriparatide. [Age-independent risk factors are: ☐ BMI ≤ 19 ☐ family history of maternal hip fracture before age 75 ☐ untreated premature menopause ☐ conditions associated with prolonged immobility]	**Criterion 20** **A postmenopausal woman diagnosed with osteoporosis AND at least one osteoporotic fracture who has either** **☐ an unsatisfactory response to bisphosphonates (see 10)** **☐ an intolerance to bisphosphonates (see 10)** **☐ an intolerance to strontium ranelate** o persistent nausea o persistent diarrhoea **and who is either** **☐ aged ≥ 65 years old with a T-Score ≤ -4 SD** **☐ aged ≥ 65 years old with a T-Score ≤ -3.5 SD and has more than two fractures** **☐ aged 55-64 years old with a T-Score ≤ -4 and has more than two fractures** is prescribed teriparatide.	This criterion was updated according to NICE 2008 TA161. The term “AND at least one osteoporotic fracture” was added because the corresponding guideline recommends the use of teriparatide for secondary prevention only. Intolerance to the new treatment option strontium ranelate, that is recommended to be preferred over teriparatide, was added. The updated guideline gives more specific recommendations concerning the combination of age and T-Score thresholds, but excludes the requirement of additional clinical risk factors. Despite this fact that contributes to increased simplicity, the practicability of this criterion still has to be questioned; the large amount of data items in the qualifier is likely to cause problems during the application of the database protocol.

Criterion 26 A patient who is a postmenopausal woman diagnosed with osteoporosis and treated with teriparatide is prescribed a daily dose of 20 µg as subcutaneous injection for a maximum of 18 months.	Included in criterion 12	It was decided by the research group to integrate this criterion into the criterion dealing with the bisphosphonate dose regimen despite the fact that the criterion assesses other information than the dose.
Criterion 27 A patient who is a postmenopausal woman diagnosed with osteoporosis and NOT treated with a bisphosphonate or raloxifene is prescribed calcitonin for the prevention of vertebral fractures.	**Criterion 21** A postmenopausal woman diagnosed with osteoporosis and NOT treated with a bisphosphonate, raloxifene, strontium ranelate and teriparatide is prescribed calcitonin.	The term 'a patient who is a postmenopausal woman' was changed to 'a postmenopausal woman' to simplify the wording of the criterion. The term "or strontium ranelate" was added to the criterion according to NICE 2008 TA 161. Calcitonin is not discussed as a treatment option in NICE guidelines; it was concluded by the study group that strontium ranelate, being a treatment option equal to raloxifene is preferred over calcitonin. Only NOGG guidelines include all treatment options. In this guideline, teriparatide is classified as 'major pharmacological intervention' and calcitonin as 'other pharmacological intervention'. Therefore the investigator concluded that teriparatide is preferred over calcitonin and therefore has to be included in the qualifying statement. The phrase "for the prevention of vertebral fractures" was excluded as it is not likely to be assessable due to the lack of recording at the GP.

Criterion 28 **A patient diagnosed with osteoporosis treated with calcitonin** is prescribed a daily dose of 200 IU administered intranasally.	Included in criterion 12	The dose regimen of calcitonin was integrated into criterion 11 in order to provide overall adherence to prescribed dosage in osteoporosis management.

4.3. Results Data Analysis

The following tables and graphs show the results of the data analysis of two GP practices in Clydebank (Practice A; N=154) and Paisley (Practice B; N=63). Patient data from a total number of 217 patients was analysed and the applicability and adherence to each criterion was measured. The tables and graphs were created for each practice alone and for both patient groups combined.

4.3.1. Data analysis: Practice A (Clydebank)

Table 4. Data Analysis: Practice A

No	Criterion	NA	Yes (%)	No(U) (%)	No(J) (%)	IDS (%)	IDQ (%)	APPL (%)	Adherence (%)	95% CI
1	**Patient with a diagnosis of osteoporosis** has a recorded DEXA scan	23	73	48	8	10	0	131 (85.1)	73 (55.7)	47.2-64.2
2	**Measurement of BMD by DEXA scan,** is performed at hip and spine	61	68	10	0	0	0	78 (50.6)	68 (87,2)	79.8-94.6
3	**A patient with a recorded diagnosis of osteoporosis** is prescribed supplementary calcium	15	99	40	0	0	0	139 (90.3)	99 (71.2)	63.7-78.7
4	**A patient with a recorded diagnosis of osteopenia** is prescribed supplementary calcium	139	14	1	0	0	1	15 (9.7)	15 (93.8)	80.7-100.0
5	**A patient with confirmed vitamin D deficiency or aged ≥ 65** is prescribed vitamin D	29	84	41	0	0	0	125 (81.2)	84 (67.2)	59.0-75.4
6	**A patient not on osteoporosis treatment** has a contraindication for each agent	110	0	44	0	0	0	44 (28.6)	0 (0.0)	0.0
7	**A patient prescribed supplementary calcium** is prescribed a daily dose of 500 – 1500 mg calcium	48	105	0	0	1	0	106 (68.8)	105 (99.1)	97.2-100.0
8	**A patient prescribed vitamin D** is prescribed a daily dose of 10 – 20 µg (400 - 800 IU) vitamin D	65	89	0	0	0	0	89 (57.8)	89 (100.0)	100.0
9	**A patient not on osteoporosis treatment** is prescribed ≥1000mg calcium plus 800 IU vitamin D	109	8	36	0	1	0	45 (29.2)	8 (17.8)	6.6-28.9
10	**A patient with a recorded diagnosis of osteoporosis** is prescribed an oral bisphosphonate as first-line therapy	15	109	30	0	0	0	139 (90.3)	109 (78.4)	71.6-85.3

No	Criterion	NA	Yes (%)	No(U) (%)	No(J) (%)	IDS (%)	IDQ (%)	APPL (%)	Adherence (%)	95% CI
11	**A patient with a recorded diagnosis of osteopenia** is prescribed an oral bisphosphonate as first-line therapy	139	12	3	0	0	0	15 (9.7)	12 (80.0)	59.8-100.0
12	**A patient who is prescribed a bisphosphonate** has no reason *on record* to avoid bisphosphonates	68	56	3	27	0	0	86 (55.8)	56 (65.1)	55.0-75.2
13	**A patient receiving treatment for osteoporosis/ osteopenia** is prescribed a standard dose regimen	55	93	6	3	0	0	99 (64.3)	93 (93.9)	89.2-98.6
14	**A patient when started on bisphosphonate therapy** was initiated on alendronate	54	86	15	0	0	0	100 (64.9)	86 (85.0)	78.0-92.0
15	**A PMW not treated with alendronate** is prescribed risedronate	141	7	6	1	0	0	13 (8.4)	7 (53.8)	26.7-80.9
16	**A PMW with ≥ 2 VFs not on alendronate or risedronate** is prescribed intermittent cyclical etidronate	154	0	0	0	0	0	0 (0.0)	0 (0.0)	0.0
17	**A patient who is on long-term glucocorticoid therapy** is prescribed a bisphosphonate	153	1	0	1	0	0	2 (0.6)	2 (100.0)	100.0
18	**A PMW with osteoporosis not on bisphosphonate** is prescribed strontium ranelate	151	1	2	0	0	0	3 (1.9)	1 (33.3)	0.0-86.7
19	**A PMW with osteoporosis with ≥ 1 fracture not on BPs** is prescribed strontium ranelate or raloxifene	154	0	0	0	0	4	0 (0.0)	0 (0.0)	0.0
20	**A PMW with osteoporosis with ≥ 1 fracture not on BPs and SR** is prescribed teriparatide	154	0	0	0	0	0	0	0	0.0
21	**A PMW with osteoporosis with ≥ 1 VF not on BPs, raloxifene or SR** is prescribed calcitonin	154	0	0	0	0	0	0 (0.0)	0 (0.0)	0.0
Total		904	285	13	39	4	1228	73.6	71.2-76.2	

PMW: postmenopausal woman; **DEXA:** Dual Energy X-ray Absorptiometry; **VF:** vertebral fracture; **BP:** bisphosphonate; **SR:** Strontium Ranelate

The sample of this GP-Practice consists of data from 154 patients with either a diagnosis for osteopenia or osteoporosis. The overall adherence of practice A is 73.6 (CI 95%, 71.2-76.2) which is classified as high adherence according to the result categorisation established by the research group. Overall 10 criteria were categorised as high, 4 as intermediate and three as low adhering criteria. The remaining 4 criteria dealing with alternative treatment options to alendronate and risedronate were not applicable in this study sample and thus did not yield any result. Criterion 8 and 17 assessing vitamin D supplementation and treatment of patients on corticosteroids respectively scored highest in this patient sample presenting 100.0 % adherence. The adherence to criteria 4 and 7 assessing a patient's calcium supplementation and the corresponding dose was 93.9% (CI 95%, 89.2-98.6) and 99.1 (CI 95%, 97.2-100.0) respectively. Criteria classified as low adhering, namely criterion 6, 9 and 18 only yield 0.0%, 17.8% (CI 95%, 6.6-28.9) and 33.3% (CI 95%, 0.0-86.7) adherence. Criterion 6 and 9 evaluate if patients not on osteoporosis treatment have a contraindication to each agent and if they are prescribed supplementary calcium and vitamin D. The low adherence in these criteria can be attributed to the lack of documentation of these data at the GP. The third criterion in the low adherence category measures weather postmenopausal women are prescribed strontium ranelate as alternative treatment option.

Highest applicability was measured in criterion 3 and 10 assessing calcium supplementation and first-line treatment options in osteoporotic patients presenting an applicability of 90.3 %. Second highest applicability was obtained in criteria 1 with 85.1%, assessing if a patient's diagnosis of osteoporosis was confirmed by a DEXA scan. This was followed by an applicability of 81.2 % for patients with a Vitamin D deficiency or an age ≥ 65 years in criterion 5. In addition to criteria 16, 19, 20 and 21 presenting 0.0 % applicability criterion 17 and 18 assessing patients on long-term glucocorticoid therapy and postmenopausal women with osteoporosis not on bisphosphonates showed low applicability with 0.6 % and 1.9 % respectively.

Table 5. Practice A: Criteria ranked as high adhering

Ranking	Level of adherence	Criterion	Applicability	Adherence (%)
1	High	**A patient prescribed vitamin D** is prescribed a daily dose of 10 – 20 μg (400 - 800 IU) vitamin D	89/154	100.0
2		**A patient who is on long-term glucocorticoid therapy** is prescribed a bisphosphonate	1/154	100.0
3		**A patient prescribed supplementary calcium is** prescribed a daily dose of 500 – 1500 mg calcium	99/154	99.1
4		**A patient receiving treatment for osteoporosis/ osteopenia** is prescribed a standard dose regimen	99/154	93.9
5		**A patient with a recorded diagnosis of osteopenia** **i**s prescribed supplementary calcium	15/154	93.3
6		**Measurement of BMD by DEXA scan** is performed at hip and spine	78/154	87.2
7		**A patient when started on bisphosphonate therapy** was initiated on alendronate	100/154	85.0
8		**A patient with a recorded diagnosis of osteopenia** is prescribed an oral BP as first-line therapy	15/154	80.0
9		**A patient with a recorded diagnosis of osteoporosis** is prescribed an oral BP as first-line therapy	139/154	78.4
10		**A patient with a recorded diagnosis of osteoporosis** is prescribed supplementary calcium	139/154	71.2

Table 6. Practice A: Criteria presenting intermediate adherence

Ranking	Level of adherence	Criterion	Applicability	Adherence (%)
11	Intermediate	**A patient with confirmed vitamin D deficiency or aged > 65** is prescribed vitamin D	125/154	67.2
12		**A patient who is prescribed a bisphosphonate** has no reason on record to avoid bisphosphonates	86/154	65.1
13		**Patient with a diagnosis of osteoporosis** has a recorded DEXA scan	131/154	55.7
14		**A PMW not treated with alendronate** is prescribed risedronate	13/155	53.8

Table 7. Practice A: Criteria presenting low adherence

Ranking	Level of adherence	Criterion	Applicability	Adherence (%)
15		**A PMW with osteoporosis not on bisphosphonate** **i**s prescribed strontium ranelate	3/15	33.3
16	Low	**A patient not on osteoporosis treatment** is prescribed ≥1000mg calcium plus 800 IU vitamin D	45/154	17.8
17		**A patient not on osteoporosis treatment** has a contraindication for each agent	45/154	0

4.3.2. Data Analysis: Practice B (Paisley)

D**ata analysis:**

The number of patients available for practice B from the original Study conducted by J. Schlais is significantly lower than for Practice B. Again, Applicability, Adherence and the corresponding confidence intervals were calculated using the algorithm that was used in prior studies. Table 8. shows the calculated output variables for all of the 21 criteria assessed for practice B.

Table 8. Data Analysis: Practice B

No	Criterion	NA	YES	NO(U)	NO(J)	IDS	IDQ	APPL	Adherence (%)	CI 95%
1	**Patient with a diagnosis of osteoporosis** has a recorded DEXA scan	0	1	57	0	5	0	63 (100.0)	1 (1.6)	0.0-4.7
2	**Measurement of BMD by DEXA scan,** is performed at hip and spine	55	0	8	0	0	0	8 (12.7)	0 (0.0)	0.0
3	**A patient with a recorded diagnosis of osteoporosis** is prescribed supplementary calcium	0	54	9	0	0	0	63 (100.0)	54 (85.7)	77.1-94.4
4	**A patient with a recorded diagnosis of osteopenia** is prescribed supplementary calcium	63	0	0	0	0	0	0 (0.0)	0 (0.0)	0.0
5	**A patient with confirmed vitamin D deficiency or aged ≥ 65** is prescribed vitamin D	15	39	9	0	0	0	48 (76.2)	39 (81.3)	70.2-92.3
6	**A patient not on osteoporosis treatment** has a contraindication for each agent	46	0	17	0	0	0	17 (27.0)	0 (0.0)	100.0
7	**A patient prescribed supplementary calcium** is prescribed a daily dose of 500 – 1500 mg calcium	10	53	0	0	0	0	53 (84.1)	100 (100.0)	100.0
8	**A patient prescribed vitamin D** is prescribed a daily dose of 10 – 20 µg (400 - 800 IU) vitamin D	14	49	0	0	0	0	49 (77.8)	49 (100.0)	100.0
9	**A patient not on osteoporosis treatment** is prescribed ≥1000mg calcium plus 800 IU vitamin D	46	9	8	0	0	0	17 (27.0)	9 (52.9)	29.2-76.7

10	**A patient with a recorded diagnosis of osteoporosis** is prescribed an oral bisphosphonate as first-line therapy	0	47	16	0	0	0	63 (100.0)	47 (74.6)	63.9-85.4
11	**A patient with a recorded diagnosis of osteopenia** is prescribed an oral bisphosphonate as first-line therapy	63	0	0	0	0	0	0 (0.0)	0 (0.0)	0.0
12	**A patient who is prescribed a bisphosphonate** has no reason *on record* to avoid bisphosphonates	17	23	3	0	20	0	46 (73.0)	23 (50.0)	35.6-64.4
13	**A patient receiving treatment for osteoporosis/ osteopenia** is prescribed a standard dose regimen	17	38	5	0	3	0	46 (73.0)	38 (82.6)	71.7-93.6
14	**A patient when started on bisphosphonate therapy** was initiated on alendronate	44	17	2	0	0	0	19 (30.2)	31 (91.2)	75.7-100.0
15	**A PMW not treated with alendronate** is prescribed risedronate	50	7	6	0	0	0	13 (20.6)	7 (53.8)	26.7-80.9
16	**A PMW with ≥ 2 VFs not on alendronate or risedronate** is prescribed intermittent cyclical etidronate	63	0	0	0	0	0	0 (0.0)	0 (0.0)	0.0
17	**A patient who is on long-term glucocorticoid therapy** is prescribed a bisphosphonate	63	0	0	0	0	0	0 (0.0)	0 (0.0)	0.0
18	**A PMW with osteoporosis not on bisphosphonate** is prescribed strontium ranelate	63	0	0	0	0	0	0 (0.0)	0 (0.0)	0.0
19	**A PMW with osteoporosis with ≥ 1 fracture not on BPs** is prescribed strontium ranelate or raloxifene	63	0	0	0	0	0	0 (0.0)	0 (0.0)	0.0
20	**A PMW with osteoporosis with ≥ 1 fracture not on BPs and SR** is prescribed teriparatide	63	0	0	0	0	0	0 (0.0)	0 (0.0)	0.0
21	**A PMW with osteoporosis with ≥ 1 VF not on BPs, raloxifene or SR** is prescribed calcitonin	63	0	0	0	0	0	0 (0.0)	0 (0.0)	0.0
Overall	818	337 (66.7)	0	28 (5.5)			505	66.7	64.7	58.1-71.3

PMW: postmenopausal woman; **DEXA:** Dual Energy X-ray Absorptiometry; **VF:** vertebral fracture; **BP:** bisphosphonate; **SR:** Strontium Ranelate

In contrast to Practice A the first criterion showed very low adherence of only 1.6 %. It was mentioned by J. Schlais in the previous study that this circumstance is due to insufficient recording of patient data in Practice B and does therefore not reflect the accurate guideline adherence. For eight out of 63 patients a DEXA scan result existed but only one patient had a confirming diagnostic result. This resulted in 0.0 % adherence again due to insufficient documentation. Seven criteria were categorised as high adhering, three criteria showed intermediate adherence and another three criteria were ranked as low adhering. The eight remaining criteria were not applicable in this patient sample and therefore did not yield any results. That was the case in all criteria assessing alternative treatment options to BPs with raloxifene, teriparatide, strontium ranelate or calcitonin. Also criterion 17 dealing with patients receiving GC therapy was not applicable in this patient group. It is not clear whether this is due to the lack of recording or if no GC therapy was present in the sample. No patients with a diagnose of osteopenia were present in this patient sample. Thus criterion 4 and 11 that were created for assessing osteopenic patients were not applicable either. Criteria 7 and 8 assessing the dosage of calcium and vitamin D presented the highest adherence in this patient sample. Also criterion 14 which assesses if a patient when started on BP therapy was initiated on alendronate showed high adherence with 89.5 %. In addition criteria 3, 13, 5 and 10 that are assessing calcium supplementation, the adherence to the standard dose regimen, vitamin D supplementation and BPs as first line treatment option showed a high level of adherence.

Highest applicability was found in criteria which only have patients with a diagnosis of osteoporosis as qualifying statement. Also, criteria assessing calcium and vitamin D supplementation and the adherence to guideline recommendations involving BP therapy showed high applicability in this patient group. Due to strict inclusion criteria of alternative treatment options, none of the corresponding criteria were applicable in this data set. The ranking of criteria by the level of adherence is displayed in the tables 10, 11 and 12 displayed below.

Table 9. Practice B: Criteria presenting high adherence

Ranking	Level of adherence	Criterion	Applicability	Adherence (%)
1	High	**A patient prescribed supplementary calcium** is prescribed a daily dose of 500 – 1500 mg calcium	53/63	100
2		**A patient prescribed vitamin D** is prescribed a daily dose of 10 – 20 µg (400 - 800 IU) vitamin D	49/63	100
3		**A patient when started on bisphosphonate therapy** was initiated on alendronate	19/63	89.5
4		**A patient with a recorded diagnosis of osteoporosis** is prescribed supplementary calcium	63/63	85.7
5		**A patient receiving treatment for osteoporosis/ osteopenia** is prescribed a standard dose regimen	46/63	82.6
6		**A patient with confirmed vitamin D deficiency or aged > 65** is prescribed vitamin D	48/63	81.3
7		**A patient with a recorded diagnosis of osteoporosis** is prescribed an oral bisphosphonate as first-line therapy	63/63	74.6

Table 10. Practice B: Criteria presenting high adherence

Ranking	Level of adherence	Criterion	Applicability	Adherence (%)
8	Intermediate	**A PMW not treated with alendronate** is prescribed risedronate	13/63	53.8
9		**A patient not on osteoporosis treatment** is prescribed ≥1000mg calcium plus 800 IU vitamin D	17/63	52.9
10		**A patient who is prescribed a bisphosphonate** has no reason on record to avoid bisphosphonates	46/63	50.0

Table 11. Practice B: Criteria presenting low adherence

Ranking	Level of adherence	Criterion	Applicability	Adherence (%)
11		**Patient with a diagnosis of osteoporosis** has a recorded DEXA scan to confirm osteoporosis	63/63	1.6
12	Low	**Measurement of BMD by DEXA scan,** is performed at hip and spine	8/63	0
13		**A patient not on osteoporosis treatment** has a contraindication for each agent	17/63	0

4.3.3. Data Analysis Results: Overall

The study population of practice A and B combined consisted of 217 patients. The overall adherence was 71.6 % which is categorised as high adhering. The overall applicability was 47.0 %. All criteria that were applicable in practice B were applicable in practice A. Only for four criteria no results were calculated because the corresponding guideline recommendations could not be applied to the patient sample. Table 12 shows the absolute and relative applicability and the percentage of adherence of the whole study sample for each criterion.

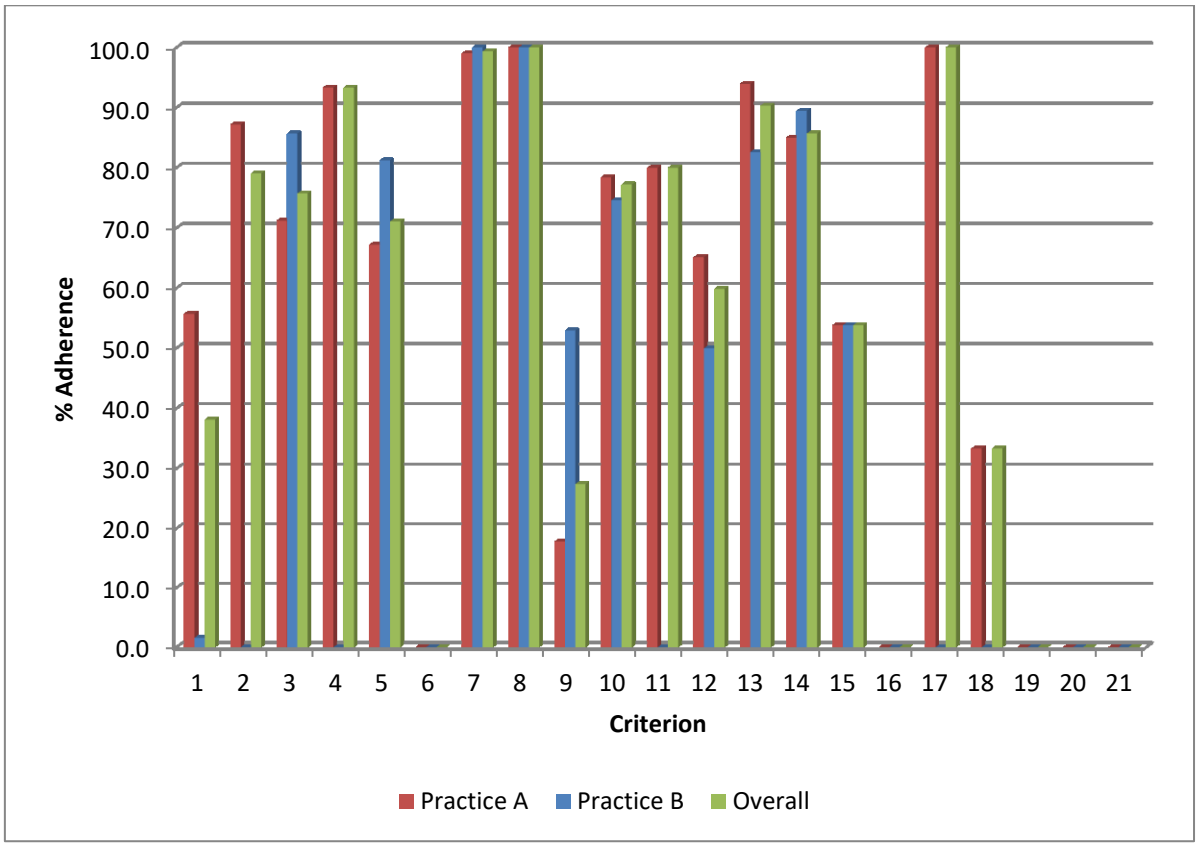
Table 12. Data analysis: Practice A & B combined

No	Criterion	NA	Yes	No(U)	No(J)	IDS	IDQ	APPL %	APPL	Adherence (%)	CI
1	**Patient with a diagnosis of osteoporosis** has a recorded DEXA scan	23	74	105	8	15	0	89.4	194	38.1	31.3-45.0
2	**Measurement of BMD by DEXA scan,** is performed at hip and spine	131	68	18	0	0	0	39.6	86	79.1	70.5-87.7
3	**A patient with a recorded diagnosis of osteoporosis** is prescribed supplementary calcium	15	153	49	0	0	0	93.1	202	75.7	69.8-81.7
4	**A patient with a recorded diagnosis of osteopenia** is prescribed supplementary calcium	202	14	1	0	0	0	6.9	15	93.3	80.7-106.0
5	**A patient with confirmed vitamin D deficiency or aged ≥ 65** is prescribed vitamin D	44	123	50	0	0	0	79.7	173	71.1	64.3-77.9
6	**A patient not on osteoporosis treatment** has a contraindication for each agent	156	0	61	0	0	0	28.1	61	0.0	0.0
7	**A patient prescribed supplementary calcium** is prescribed a daily dose of 500 – 1500 mg calcium	58	158	0	0	1	0	73.3	159	99.4	98.1-100.6
8	**A patient prescribed vitamin D** is prescribed a daily dose of 10 – 20 µg (400 - 800 IU) vitamin D	79	138	0	0	0	0	63.6	138	100.0	100.0
9	**A patient not on osteoporosis treatment** is prescribed ≥1000mg calcium plus 800 IU vitamin D	155	17	44	0	1	0	28.6	62	27.4	16.3-38.5

10	**A patient with a recorded diagnosis of osteoporosis** is prescribed an oral bisphosphonate as first-line therapy	15	156	46	0	0	0	93.1	202	77.2	71.4-83.0
11	**A patient with a recorded diagnosis of osteopenia** is prescribed an oral bisphosphonate as first-line therapy	202	12	3	0	0	0	6.9	15	80.0	59.8-100.2
12	**A patient who is prescribed a bisphosphonate** has no reason on record to avoid bisphosphonates	85	79	6	0	47	0	60.8	132	59.8	51.5-68.2
13	**A patient receiving treatment for osteoporosis/ osteopenia** is prescribed a standard dose regimen	72	131	11	3	3	0	66.8	145	90.3	85.5-95.2
14	**A patient when started on bisphosphonate therapy** was initiated on alendronate	98	102	17	0	0	0	54.8	119	85.7	79.4-92.0
15	**A PMW not treated with alendronate** is prescribed risedronate	191	14	12	1	0	0	12.0	26	53.8	34.7-73.0
16	**A PMW with ≥ 2 VFs not on alendronate or risedronate** is prescribed intermittent cyclical etidronate	217	0	0	0	0	0	0	0	0.0	0,0
17	**A patient who is on long-term glucocorticoid therapy** is prescribed a bisphosphonate	216	1	0	1	0	0	0.5	1	100.0	100.0
18	**A PMW with osteoporosis not on bisphosphonate** is prescribed strontium ranelate	214	1	2	0	0	0	1.4	3	33.3	
19	**A PMW with osteoporosis with ≥ 1 fracture not on BPs** is prescribed strontium ranelate or raloxifene	217	0	0	0	0	4	0.0	0	0.0	
20	**A PMW with osteoporosis with ≥ 1 fracture not on BPs and SR** is prescribed teriparatide	217	0	0	0	0	0	0.0	0	0.0	
21	**A PMW with osteoporosis with ≥ 1 VF not on BPs, raloxifene or SR** is prescribed calcitonin	217	0	0	0	0	0	0.0	0	0.0	
Total			1241	425	13	67	4	47.0	1733	71.6	71.2-76.2

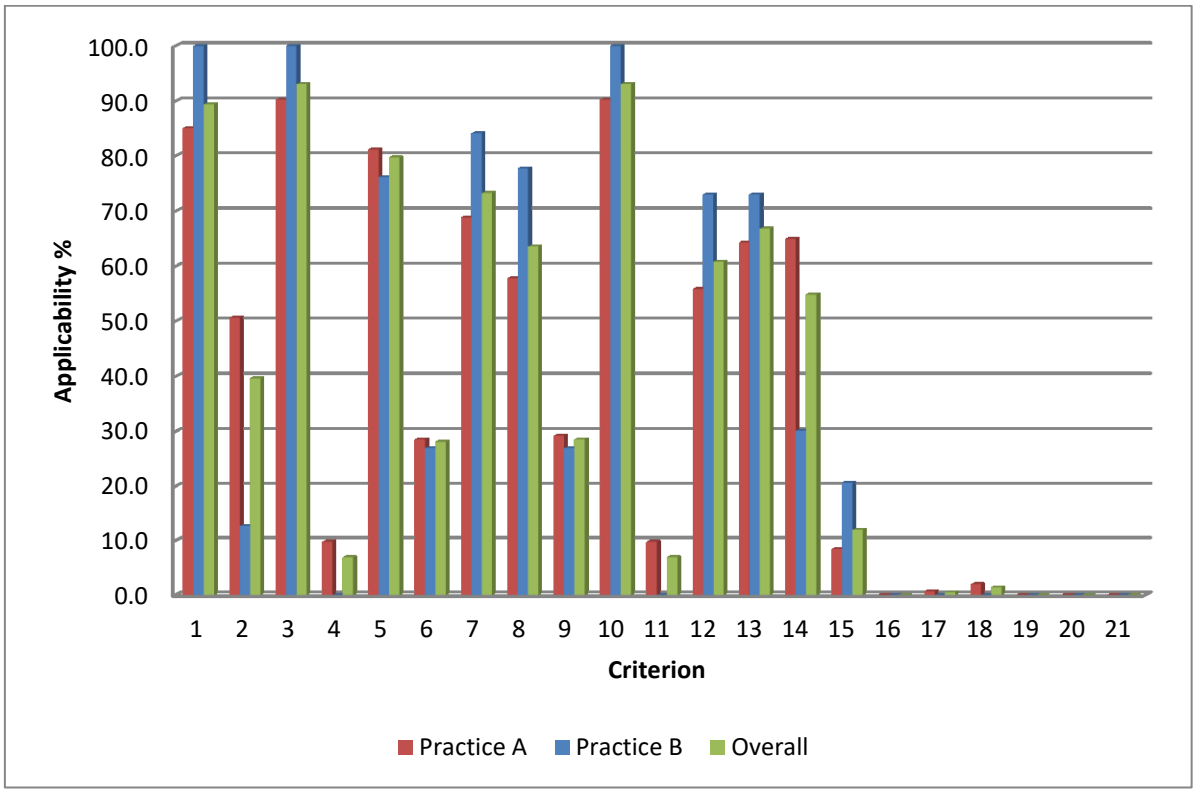
The graphs displayed below illustrate the adherence and applicability in practice A and B and the overall adherence and applicability. The most remarkable discrepancies can be found in the criteria 1 and 2 that assess a diagnosis of osteoporosis by DEXA scan.

Graph 5.1 – Adherence Practice A, B and overall



The graph below displays the applicability for practice A, B and combined in percent. The graph highlights that the majority of criteria, which were applicable in the prevailing study population. Only the criteria 16, 19, 20 and 21 which assess alternative treatment options to the first line therapy with etidronate, teriparatide, raloxifene or calcitonin could not be applied to the combined patient sample.

Graph 5.2 - Applicability: Practice A, B and overall



4.4. Pharmaceutical Care Model Design

4.4.1. Overview

A pharmaceutical care model to apply pharmaceutical care to patients with a diagnosis of osteopenia or osteoporosis and to patients with an increased risk of developing either one of the conditions was created. Thirteen stages that hyphenate two principal pharmaceutical care measures, in specific a screening phase and a diagnosis and treatment phase were developed. The stages are interlinked and verification steps to assure best application of pharmaceutical care to this subgroup of patients. During the development process it was decided by the study group to base the screening on the FRAX® risk calculator created by the WHO, based on a comprehensive review on the available risk assessment tools. The revised version of MAT_{osteo} again was integrated into the diagnosis and treatment strand of the model, to assure that best practice based on guideline recommendations is applied to the individual patient. The hereby developed model was divided into three sections from the operator's point of view:

1. the scheme of the model
2. a table which links each stage to its purpose and the practical application and
3. a questionnaire to acquire all necessary patient data.

Both table 14 and the questionnaire are linked to the corresponding stages of the model by number. The scheme of the model and the annexed table describing the screening stages and their purpose including practical application are listed below. The questionnaire to collect data in a community pharmacy setting can be found in the Appendix of this thesis.

4.4.2. Scheme of the Pharmaceutical Care Model

Figure 3. Flow diagram of the pharmaceutical care model

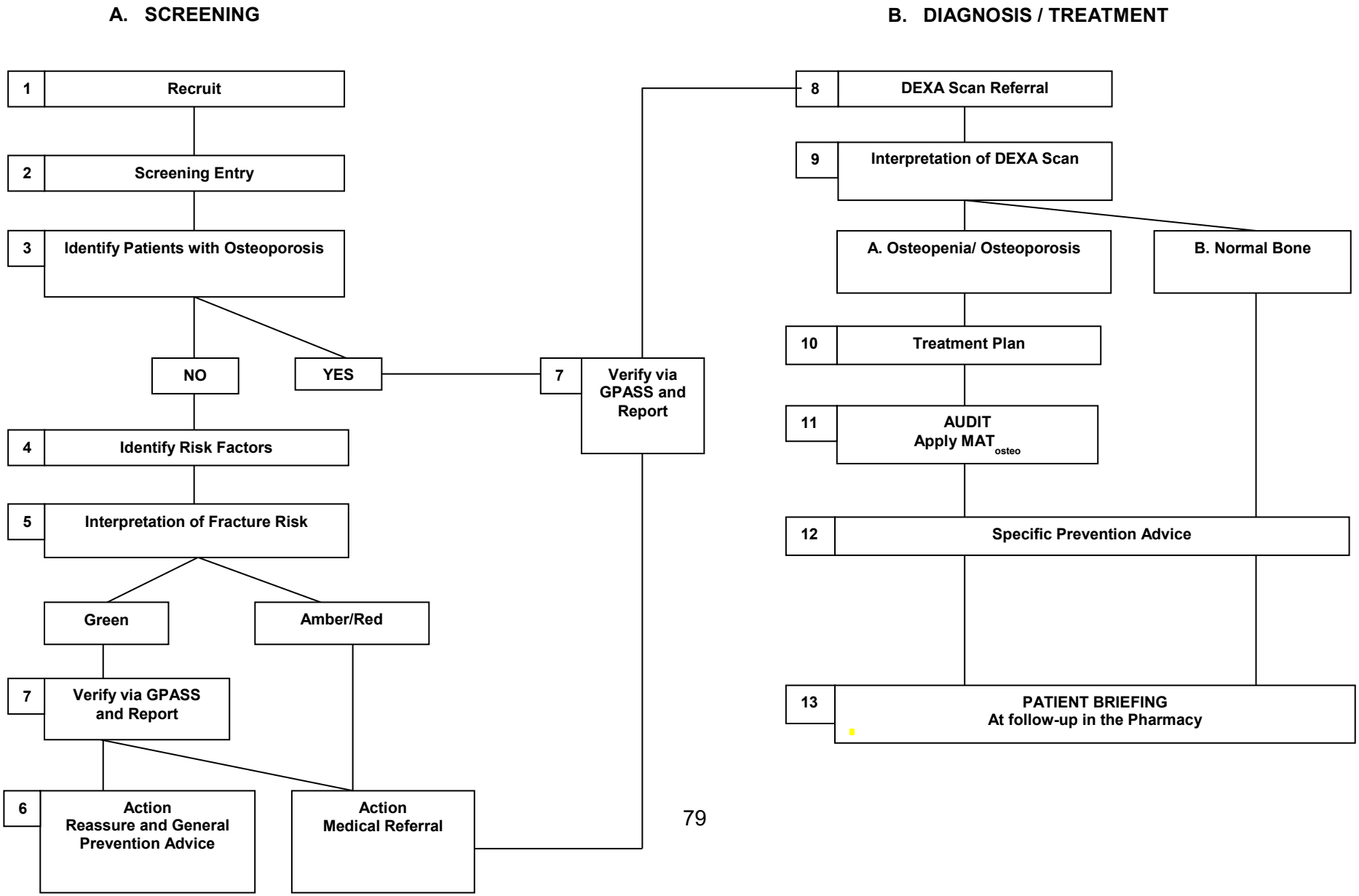


Table 13. Pharmaceutical care tool: Screening stages

Stage		Purpose	Practical Application
1	**Recruit**	Recruitment of CP customers into opportunistic screening using FRAX® questions.	Customers (men>50 yrs. and PMW) presenting a prescription for chronic medication are invited to the screening process. **(Questionnaire OS)**
2	**Screening Entry**	Document that patient has been recruited Pharmacy Medication Record (PMR).	Document screening entry in patients' PMR.
3	**Identify Patients with Osteoporosis and other relevant co-morbidity**	Exclude osteoporotic patients from 'primary' prevention.	Administer **Pharmacist/Assistant** Questions while inviting patients to take part and ask question **OS.1 to OS.4**. Record patients that have a known diagnosis of Osteoporosis for evaluation using GPASS data as described in step 7.
4	**Identify Risk Factors**	To apply FRAX®	Patient self-completion of written questionnaire (**OS5 – OS11**). Pharmacist completes questionnaire by accessing patient data from PMR at the pharmacy (**Apply OS 12**).
5	**Interpretation of Risk**	To calculate 10 year fracture probability in order to inform the patient on a future visit.	Take a set of questionnaire responses and obtain computed fracture risk from FRAX® website (www.shef.ac.uk/FRAX) and identify action required.
6	**Action**	Confirm the response to screening.	Refer patients with fracture probability in amber and red zone to GP (BMD measurement). Reassure patients with verified probability in green zone.
7	**Verify via GPASS and Report**	Refer and follow up patients with the GP.	1. Verify patients with reported diagnosis from stage 3 as candidates for MAT_{osteo} assessment. 2. Verify patients with reported diagnosis of RA, T1DM **(OS2 &OS3)**. 3. Refer patients at risk and follow up using $MAT_{osteo.}$ 4. Verify **(apply OS13 & 14)** patients with fracture probabilities below the assessment threshold (green zone) by accessing GPASS®; refer those that now exceed the assessment threshold (amber/red zone) to GP for DEXA scan.

Table 14. Pharmaceutical care tool: Diagnosis and treatment stages

Stage		Purpose	Practical Application
8	**DEXA Scan Referral**	Measure bone mineral density.	Measure BMD at least at two specific sites.
9	**Interpretation of DEXA scan**	Identify osteopenic/ osteoporotic patients by using WHO T-Score thresholds.	Consider patients presenting a T-Score > -1.5 SD to have normal bone, patients presenting a T-Score between -1.5 and -2.5 SD to have osteopenia, and patients presenting a T-Score < -2.5 SD to have osteoporosis.
10	**Treatment Plan**	Make treatment decisions to deliver appropriate medication according to a patient's individual need.	Make treatment decisions according to guideline recommendations for primary and secondary prevention of the condition.
11	**AUDIT Apply MAT_{osteo}**	Measure adherence to national and international guideline recommendations.	Apply patient data to MAT_{osteo} and calculate individual and overall applicability and adherence for each criterion. Use audit findings to identify care issues for follow up with GP.
12	**Specific Prevention Advice/ Reassurance**	To give specific advice to osteopenic/osteoporotic patients on prevention of further bone loss	Advice is given on following topics: • regular low impact weight bearing exercise • high intensity strength training • smoking cessation • reduction of alcohol consumption to < 10 units/week • calcium rich diet with an aimed intake of >1000 mg/day
13	**Patient Briefing At follow up in the pharmacy**	Inform patient about treatment decisions and ensure their understanding of prevention advice. Reassure healthy individuals	Check patients' understanding of prevention advice • Inform patient of any treatment changes agreed with doctors after applying the MAT • Check Patients' understanding of treatment administration instructions • Identify independent CRFs e.g. falls • Reassure patients presenting normal BMD

QUESTIONNAIRE

A) Pharmacist Questions

For Pharmacist Administration

OS1. Patient is

☐ male ☐ female

Thank you, this questionnaire is short and is to help us include information in our records that might help us to identify people who are at greater risk of bone fractures.
First, have you had a hospital bone scan?

☐ yes ☐ no

If answered yes, did the finding show

normal ☐ or 'brittle bones' (osteoporosis) ☐

(If answered 'normal' , we don't need to proceed with questionnaire)

Patient name……

Patient address……..

Name, address of GP (verify with patient)……..
.....

Patients asked to check if they have
OS2. A diagnosis of osteoporosis ('brittle bones'), beware any confusion with genetic condition osteogenesis imperfecta or osteoarthritis for which you would record 'No')?

☐ yes ☐ no

OS3. Rheumatoid arthritis (establish patient differentiates RA and osteoarthritis)?

☐ yes ☐ no

OS4. Diabetes type 1 (usually insulin dependent)?

☐ yes ☐ no

Pharmacist hands questionnaire to patient with request to complete it.

B) Patient Questions
For Patient Self Completion

OS5. What age are you? ____ years

OS6. How much do you weigh? ____ pounds

OS7. How tall are you? ____ feet ____ inches

OS8. As an adult, have you ever had a fracture of one of these types? (Please check the corresponding boxes.)

- ☐ a bone fracture after only a mild fall?
- ☐ small fractures in your back that doctors have told you are present?

OS9. Has your mother or your father ever suffered from a hip fracture?

☐ yes ☐ no

OS10. Do you smoke?

☐ yes ☐ no

If you chose yes, how many cigarettes do you smoke? ____ cigarettes/day

OS11. Do you take 3 or more units of alcohol daily? A unit equals a standard glass of beer (half pint), a single measure of spirits (30ml), a small glass of wine (120ml), or 1 measure of an aperitif (60ml)

☐ yes ☐ no

Thank You for Your Help. Please hand this to the pharmacist or assistant.

C) Patient Data Access

PHARMACY PATIENT MEDICATION RECORD

OS12. Exposure to oral Glucocorticoids > 3 months?

Drug Name	Dose	Brand
☐ Betamethasone	≥ 750 mcg	Betnelan®, Betnesol®, Betamethasone®
☐ Dexamethasone	≥ 750 mcg	Dexamethasone®, Dexsol®
☐ Methylprednisolone	≥ 4 mg	Medrone®, Methylprednisolone®
☐ Prednisolone	≥ 5 mg	Prednisolone®, Deltacortil®
☐ Deflazacort	≥ 6 mg	Deflazacort®, Calcort®
☐ Hydrocortisone	≥ 20 mg	Hydrocortisone®, Hydrocortone®
☐ Cortisone acetate	≥ 25 mg	Cortisone®

GPASS® OR OTHER PATIENT DATA STORAGE SYSTEM

OS13. Has the patient a recorded diagnosis of

Rheumatoid Arthritis?

☐ yes ☐ no

Osteoporosis?

☐ yes ☐ no

If rheumatoid arthritis is chosen yes, OS 14 does not have to be applied

OS14. Secondary Osteoporosis?

- ☐ Diabetes mellitus type I
- ☐ Hypogonadism or premature menopause (< 45 yrs.)
- ☐ Chronic malnutrition or malabsorption
- ☐ Chronic liver disease
- ☐ Osteogenesis Imperfecta
- ☐ Untreated longstanding hyperthyroidism

10 Year fracture Probability (Major osteoporotic)
Score:

4.5. Validation of the Pharmaceutical Care Model

The pharmaceutical care model was validated by seven health care experts in the field of osteoporosis during six interviews. The interviews were scheduled to take approximately 40 minutes, consisting of a general period of 20 minutes during which the pharmacists get familiar with the pharmaceutical care model and two specific periods lasting 10 minutes each to express their views considering the utility of the model and obstacles for the implementation. Table 16. below lists each of the stages pharmaceutical care model, its purpose and correspondingly specific evaluation of the seven experts. Table 15. lists all the components of the adjacent questionnaire and again the expert's view on each item. In general all pharmacists interviewed agreed that the model will be of great benefit for both osteoporotic patients and for those at risk of developing the disease. In addition there was general agreement that the model is suitable for the application in a CP-GP collaboration. The major obstacle that was identified by all osteoporosis experts was the time the processing of all eligible patients will take and that without reimbursement the likelihood that CPs will collaborate is rather low.

Table 15. Expert opinions (Diagnosis and treatment stages)

Stage		Purpose	Expert Opinion
1	**Recruit**	Recruitment of CP customers into opportunistic screening using FRAX® questions.	E2: also housebound patients could profit from application of the model. E3 & E7: the inclusion criteria of the model yield a great number of patients eligible for risk assessment, which will result in a great amount of work for who is conducting the study. E7 therefore suggests limiting the number of patient for the proof of concept study.
2	**Screening Entry**	Document that patient has been recruited Pharmacy Medication Record (PMR).	E1, E2 & E6: PMR alone is not a reliable variable to link a patient to a GP. The name and address of the GP should be recorded in addition. This suggestion was implemented in the questionnaire in consultation with the study group. E6: it is also more time consuming to use the PMR number compared to the Name.
3	**Identify Patients with Osteoporosis and other relevant co-morbidity**	Exclude osteoporotic patients from 'primary' prevention.	
4	**Identify Risk Factors**	To apply FRAX®	
5	**Interpretation of Risk**	To calculate 10 year fracture probability in order to inform the patient on a future visit.	
6	**Action**	Confirm the response to screening.	
7	**Verify via GPASS and Report**	Refer and follow up patients with the GP.	E1: not all osteoporotic patients have a record of a DEXA scan especially "when the diagnosis is older than 10 years." Therefore C suggests taking osteoporosis medication into account when accessing GPASS data. For the application of MAT_{osteo} this measure has been agreed on by the study group and can easily be implemented during the use of the PC model. E5: it might not be a problem if a student accesses the patient data with a "load" of questionnaires, but it could be difficult for a pharmacist to access the GPASS system more frequently with only a few questionnaires, depending on the relationship with the GP.

Stage		Purpose	Expert Opinion
8	**DEXA Scan Referral**	Measure bone mineral density.	**E1:** The wording of step 8 “DEXA scan referral” in the PC-model could be misleading. Step three filters out patients with a diagnosis of osteoporosis and directly links them to section B “diagnosis and treatment” after their diagnosis of osteoporosis is verified via GPASS data, which implies that osteoporotic patients are assessed by a DEXA scan. To circumvent this inconsistency a dotted line that leads directly to the audit step with MAT_{osteo} was added.
9	**Interpretation of DEXA scan**	Identify osteopenic/ osteoporotic patients by using WHO T-Score thresholds.	
10	**Treatment Plan**	Make treatment decisions to deliver appropriate medication according to a patient’s individual need.	
11	**AUDIT Apply MAT_{osteo}**	Measure adherence to national and international guideline recommendations.	
12	**Specific Prevention Advice/ Reassurance**	To give specific advice to osteopenic/osteoporotic patients on prevention of further bone loss	**E3:** The PMR could be utilised to remind a pharmacist of giving specific prevention advice when picking up medicine. E3: Not every pharmacist is trained or capable of applying the patient briefing for secondary prevention of osteoporosis. E3: At certain times of the day the pharmacist may not have the time to give advice to a patient.
13	**Patient Briefing At follow up in the pharmacy**	Inform patient about treatment decisions and ensure their understanding of prevention advice. Reassure healthy individuals	

Table 16. Expert opinions (Questionnaire)

A) Pharmacist Questions

OS	Question	Expert Opinion
1	Patient is ☐ male ☐ female	
2	"Brittle bones" (Do you have a diagnosis of osteoporosis, beware any confusion with genetic condition osteogenesis imperfecta or osteoarthritis for which you would record 'No')? ☐ yes ☐ no	E1 & E2 state that the term "osteoarthritis" is likely to be confused with osteoporosis. It was decided by the study group after the pilot interview to include this term in the question for the pharmacist to differentiate between the conditions.
3	Rheumatoid arthritis (establish patient differentiates RA and osteoarthritis)? ☐ yes ☐ no	E7: Patients might not know the name of their condition and answer incorrectly. Therefore validation with PMR and GPASS® data is mandatory.
4	Diabetes type 1 (usually insulin dependent)? ☐ yes ☐ no	E7: Patients might not know the name of their condition and answer incorrectly. Therefore validation with PMR and GPASS® data is mandatory.

B) Patient Questions

OS	Question	Expert Opinion
5	What age are you? ____ years	
6	How much do you weigh? ____ pounds	E3 & E4: Not all patients might know their weight. E3 states that there is no possibility of weighing patients at their pharmacy. E7 suggests providing scales to the CP during the study period. E7 also suggests changing the wording to stones and to provide a formula to the investigator to convert stones to pounds.

7	How tall are you? _____ feet _____ inches	**E3:** some patients might not know their actual height. **E7:** Again a measurement device should be provided for the study period.
8	As an adult, have you ever had a fracture of one of these types? (Please check the corresponding boxes.) ☐ a bone fracture after only a mild fall? ☐ small fractures in your back that doctors have told you are present?	**E1** states that the phrase "a bone fracture after only a mild fall for example after falling off a chair" could be misinterpreted. E1 and E2 confirm that the investigator's suggestion to change the wording to "a bone fracture after only a mild fall for example falling off a height equal to or less than a chair". In addition E2 suggests including all vertebral fractures in the second part of the question, because vertebral fractures are not always associated with pain.
9	**OS9.** Has your mother or your father ever suffered from a hip fracture? ☐ yes ☐ no	**E3:** not all patients are able to recall if a parental history of hip fracture is present in their family. Although chances are high that CP customers are aware of these incidents due to the great burden a hip fracture has on one's life, this lack of knowledge might lead to patients with increased fracture risk not being included in the scheme.
10	Do you smoke? ☐ yes ☐ no If you chose yes, how many cigarettes do you smoke? _____ cigarettes/day	**E3:** Both smoking and drinking habits are likely to be underestimated by the patient, "resulting in a lower number of patients eligible for assessment". It has to be examined if this information can be verified by accessing GPASS® data.
11	Do you take 3 or more units of alcohol daily? A unit equals a standard glass of beer (half pint), a single measure of spirits (30ml), a small glass of wine (120ml), or 1 measure of an aperitif (60ml)	See OS9.

☐ yes ☐ no

C) Patient Data Access

OS	Question	Expert Opinion
12	Exposure to oral Glucocorticoids > 3 months?	**E1** suggests to specify the dose for corticosteroids by using the term “a dose equal to or greater than” to avoid misinterpretation. This change was discussed in the study group and implemented in the final version of the model.

Drug Name	Dose	Brand
☐ Betamethasone	≥ 750 mcg	Betnelan®, Betnesol®, Betamethasone®
☐ Dexamethasone	≥ 750 mcg	Dexamethasone®, Dexsol®
☐ Methylprednisolone	≥ 4 mg	Medrone®, Methylprednisolone®
☐ Prednisolone	≥ 5 mg	Prednisolone®, Deltacortil®
☐ Deflazacort	≥ 6 mg	Deflazacort®, Calcort®
☐ Hydrocortisone	≥ 20 mg	Hydrocortisone®, Hydrocortone®
☐ Cortisone acetate	≥ 25 mg	Cortisone®

E3: depending on how long a pharmacy was been working with a computer system, the information can be obtained for a few years back. In order to get precise information about this data item E3 agrees that validation using GPASS data is necessary. E3 also points out that not all data available on GPASS® can be processed automatically (scanned documents) and notes that this factor could increase the time needed to process a patient’s risk assessment.

E4: F states that the PMR of some pharmacies only lists results from the last 6 months. Obtaining patient data older than 6 month is more time-consuming since the patient data would have to be searched for concerning entries.

E5: Corticosteroids can be accessed through the PMR but not all of the information might be available because customers pick up their medication at different pharmacies. Depending on the computer system, the PMR can be used to fully obtain the patient data needed. Patient data is available from back to a few

		years to only a few months, depending on the pharmacy.
13	**OS13.** Has the patient a recorded diagnosis of Rheumatoid Arthritis? ☐ yes ☐ no Osteoporosis? ☐ yes ☐ no If rheumatoid arthritis is chosen yes, OS 14 does not have to be applied	
14	**OS14.** Secondary Osteoporosis? ☐ Diabetes mellitus type I ☐ Hypogonadism or premature menopause (< 45 yrs) ☐ Chronic malnutrition or malabsorption ☐ Chronic liver disease ☐ Osteogenesis Imperfecta ☐ Untreated longstanding hyperthyroidism	**E4:** Patients might not know if they have chronic liver disease and this should therefore be included in the section of the questionnaire that is filled in by the pharmacist. **E4** also states that the prevalence of type 1 diabetes mellitus could be verified using the PMR.

5. Discussion

5.1. MAT_{osteo} and the implementation of Guideline Recommendations

The investigator detected a few inconsistencies regarding guideline recommendations. First different classification of patients and the corresponding treatment was found in the corresponding guidelines SIGN and NICE 2008. SIGN categorises in patients with and without fractures and in the fracture subgroup additional differentiation between fracture site and number is done. NICE 2008 also differentiates between patients with and without osteoporotic fractures but with no further classification of the site and the type of fracture. SIGN also states recommendations for the management of osteoporosis in men, whereas NICE applies for the use in postmenopausal women only. As it has become evident in the literature review, the need to integrate male risk factors is of great importance and none of the hereby reviewed guidelines takes sex-differences into account.

Additionally, inconsistencies regarding treatment options were found for the use of bisphosphonates and raloxifene. In SIGN 71 the use of both alendronate and risedronate are recommended to be used first in all cases except for the use in men whereas in NICE TA160 & TA161 alendronate is to be preferred over risedronate and etidronate. The decision which of the latter to use, is based on clinical judgement in NICE 2008. Whereas SIGN recommends the use of etidronate in a specific scenario, namely in postmenopausal women with multiple vertebral fractures only. Despite the lack of actuality of SIGN compared to NICE the recommendations of the Scottish guideline are more suitable for the use in the actual version of MAT_{osteo} crated in this study, as they are based on clinical outcomes of the evidence base rather than on cost utility models.

The percentage of insufficient data for a specific criterion in the MAT does not always indicate insufficient patient data records. It additionally shows insufficient adaption of all versions of the MAT_{osteo} to the data that is available. One of the reasons for this circumstance is that certain details of published guideline recommendations e.g. T-score thresholds may be taken into consideration for treatment decisions, but are not put on record once the decision is made. Therefore, when considering the use of MAT_{osteo} as a modular component of the pharmaceutical care tool, the participating health experts should be trained to acquire the specific patient data in advance to make full use of the model. Again, the model was not created to identify GPs with low adherence to guideline recommendations, but to employ a model of pharmaceutical care that is aimed to deliver best health care practice to patients at risk of osteoporosis.

The original algorithm of MAT_{osteo} computes IDS equal to No(U), which again negatively influences the adherence of a patient and the overall adherence in a GP. This formula does not differentiate between these two cases and the adherence does therefore not indicate whether the decreased percentage is due to low compliance with guideline recommendations or insufficient documentation. To decrease this effect in the revised version of MAT_{osteo} two criteria that are likely to produce low adherence due to documentation difficulties were excluded. This was done for criterion 12 that assessed if specific non-pharmacological prevention advice was communicated to the patient and for criterion 17 which determines if a patient was given special instructions for the application of bisphosphonates from the original MAT_{osteo} created by E. Past. To assure that these essential recommendations are still communicated to the patient, it was decided in the research group to implement these two criteria in the pharmaceutical care model (stages 12 and 13). Another way of circumventing the decrease in adherence by insufficient documentation would be to change the algorithm of MAT_{osteo} and exclude the IDS variable from the formula and calculate IDS separately. This would again increase the value of the tool, as it could indicate where the quality of documentation should be increased at the GP. The original purpose of any MAT created so far, was to measure guideline adherence. With this major adjustment, the MAT would gain relevance in applied pharmaceutical care, but these changes would also imply the change of the use of the tool as a prospective measure. It is vital to update the criteria on a regular basis when new guideline recommendations become available. For example in the current version of MAT_{osteo}, calcitonin is still treatment option, but current guidelines do not support the use of this agent for the treatment of osteoporosis any more.

5.2. Microsoft Access and Database Protocol Implementation

The database protocol enables pharmacists to follow strict rules to analyse patient data according to the rules given in the MAT_{osteo}. Once the protocol is implemented in Microsoft Access® and a database is created, it can be reused for any compatible patient data available. Given that the new patient data has the same format and same alignment of information and the tables have the exact same name, each query will yield the desired information. It was shown though in this study that the patient data differed in the two practices analysed. Therefore, some of the queries created for the first practice had to be adapted in order to be applicable for the second practice as well. To increase the usability of such a tool, it would be a great step forward to consult experts on database design and bioinformatics in the research group in order to increase data consistency and to speed up

the process of data analysis when further developing the hereby modified MAT_{osteo}. The latter one would allow experts in the field of osteoporosis (pharmacists, GPs, clinicians and nursing staff) to instantly assess a patient's guideline adherence and perform adaptions in medical treatment of osteoporosis and osteopenia and give advice on lifestyle and behavioural changes as preventive measures.

5.3. Design and Application of the Pharmaceutical Care Model

The investigator concludes that the model presented above can be a complementary source for primary and secondary prevention of osteoporosis to the schemes already established in the Greater Glasgow area. The inclusion criteria used in the scheme address additional patient groups. Especially the use of certain medical history and certain medication, which is strongly linked with to the development or exacerbation of osteoporosis is likely to be implemented in a CP-GP collaboration setting. Once a patient participates in the scheme and is confirmed to be osteoporotic or osteopenic, his or her diagnosis and pharmacological treatment will be assessed by MAT_{osteo}. As it has been shown in previously published work, MAT_{osteo} is a valuable and valid resource to assess guideline adherence of selected GP practices as well as applying the tool to a single patient's data. In the model the latter purpose could be used by the investigating pharmacist to assure that each patient is diagnosed and treated according to the latest guideline recommendations and propose changes if necessary. This benefit could increase the value of a cooperation between GPs and clinical and community pharmacists.

The review of available fracture risk assessment tools (see introduction section 1.1.7) showed that the FRAX® algorithm is most suitable to be integrated into the PC model since it is the most comprehensive tool and the assessed risk factors are most likely to be applied in a Scottish CP-PC collaboration setting. After the design of the model, an application for mobile devices like tablets and smartphones became available. The data collection for CRFs at the community pharmacy is currently done by filling out a questionnaire on paper. The integration and application of the use of such technological advances could simplify the collection of patient data at the pharmacy and facilitate the use of the PC model. It is to be evaluated in further research, if the integration of this mobile app can be implemented. Due to inconsistencies of availability of patient data at the various pharmacies further investigation is necessary to identify a common data set that is available at all pharmacies.

During the validation process of the model, the question occurred whether every pharmacy is capable of measuring a patient's height and weight to calculate the BMI. To overcome this obstacle, the pharmacy involved should be provided with a scale and a device to measure a person's height as this would not be a financial burden for the pharmacies involved in the scheme.

During the validation process of the PC-model, it became clear that one of the major limitations of the implementation of such a model of care is the amount of time that can be attributed to the model's process by the community pharmacist rather than the technical barriers concerning patient data handling. All pharmacists that were interviewed agreed on the fact that reimbursement could help overcome this barrier. Additionally, attributing a certain time of the day during which the investigating pharmacists are likely to have enough time resources to process all the required stages of the pharmaceutical care model is essential. It is most likely that during the "rush-hour" in a CP it will not be possible for involved pharmacists to process all the necessary stages of the PC-model.

All experts that were consulted during the validation process of the PC-model agreed on the fact that a patient's name should be used during the screening entry stage, because it is more reliable and less time consuming for the pharmacists participating in the scheme. However in the study group it was agreed on that during data processing it is crucial that a unique primary key is created and used to link patients to their data to guarantee anonymity and to avoid confusions of patients with similar names. It has to be assessed in future research if the primary patient key derived from the GPASS® system is sufficient to address this issue.

5.4. Recommendation for Further Research

A major component of the model created in this study is a method of assessing a patient's risk of fracture, referring those exceeding a certain threshold to BMD measurement. The investigator suggests for further research to include a criterion that examines whether a patient with a fracture probability above the assessment threshold was referred to a DEXA scan or not. This change would result partly in the implementation of the previously published guidelines by the National Osteoporosis Guideline Group for this criterion only.
Further, the integration of the automated database form created by T. Dreischulte would enhance the utility of the tool by allowing higher patient numbers to be processed. This requires reviewing and adjusting the current database protocol in order to apply the

method to the current MAT_{osteo}. In return, adjustments at the Microsoft Access® tool have to be made in order to be implemented in the analysis process. The implementation of this method also requires the design of master files for items like risk factors, contraindications and drugs.

It would be interesting to use the actualised MAT_{osteo} in a clinical setting. It has to be examined if the criteria of the tool can be applied to this specific group of patients. Also during the validation of the PC model it became apparent, that especially housebound patients would profit from participating in the scheme. This is especially important, since it is highly likely that especially bedridden patients have a higher fracture risk because of lack of exercise and an additional higher risk of falls. Therefore, for a future field of research could be to adapt the PC model for this specific patient group and test the validity of applying the model in this field.

6. Appendices

6.1. Appendix 1: MAT_{osteo} Luf [final]

Medication Assessment Tool for use in osteoporosis/osteopenia (MAT_{osteo}) – (Luf [final])

Patient Code:

Date and setting:

Key for the six answer categories:

NA	Not applicable
Yes	Standard is adhered to in eligible patients
No (J)	No, but justified
No (U)	No, unjustified
ID_Q	Insufficient data to address the qualifying statement
ID_S	Insufficient data to address the standard statement

Definitions:

Osteoporosis	… is defined as a value of bone mineral density at least 2.5 standard deviations below the young adult mean (T-score $\leq$ - 2.5).
Osteopenia	… is defined as a value of bone mineral density between 1 and 2.5 standard deviations below the young adult mean (T-score < - 1 and > - 2.5).
DEXA scan	Dual-energy X-ray absorptiometry is a method to assess the bone mineral density. The result is expressed in relation to the young adult mean (T-score) in standard deviation units.
BMD	Bone mineral density (g/cm^2) = Bone mineral content (g/cm) / width at the scanned line (W)

References:

1 Scottish Intercollegiate Guidelines Network (SIGN) Management of Osteoporosis 71 (April 2004 Update)

2 National Institute for Clinical Excellence (NICE) Alendronate, etidronate, risedronate, raloxifene, strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women Technology Appraisal TA160, October 2008

3 National Institute for Clinical Excellence (NICE) Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women Technology Appraisal TA161, October 2008

4 Summary of the 2002 Canadian Guidelines for the Diagnosis and Management of Osteoporosis (2005 Update)

5 British National Formulary (BNF) 56, September 2008

		NA	Yes	No (J)	No (U)	ID_Q	ID_s	Ref
	Diagnosis of osteoporosis/osteopenia							
1	**A patient with a diagnosis of osteoporosis** has a recorded DEXA Scan to confirm osteoporosis [Justification for not being assessed by DEXA scan to confirm osteoporosis Patient ≥ 60 years and ≥ 2 vertebral fractures imply a diagnosis of osteoporosis or a postmenopausal woman ≥ 75 years and two or more independent clinical risk factors for fracture or indicators of low BMD] **Independent clinical risk factors** ❑ low body mass index defined as less than 22 kg/m² ❑ ankylosing spondylitis ❑ Crohn's disease ❑ conditions that result in prolonged immobility ❑ untreated premature menopause **Indicators for low BMD** ❑ parental history of hip fracture, ❑ alcohol intake of 4 or more units/d ❑ rheumatoid arthritis	☐	☐	☐	☐	☐	☐	1,2,3
2	**Measurement of the BMD by DEXA scan** is performed at least at the two specific sites – namely, anteroposterior spine and hip.	☐	☐	☐	☐	☐	☐	1
	Calcium and vitamin D supplementation							
3	**A patient with a recorded diagnosis of osteoporosis** is prescribed supplementary calcium (± vitamin D). **[Justification for non-prescribing calcium and vitamin D: There is a record that the patient has an adequate dietary intake of calcium and no vitamin D deficiency.]**	☐	☐	☐	☐	☐	☐	1
4	**A patient with a recorded diagnosis of osteoPENIA** is prescribed supplementary calcium (± vitamin D) for the prevention of osteoporosis. [Justification for non-prescribing calcium and vitamin D: There is a record that the patient has an adequate dietary intake of calcium and no vitamin D deficiency.]	☐	☐	☐	☐	☐	☐	4
5	**A patient with confirmed vitamin D deficiency or aged ≥ 65** is prescribed vitamin D.	☐	☐	☐	☐	☐	☐	1
6	**A patient with osteoporosis and NOT prescribed any of the following: bisphosphonates, raloxifene, strontium ranelate or calcitonin** has a recorded contra-indication to each agent (see below) [Contraindications to bisphosphonates are: ☐ oesophageal strictures or achalasia ☐ inability to remain upright for > 30 min after ingestion ☐ hypocalcaemia ☐ osteomalacia (etidronate) ☐ moderate renal impairment (CrCl < 35 mL/min) ☐ pregnancy and breast feeding] [Contraindications to raloxifene are: ☐ past/present venous thromboembolic events ☐ hepatic impairment ☐ cholestasis ☐ severe renal impairment (CrCl < 10 mL/min) ☐ endometrial cancer ☐ uterine bleeding ☐ pregnancy and breast feeding] [Contraindications to strontium ranelate are: ☐ pregnancy and breast feeding ☐ hypersensitivity] [Contraindications to calcitonin are: ☐ hypocalcaemia ☐ hypersensitivity]	☐	☐	☐	☐	☐	☐	1,2,5

		NA	Yes	No (J)	No (U)	ID_Q	ID_s	Ref
7	**A patient prescribed supplementary calcium** is prescribed a daily dose of 500 – 1500 mg calcium.	☐	☐	☐	☐	☐	☐	**1,4**
8	**A patient prescribed vitamin D** is prescribed a daily dose of 10 – 20 µg (400 - 800 IU) vitamin D.	☐	☐	☐	☐	☐	☐	**1**
9	**A patient with osteoporosis and NOT prescribed any of the following: bisphosphonates, raloxifene, strontium ranelate or calcitonin** is prescribed ≥1000mg calcium plus 800 IU vitamin D per day	☐	☐	☐	☐	☐	☐	**1**
10	**A patient with a recorded diagnosis of osteoporosis** is prescribed an oral bisphosphonate as first-line therapy. Recorded reasons for non-conformance (justification): _____	☐	☐	☐	☐	☐	☐	**1,4**
11	**A patient with a recorded diagnosis of osteoPENIA** is prescribed an oral bisphosphonate as first-line therapy. Recorded reasons for non-conformance (justification): _____	☐	☐	☐	☐	☐	☐	**4**
12	**A patient who is prescribed a bisphosphonate** has no reason *on record* to avoid bisphosphonates. [Reasons to avoid bisphosphonates are: ❑ **contraindication to bisphosphonates** o oesophageal strictures or achalasia o inability to remain upright for > 30 min after ingestion o hypocalcaemia o osteomalacia (etidronate) o moderate renal impairment (CrCl < 35 mL/min) o pregnancy and breast feeding ❑ inability to comply with the instructions for use of bisphosphonates o ingestion on an empty stomach o washing the medication down with 250 ml water o avoidance of food for 30 min o avoidance of lying flat within 30 min of ingestion ❑ unsatisfactory response to bisphosphonates o another fracture occurs o decrease in BMD despite adherence to treatment ❑ intolerance to bisphosphonates o oesophageal ulceration o erosion or stricture o severe lower GI symptoms]	☐	☐	☐	☐	☐	☐	**1,2,5**

		NA	Yes	No (J)	No (U)	ID_Q	ID_s	Ref
13	**A patient receiving treatment for osteoporosis/osteopenia** is prescribed a standard dose regimen.	☐	☐	☐	☐	☐	☐	**1,5**

❑ **Prevention (in osteopenia)**	❑ **Treatment (of osteoporosis)**
Postmenopausal Osteoporosis	
❑ Alendronic acid	
□ 5 mg daily PO	□ 10 mg daily or 70 mg once weekly PO
❑ Disodium etidronate	
□ 400 mg for 14 days PO; 1,25 g calcium carbonate for 76 days PO	□ 400 mg for 14 days PO, 1,25 g calcium carbonate for 76 days PO
❑ Ibandronic acid (not in guidelines)	
	□ 150 mg once a month PO or 3 mg every 3 months IV
❑ Risedronate sodium	
□ 5 mg daily PO	□ 5 mg daily PO or 35 mg weekly PO
❑ Calcitonin	
	□ 200 units daily intranasally
❑ Raloxifene	
□ 60 mg daily PO	□ 60 mg daily PO
❑ Strontium ranelate	
	□ 2 g daily PO
❑ Teriparatide	
	□ 20 micrograms daily, for a maximum duration of treatment of 18 months
Osteoporosis in men	
❑ Alendronic acid	
	□ 10 mg daily PO
Glucocorticoid-induced Osteoporosis	
❑ Alendronic acid	
□ 5 mg daily PO	□ 5 mg daily PO
❑ Disodium etidronate	
□ 400 mg for 14 days PO, 1,25 g calcium carbonate for 76 days PO	□ 400 mg for 14 days PO, 1,25 g calcium carbonate for 76 days PO
❑ Risedronate sodium	
□ 5 mg daily PO	
❑ Teriparatide	
	□ 20 micrograms daily, for a maximum duration of treatment of 18 months

14	**A patient when started on bisphosphonate therapy** was initiated on alendronate.	☐	☐	☐	☐	☐	☐	**2,3**
15	**A postmenopausal woman diagnosed with osteoporosis/osteopenia and not treated with alendronate** is prescribed risedronate.	☐	☐	☐	☐	☐	☐	**1**
16	**A postmenopausal woman with ≥ 2 vertebral fractures and NOT treated with alendronate or risedronate** is prescribed intermittent cyclical etidronate (standard dose regime see criterion 13)	☐	☐	☐	☐	☐	☐	**1**

		NA	Yes	No (J)	No (U)	ID_Q	ID_s	Ref
17	**A patient who is on long-term glucocorticoid therapy (≥ 7.5 mg prednisolone or equivalents for ≥ 3 months)** is prescribed a bisphosphonate.	☐	☐	☐	☐	☐	☐	1
18	**A postmenopausal woman with a diagnosis of osteoporosis, who has an identifiable reason for not being prescribed a bisphosphonate** is prescribed strontium ranelate. [Reasons for non-use of bisphosphonates are Contraindications to bisphosphonates ❑ contraindication to bisphosphonates (see 12) ❑ inability to comply with the recommendations for use of bisphosphonates (see 12) ❑ intolerance to bisphosphonates (see12)]	☐	☐	☐	☐	☐	☐	2
19	**A postmenopausal woman diagnosed with osteoporosis with at least one osteoporotic fractures who has an identifiable reason for not being prescribed a bisphosphonate** is prescribed strontium ranelate or raloxifene. [Reasons for non-use of bisphosphonates are Contraindications to bisphosphonates ❑ contraindication to bisphosphonates (see 12) ❑ inability to comply with the recommendations for use of bisphosphonates (see 12) ❑ intolerance to bisphosphonates (see 12)]	☐	☐	☐	☐	☐	☐	3
20	**A postmenopausal woman diagnosed with osteoporosis and at least one osteoporotic fractures who has either** ❑ **a reason to avoid bisphosphonates (See 12)** ❑ **a contraindication to strontium ranelate** o pregnancy o breast-feeding ❑ **an intolerance to strontium ranelate** o persistent nausea o persistent diarrhoea **and who is either** ❑ **aged ≥ 65 years with a T-Score ≤ -4 SD** ❑ **aged ≥ 65 years with a T-Score ≤ -3.5 SD and has more than two fractures** ❑ **aged 55-64 years with a T-Score ≤ -4 and has more than two fractures** is prescribed teriparatide.	☐	☐	☐	☐	☐	☐	3
21	**A postmenopausal woman diagnosed with osteoporosis with at least one vertebral fracture and NOT treated with a bisphosphonate, raloxifene or strontium ranelate,** is prescribed calcitonin.	☐	☐	☐	☐	☐	☐	1

6.2. Appendix 2: Database Protocols

Database Protocol		
Criterion 1		
A patient with a diagnosis of osteoporosis has a recorded DEXA Scan to confirm osteoporosis.		
Identify patients, who comply with qualifier as follows (Qualifier):		
Identify patients with a diagnosis of osteoporosis		
Step 1	Apply a Query using READ code N330.	**GPASS Sampling**
has a recorded DEXA Scan to confirm osteoporosis.		
Step 2	Inclusion of those with a recorded DEXA scan result to confirm osteoporosis	
Step 2a	Apply a Query using READ code [58EM., 58EG., 58E4., 58EA., 58E5.]	**Access Query**
Step 2b	Complete list of patients with a recorded DEXA scan to confirm osteoporosis by using supplementary paper records	**Manually**
Justification for not being assessed by a DEXA scan to confirm osteoporosis: [Patient ≥ 60 years and ≥ 2 vertebral fractures imply a diagnosis of osteoporosis or a postmenopausal woman ≥ 75 years and two or more independent clinical risk factors for fracture or indicators of low BMD]		
Step 3	Identify patients ≥ 60 years with ≥ 2 vertebral fractures	
Step 3a	Apply a Query identifying patients ≥ 60 years	**Access Query**
Step 3b	Apply a Query using READ code [14G8.., S15.., N3310, N331, N3318, N3319, N331A, N331C, N331D, N331E, N331F, N331G, N331H, N331J, N331K, N331L, N3746, N3741, N371.., S102.., S104.., S106.., S10B0, S10B1, S10B6, S10x, S10z]	**Access Query**
Step 4	**Identify postmenopausal women**	
Step 4a	Apply a Query identifying patients > 59 years	**Access Query**
Step 4b	Complete list of postmenopausal women	**Manually**
Step 4c	Apply a Query identifying postmenopausal women ≥ 75 years	**Access Query**
Step 5	**Identify postmenopausal women presenting two or more independent clinical risk factors or indicators for low BMD.**	
Categorise sample by independent clinical risk factors and indicators for low BMD low body mass index defined as less than 22 kg/m² ankylosing spondylitis Crohn's disease conditions that result in prolonged immobility untreated premature menopause Parental history of hip fracture Alcohol intake of 4 or more units/d		

Rheumatoid arthritis		
Step 5a	Apply a Query using READ code 22K and like ≤ 22 using the query of postmenopausal women ≥ 75 years	**Access Query**
Step 5b	Apply a using READ code N100. using the query of postmenopausal women ≥ 75 years	**Access Query**
Step 5c	Apply a using READ code [J40.., J4002, J4003, J4004, J4005, J400z, J4012, J401z, Jyu40] using the query of postmenopausal women ≥ 75 years	**Access Query**
Step 5d	Identify patients with conditions that result in prolonged immobility using the query of postmenopausal women ≥ 75 years	**Manually**
Step 5e	Apply a query using READ code C1631 using the query of postmenopausal women ≥ 75 years	**Access Query**
Step 5f	Identify patients with a family history of hip fracture using the query of postmenopausal women ≥ 75 years	**Manually**
Step 5g	Apply a Query using READ code [1366.., 136K., 136Q., 136S., 136T., E23…, E250.., like “4units”]	**Access Query, Manually**
Step 5h	Apply a Query using READ code [N0400-9, N040A-N, N040Q, N040R, N040S, N040T, F3712, F3964] using the query of postmenopausal women ≥ 75 years	**Access Query**

Database Protocol		
Criterion 2		
Measurement of the BMD by DEXA scan *Is performed at least at the two specific sites – namely anteroposterior spine and hip*		
Identify patients, who comply with qualifier as follow (qualifier):		
Identify patients in whom the BMD was measured by DEXA scan		
Step 1	Inclusion of patients with a measured BMD by DEXA scan	
Step 1a	At least one READ code [58EG, 58EH, 58EC, 58ED, 58EE, 58EF, 58EG, 58EH, 58EI, 58EJ, 58EL, 58EM, 58EN, 58EK, 58EN, 58EM]	**GPASS sampling**
DEXA scan is performed at least the two specific sites (Standard)		
Step 2	Inclusion of those with measurement of the BMD by DEXA scan – anteroposterior spine and hip	
Step 2a	Apply a Query using READ code [58EC, 58ED, 58EE, 58EG, 58EH, 58EI, 58EJ, 58EK, 58EM, 58EN]	**Access Query, Manually**

Database Protocol		
Criterion 3		
Patient with a recorded diagnosis of osteoporosis *Is prescribed supplementary calcium (vitamin D)*		
Identify patients, who comply with qualifier as follows (qualifier):		
Identify patients with a recorded diagnosis of osteoporosis		
Step 1	Inclusion of patients with a recorded diagnosis of osteoporosis	
Step 1a	At least one READ code [N330.. and 58EM, 58EG, 58E4, 58EA]	**GPASS sampling**
Is prescribed supplementary calcium (vitamin D) (standard)		
Step 2	Inclusion of those with prescribed supplementary calcium (vitamin D)	
Step 2a	Apply a Query using READ code [Ip3.., like "*PMO*" and the names of the calcium containing products] Possible drugs containing calcium (vitamin D) are the following drugs: Calcium carbonate (Adcal®, Cacit®, Calcichew®, Calcium-500®, Sandocal®400, Sandocal®1000), calcium plus vitamin D (Adcal D_3®, Cacit D_3®, Calceos®, Calcichew D_3®, Calcichew® D_3 forte, Calfovit® D_3 Calfovit® D_3) and Didronel PMO® (combination product of disodium etidronate and calcium carbonate),	**Access Query**
Justification for non-prescribing calcium and vitamin D: There is a record that the patient has an adequate dietary intake of calcium and no vitamin D deficiency		
Step 3	Categorise sample by adequate dietary intake of calcium	
Step 3a	Apply a Query using READ code [8I6S]	**Access Query**
Step 3b	Complete number of patients with adequate dietary intake and no vitamin D deficiency	**Manually**

Database Protocol		
Criterion 4		
Patient with a recorded diagnosis of osteoPENIA *Is prescribed supplementary calcium (vitamin D)*		
Identify patients, who comply with qualifier as follows (qualifier):		
Identify patients with a recorded diagnosis of osteopenia		
Step 1	Inclusion of patients with a recorded diagnosis of osteopenia	
Step 1a	At least one READ code [NyuBC, 66aD, 58E5, 58EB, 58EH, 58EN]	**GPASS sampling**
Is prescribed supplementary calcium (vitamin D) (standard)		
Step 2	Inclusion of those with prescribed supplementary calcium (vitamin D)	
Step 2a	Apply a Query using READ code [Ip3.., like "*PMO*" and the names of the calcium containing products] Possible drugs containing calcium (vitamin D) are the following drugs: Calcium carbonate (Adcal®, Cacit®, Calcichew®, Calcium-500®,	**Access Query**

	Sandocal®400, Sandocal®1000), calcium plus vitamin D (Adcal D_3®, Cacit D_3®, Calceos®, Calcichew® D_3, Calcichew® D_3 forte, Calfovit® D_3) and Didronel PMO® (combination product of disodium etidronate and calcium carbonate)	
Justification for non-prescribing calcium and vitamin D: There is a record that the patient has an adequate dietary intake of calcium and no vitamin D deficiency		
Step 3	Categorise sample by adequate dietary calcium intake and no vitamin D deficiency	**Access Query**
Step 3a	Apply a Query using READ code [8I6S]	**Access Query**
Step 3b	Complete information of adequate dietary intake and no vitamin D deficiency	**Manually**

Database Protocol		
Criterion 5		
Patient with confirmed vitamin D deficiency or aged ≥ 65 *Is prescribed vitamin D*		
Identify patients, who comply with qualifier as follows (qualifier):		
Identify patients with confirmed vitamin D deficiency or aged ≥ 65		
Step 1a	Apply a Query using READ code [C28..]	**Access Query**
Step 1b	Complete list of patients with confirmed vitamin deficiency.	**Manually**
Step 1c	Apply a Query to identify patients aged ≥ 65	**GPASS sampling**
Is prescribed vitamin D (standard)		
Step 2	Apply a Query using READ code [like “vitamin D”, Ip3.., like “*Adcal D*”, like, “*cacit D*”, like “*calceos*”, like “*calceos*”, like “calcichew d*”, like “*calfovit d*”, like “*alfacalcidol*”, like “*one alpha*”, like “*fosavance*”, like “*cholecalciferol*”] by using query form step 1 Vitamin D containing drugs are the following: Adcal D_3®, Cacit D_3®, Calceos®, Calcichew D_3®, Calcichew® D_3 forte, Calfovit® D_3, Alfacalcidool®, One Alpha®, Fosavance®	**Access Query**

Database Protocol
Criterion 6
A patient with osteoporosis and NOT prescribed any of the following: bisphosphonates, raloxifene, strontium ranelate or calcitonin *has a recorded contraindication to each agent (see below)*

Identify patients, who comply with qualifier as follows (qualifier):		
Identify patients with a contraindication to all of the following : bisphosphonate, raloxifene, strontium ranelate AND calcitonin		
Step 1	Inclusion of patients with a diagnosis of osteoporosis	
Step 1a	Apply a Query using READ code N330	**Access Query**
Identify patients prescribed any of the following: bisphosphonates, raloxifene, strontium ranelate or calcitonin		
Step 2	Identify patients treated with bisphosphonate, raloxifene, strontium ranelate, OR calcitonin	
Step 2a	Apply a Query using READ codes [fo.., fv1.., like “bisphos*”, like “*dronate*”, like “alendronic*”, like “fosamax”, like “fosavance”, like “didronel”, like “actonel”, like “aredia”, like “bondronate”, like “bonviva”, like “bonefos”, like “loron”, like “tiludronic*”, like “*ibandronic*” like “skelid” like “zoledronic*”, like “zometa” like “*raloxif*”, like “*evista*”, like “*calcito*”, like “miacal*” , like “*strontium*” like “*protelos*”] Treatment options in patients with osteoporosis: Bisphosphonates: Alendronic acid (Fosamax®, Fosavance®), disodium etidronate (Didronel®, Didronel PMO®), ibandronic acid (Bonviva®, Bondronate®), risedronate sodium (Actonel®), sodium clodronate (Bonefos®, Loron®), tiludronic acid (Skelid®), zoledronic acid (Zometa®) Raloxifene: Raloxifene (Evista®) Calcitonin: Miacalcic® Strontium Ranelate: Protelos®	**Access Query**
Step 3	Identify patients not treated with a bisphosphonate or raloxifene, strontium ranelate and calcitonin using the table from step 2a by comparing with the table from step 1	
	Categorise sample by contraindications to bisphosphonates, raloxifene, strontium ranelate AND calcitonin Bisphosphonates: Oesophageal strictures and achalasia Inability to remain upright for > 30 min after ingestion Hypocalcaemia Osteomalacia (etidronate) Moderate renal impairment (CrCl < 35 mL/min) Pregnancy and breast feeding Raloxifene: Past/present venous thromboembolic events Hepatic impairment Cholestasis Severe renal impairment (CrCl < 10 mL/min) Endometrial cancer Uterine bleeding Pregnancy and breast feeding	

	Strontium Ranelate: Pregnancy and breast feeding Hypersensitivity Calcitonin: Hypocalcaemia Hypersensitivity	
Step 3a	Apply a query using READ code [8I2V, 8I7E, 14LT] (contraindications for bisphosphonates)	**Access Query**
Step 4	Complete information about contraindications for bisphosphonates, raloxifene, strontium ranelate and calcitonin	**Manually**

Database Protocol		
Criterion 7		
Patient prescribed supplementary calcium *Is prescribed a daily dose of 500-1500 mg calcium*		
Identify patients, who comply with qualifier as follows (qualifier):		
Identify patients in whom supplementary calcium is prescribed		
Step 1	At least one READ code [Ip3.., like "*ca*", like "*PMO*"]	**GPASS sampling**
Is prescribed a daily dose of 500-1500 mg calcium (standard)		
	Possible drugs containing 500 mg calcium carbonate are the following: Cacit®, Calceos®, Calcichew®, Didronel PMO® Dose: frequency = 1:1, 1:2, 1:3, 3:1, 2:1 Possible drugs containing 600 mg calcium carbonate are the following: Adcal® Dose: frequency = 1:1, 1:2, 2:1 Possible drugs containing 400 mg calcium carbonate are the following: Sandocal®400 Dose: frequency = 1:2, 1:3, 3:1, 2:1 Possible drugs containing 1000 mg calcium carbonate are the following: Sandocal®1000 Dose:frequency = 1:1 Possible drugs containing 1200 mg calcium carbonate are the following: Calfovit® D_3 Dose:frequency = 1:1	
Step 2	Apply a Query using READ code [ip3h, ip39, ip3b, ip3f, like "cacit*", like "Calceos", like "calcichew*", like "*PMO*"] and use	**Access Query**

	for frequency and dose For each patient, identify dose and frequency using the table and apply to a new Query using [like “*1*”, like “*2*”, like “*3*”, like “*one*”, like “*two*”, like “*three*”] for dose and using [like “*dai*”, like “*twice*”, like “as directed”, like “morning”, like “night”] for frequency	
Step 3	Apply a Query using READ code [ip3j, like “adcal*”] For each patient, identify dose and frequency using [like “*1*”, like “*2*”, like “*one*”, like “*two*”] for dose and using [like “*dai*”, like “*twice*”, like “as directed”, like “morning”, like “night”] for frequency	**Access Query**
Step 4	Apply a Query using READ code [like “*sandocal 400*”] For each patient, identify dose and frequency using the table and apply to a new Query using [like “*1*”, like “*2*”, like “*3*”, like “*one*”, like “*two*”, like “*three*”] for dose and using [like “*dai*”, like “*twice*”, like “as directed”, like “morning”, like “night”] for frequency	**Access Query**
Step 5	Apply a Query using READ code [like “*Sandocal 1000*”, like “*calfovit*”] For each patient, identify dose and frequency using the table and apply to a new Query using [like “*1*”, like “*one*”] for dose and using [like “*dai*”, like “as directed”, like “morning”, like “night”] for frequency	**Access Query**

Database Protocol		
Criterion 8		
Patient prescribed vitamin D *Is prescribed a daily dose of 10 – 20 microgram (400 – 800 IU) vitamin D*		
Identify patients, who comply with qualifier as follows (qualifier):		
Identify patients in whom vitamin D is prescribed		
Step 1	At least one READ code [Ip3.., like “vitamin D” or like “*Adcal D*”, like, “*cacit D*”, like “*calceos*”, like “*calceos*”, like “calcichew d*”, like “*calfovit d*”, like “*alfacalcidol*”, like “*one alpha*”, like “*fosavance*”, like “*cholecalciferol*”	**GPASS sampling**
Is prescribed a daily dose of 10 – 20 microgram (400 – 800 IU) vitamin D (standard)		
Step 2	Inclusion of those with a prescription of vitamin D at a daily dose of 10 – 20 microgram (400 – 800 IU)	
	Possible drugs containing 10 micrograms (400 units) colecalciferol are the following: Adcal D_3®, Calceos®, Calcichew D_3® forte	

	Dose:frequency = 1:1, 1:2, 2:1 Possible drugs containing 11 micrograms (500 units) colecalciferol are the following: Cacit D_3® Dose:frequency = 1:1 Possible drugs containing 10 micrograms (200 units) colecalciferol are the following: Calcichew D_3® Dose:frequency = 1:1, 1:2, 1:3, 1:4, 4:1, 3:1, 2:1 Possible drugs containing 20 micrograms (800 units) colecalciferol are the following: Calfovit D_3 Dose:frequency = 1:1	
Step 2a	Apply a Query using READ code [ip3j, ip39, ip3f, like “adcal D” like “Calceos”, like “calcichew forte ”] For each patient, identify dose and frequency using the table and apply to a new Query using [like “*1*”, like “*2*”, like “*3*”, like “*one*”, like “*two*”, like “*three*”] for dose and using [like “*dai*”, like “*twice*”, like “as directed”, like “morning”, like “night”] for frequency	**Access Query**
Step 2b	Apply a Query using READ code [ip3h, like “cacit D”] For each patient, identify dose and frequency using the table and apply to a new Query using [like “*1*”, like “*one*”] for dose and using [“*dai*”, like “as directed”, like “morning”, like “night”] for frequency	**Access Query**
Step 2c	Apply a Query using READ code [ip3b, like “calcichew D”] For each patient, identify dose and frequency using the table and apply to a new Query using [like “*1*”, like “*2*”, like “*3*”, like “*4*”, like “*one*”, like “*two*”, like “*three*”, like “*four*”] for dose and using [like “*dai*”, like “*twice*”, like “as directed”, like “morning”, like “night”] for frequency	**Access Query**
Step 2d	Apply a Query using READ code [like “*Calfovit*”] For each patient, identify dose and frequency using the table and apply to a new Query using [like “*1*”, like “*one*”] for dose and using [like “*dai*”, like “as directed”, like “morning”, like “night”] for frequency	**Access Query**

Database Protocol		
Criterion 9		
A patient with osteoporosis and NOT prescribed any of the following: bisphosphonates, raloxifene, strontium ranelate or calcitonin *Is prescribed ≥ 1000 mg calcium plus 800 IU vitamin D per day.*		
Identify patients, who comply with qualifier as follows (qualifier):		
Identify patients not treated with either one of the following: bisphosphonate, raloxifene, strontium ranelate AND calcitonin		
Step 1	Inclusion of patients with a diagnosis of osteoporosis	
Step 1a	Apply a Query using READ code N330.	**Access Query**
Step 2	Identify patients prescribed any of the following: bisphosphonates, raloxifene, strontium ranelate or calcitonin	
Step 2a	Apply a Query using READ codes [fo.., fv1.., like “bisphos*”, like “*dronate*”, like “alendronic*”, like “fosamax”, like “fosavance”, like “didronel”, like “actonel”, like “aredia”, like “bondronate”, like “*Ibandronic*”, like “bonviva”, like “bonefos”, like “loron”, like “tiludronic*”, like “skelid” like “zoledronic*”, like “zometa” like “*raloxif*”, like “*evista*”, like “*calcito*”, like “miacal*” like “*protelos*”, like “*strontium*”] Treatment options in patients with osteoporosis: Bisphosphonates: Alendronic acid (Fosamax®, Fosavance®), disodium etidronate (Didronel®, Didronel PMO®), ibandronic acid (Bonviva®, Bondronate®), risedronate sodium (Actonel®), sodium clodronate (Bonefos®, Loron®), tiludronic acid (Skelid®), zoledronic acid (Zometa®) Raloxifene: Raloxifene (Evista®) Calcitonin: Miacalcic® Strontium Ranelate: Protelos®	
Step 3	Identify patients not treated with a bisphosphonate or raloxifene, strontium ranelate and calcitonin using the table from step 2a by comparing with the table from step 1	
Is prescribed ≥ 1000 mg calcium plus 800 IU vitamin D (standard)		
Step 4	Inclusion of those in whom ≥ 1000 mg calcium plus 800 IU vitamin D is prescribed.	
	Possible drugs containing 500 mg calcium carbonate are the following: Cacit®, Calceos®, Calcichew®, Didronel PMO® Dose:frequency = 1:2, 1:3, 3:1, 2:1 Possible drugs containing 600 mg calcium carbonate are the following: Adcal®	

	Dose:frequency = 1:2, 2:1 Possible drugs containing 400 mg calcium carbonate are the following: Sandocal®400 Dose:frequency = 1:3, 1:4, 4:1, 3:1 Possible drugs containing 1000 mg calcium carbonate are the following: Sandocal®1000 Dose:frequency = 1:1 Possible drugs containing 1200 mg calcium carbonate are the following: Calfovit® D_3 Dose:frequency = 1:1	
Step 5	Apply a Query using READ code [ip3h, ip39, ip3b, ip3f, like "cacit*", like "Calceos", like "calcichew*", like "*PMO*"] and use for frequency and dose For each patient, identify dose and frequency using the table and apply to a new Query using [like "*2*", like "*3*", like "*two*", like "*three*"] for dose and using [like "*dai*", like "*twice*", like "as directed", like "morning", like "night"] for frequency	**Access Query**
Step 6	Apply a Query using READ code [ip3j, like "adcal*"] For each patient, identify dose and frequency using [like "*2*", like "*two*"] for dose and using [like "*dai*", like "*twice*", like "as directed", like "morning", like "night"] for frequency	**Access Query**
Step 7	Apply a Query using READ code [like "*sandocal 400*"] For each patient, identify dose and frequency using the table and apply to a new Query using [like "*3*", like "*three*"] for dose and using [like "*dai*", like "*twice*", like "as directed", like "morning", like "night"] for frequency	**Access Query**
Step 8	Apply a Query using READ code [like "*Sandocal 1000*", like "calfovit*"] For each patient, identify dose and frequency using the table and apply to a new Query using [like "*1*", like "*one*"] for dose and using [like "*dai*", like "as directed", like "morning", like "night"] for frequency	**Access Query**

Database Protocol		
Criterion 10		
Patient with a recorded diagnosis of osteoporosis *Is prescribed an oral bisphosphonate as first-line therapy*		
Identify patients, who comply with qualifier as follows (qualifier):		
Identify patients with a recorded diagnosis of osteoporosis		
Step 1	Inclusion of patients with a recorded diagnosed osteoporosis	
Step 1a	At least one READ code [N330.. AND 58EM, 58EG, 58E4, 58EA]	**GPASS sampling**
Is prescribed an oral bisphosphonate as first-line therapy (standard)		
Step 2	Inclusion of those with an oral bisphosphonate (alendronic acid, disodium etidronate, disodium pamidronate, ibandronic acid, risedronate sodium, sodium clodronate, tiludronic acid, zoledronic acid) as first-line therapy	
Step 2a	Apply a Query using READ code [fo.., fv1.., like “bisphos*”, like “*dronate*”, like “alendronic*”, like “fosamax”, like “fosavance”, like “didronel”, like “actonel”, like “aredia”, like “bondronate”, like “*ibandr*” like “bonviva”, like “bonefos”, like “loron”, like “tiludronic*”, like “skelid” like “zoledronic*”, like “zometa”] For each patient, identify the first date recorded for the prescribed medication Drugs containing bisphosphonates are the following: Alendronic acid (Fosamax®, Fosavance®), disodium etidronate (Didronel®, Didronel PMO®), ibandronic acid (Bonviva®, Bondronate®), risedronate sodium (Actonel®), sodium clodronate (Bonefos®, Loron®), tiludronic acid (Skelid®), zoledronic acid (Zometa®)	**Access Query**

Database Protocol		
Criterion 11		
Patient with a recorded diagnosis of osteoPENIA *Is prescribed an oral bisphosphonate as first-line therapy*		
Identify patients, who comply with qualifier as follows (qualifier):		
Identify patients with a recorded diagnosis of osteoPENIA		
Step 1	Inclusion of osteopenia	
	At least one READ code [NyuBC, 66aD, 58E5, 58EB, 58EH, 58EN]	**GPASS sampling**
Is prescribed an oral bisphosphonate as first-line therapy (standard)		
Step 2	Inclusion of those with an oral bisphosphonate (alendronic acid, disodium etidronate, disodium pamidronate, ibandronic acid, risedronate sodium, sodium clodronate, tiludronic acid, zoledronic acid) as first-line therapy	
	Apply a Query using READ code [fo.., fv1.., like “bisphos*”, like “*dronate*”, like “alendronic*”, like “fosamax”, like “fosavance”, like “didronel”, like “actonel”, like “aredia”, like “bondronate”, like “*ibandr*”, like “bonviva”, like “bonefos”, like “loron”, like “tiludronic*”, like “skelid” like “zoledronic*”, like “zometa”] For each patient, identify the first date recorded for the prescribed medication Drugs containing bisphosphonates are the following: Alendronic acid (Fosamax®, Fosavance®), disodium etidronate (Didronel®, Didronel PMO®), ibandronic acid (Bonviva®, Bondronate®), risedronate sodium (Actonel®), sodium clodronate (Bonefos®, Loron®), tiludronic acid (Skelid®), zoledronic acid (Zometa®)	**Access Query**

Database Protocol		
Criterion 13		
Patient receiving treatment for osteoporosis or osteopenia *Is prescribed a standard dose regimen*		

Database Protocol		
Criterion 12		
Patient who is prescribed a bisphosphonate *has no reason on record to avoid bisphosphonate*		
Identify patients, who comply with qualifier as follows (qualifier):		
Identify patients in whom bisphosphonates are prescribed		
Step 1	Inclusion of bisphosphonates (alendronic acid, disodium etidronate, disodium pamidronate, ibandronic acid, risedronate sodium, sodium clodronate, tiludronic acid, zoledronic acid)	
Step 1a	At least one READ code [fo.., fv1.., like “bisphos*”, like “*dronate*”, like “alendronic*”, like “fosamax”, like “fosavance”, like “didronel”, like “actonel”, like “aredia”, like “bondronate”, like “*ibandr*”, like “bonviva”, like “bonefos”, like “loron”, like “tiludronic*”, like “skelid” like “zoledronic*”, like “zometa”] Drugs containing bisphosphonates are the following: Alendronic acid (Fosamax®, Fosavance®), disodium etidronate (Didronel®, Didronel PMO®), ibandronic acid (Bonviva®, Bondronate®), risedronate sodium (Actonel®), sodium clodronate (Bonefos®, Loron®), tiludronic acid (Skelid®), zoledronic acid (Zometa®)	**GPASS sampling**
Has no recorded reason to avoid bisphosphonates (standard)		
Step 2	Inclusion of those with no reason to avoid bisphosphonates	
Step 2a	Identify patients with reasons to avoid bisphosphonates and exclude them from the list of patients who are prescribed a bisphosphonate from step 1	**Manually**
Demographic categorisation: reasons to avoid bisphosphonates		
Categorise sample by: contraindication to bisphosphonate (see 10) Oesophageal strictures and achalasia Inability to remain upright for > 30 min after ingestion Hypocalcaemia Osteomalacia (etidronate) Moderate renal impairment (CrCl < 35 mL/min) Pregnancy and breast feeding inability to comply with the instruction for use of bisphosphonates: (see 10) ingestion on an empty stomach washing the medication down with 250 ml water avoidance of food for 30 min avoidance of lying flat within 30 min of ingestion unsatisfactory response to bisphosphonates (another fracture occurs, decrease in BMD despite adherence to treatment) intolerance to bisphosphonates (oesophageal ulceration, erosion or stricture, severe lower GI symptoms)		
Identify patients, who comply with qualifier as follows (qualifier):		
Identify patients treated with bisphosphonate		

Step 1	Inclusion of bisphosphonate (alendronic acid, disodium etidronate, disodium pamidronate, ibandronic acid, risedronate sodium, calcitonin, raloxifene, strontium ranelate, teriparatide	
Step 1a	At least one READ code [fo.., fv1.., like “bisphos*”, like “*dronate*”, like “alendronic*”, like “fosamax”, like “fosavance”, like “didronel”, like “actonel”] Drugs containing bisphosphonates are the following: Alendronic acid (Fosamax®, Fosavance®), disodium etidronate (Didronel®, Didronel PMO®), risedronate sodium (Actonel®), sodium clodronate (Bonefos®, Loron®), tiludronic acid (Skelid®), zoledronic acid (Zometa®)	**GPASS sampling**
Is prescribed a standard dose regimen (standard)		
Step 2	Inclusion of those with a standard dose regimen for prevention (in osteopenia) and treatment (of osteoporosis)	
Step 2a	Categorise sample by: postmenopausal osteoporosis (alendronic acid, disodium etidronate, ibandronic acid, risedronate), osteoporosis in men (alendronic acid), glucocorticoid-induced osteoporosis (alendronic acid, disodium etidronate, risedronate)	
Step 3	Identify postmenopausal women	
Step 3b	Apply a Query identifying patients > 59 years	**Access Query**
Step 4	Identify number of postmenopausal women who are on a standard dose regimen for prevention in osteopenia (alendronic acid)	
Step 4a	Apply a Query using READ codes [fo42, fo4z, like “alendron*”, like “fosamax”, AND like “*5*”] using the table from step 3c	**Access Query**
Step 5	Identify number of postmenopausal women who are on a standard dose regimen for prevention of osteopenia and treatment for osteoporosis (Disodium etidronate)	
Step 5a	Apply a Query using READ codes [fo1.., like “etidron*”, like “didronel”, like “cacit”, like Calcichew”, like “*500*”]	**Access Query**
Step 5b	Identify patients who are on 1.25g calcium carbonate for 76 days p.o.	**Manually**
Step 6	Identify number of postmenopausal women who are on a standard dose regimen for prevention in osteopenia (risedronate sodium)	
Step 6a	Apply a Query using READ codes [fo61, fo6y, like “actonel”, like “risedron*”, AND “*5*” (preparation)	**Access Query**
Step 7	Identify number of postmenopausal women who are on a standard dose regimen for treatment of osteoporosis (alendronic acid)	
Step 7a	Apply a Query using READ codes [fo41, fo42, fo44., fo45., fo4x., fo4y., like “alendron*”, like “fosa*”] AND using [like “*10*” or like “*70*”] for the field preparation	**Access Query**
Step 8	Identify number of postmenopausal women who are on a standard dose regimen for treatment of osteoporosis (ibandronic acid)	
Step 8a	Apply a Query using READ codes [fo85., fo8x., like “bonviva”, like “ibandron*”] AND using [like “*150*” or “*1*” or “*3*”] for preparation AND using [“*month*”] for frequency	**Access Query**
Step 9	Identify number of postmenopausal women who are on a standard dose regimen for treatment for osteoporosis	

	(risedronate sodium)	
Step 9a	Apply a Query using READ codes [fo61., fo63., fo6x., like “actonel”, like “risedron*”] AND using [like “*5*”] (preparation)	**Access Query**
Step 10	Identify patients treated with calcitonin	**Access Query**
Step 10a	Apply a Query using READ codes [like “*calcito*”, like “miacal*”]	
Is prescribed a daily dose of 200 IU calcitonin administered intranasally (standard)		
Step 11	Inclusion of those with a prescribed daily dose of 200 IU calcitonin administered intranasally	
Step 11a	Apply a query using READ code like “[*calcito”* like “*miacal*”] using the table from step … For each patient identify the frequency (	
	Inclusion of those with a prescribed daily dose of 60 mg raloxifene administered orally	
Step 12b	Ensure that tibolone and ethinylestradiol is prescribed for oestrogen deficiency and not for osteoporosis treatment	**Manually**
Step 12c	Complete list of postmenopausal women	**Manually**
Step 13	Identify postmenopausal women treated with raloxifen	**Access Query**
Sstep 13 c	Apply a Query using READ codes [fv1.., like “raloxi*”, like “evist*”] using table from step 1c	
Is prescribed a daily dose of 60 mg raloxifene (standard)		
Step 14	Inclusion of those with prescribed 60 mg raloxifene	
Step 14a	Apply a Query using READ code [fv1.., like “raloxi*”, like “evist*”] For each patient, identify the frequency as daily using [like “*dai*”] Raloxifene containing preparations are the following: Raloxifene (Evista®)	**Access Query**
Step 15	Identify postmenopausal women treated with strontium ranelate	
Step 15a	Apply Query using READ code [fu51., fu5z., like”*stronti*”, like”*ranelat*”, like”*protelo*”]	
Step 15b	Apply a Query using READ code [fu51., fu5z., like”*stronti*”, like”*ranelat*”, like”*protelo*”] For each patient, identify the frequency as daily using [like “*dai*”] Strontium ranelate containing preparations are the following: Strontium ranelate (Protelos®)	
Step 16	Identify postmenopausal women diagnosed with osteoporosis treated with teriparatide	**Access Query**
Step 16a	Apply a query using READ codes [fu3.., 8BP1, like “terpar*”, like “forst*”] using the query from step 1 For each patient, identify the preparation and quantity Teriparatide containing preparations are the following: Forsteo®	
Is prescribed a daily dose of 20 microgram as subcutaneous injection for a		

maximum of 18 months (Numerator)		
Step 17	Inclusion of those prescribed a daily dose of 20 microgram as subcutaneous for maximum of 18 months	
Step 17a	For each patient, identify the preparation (=20) and quantity (=19)	**Access Query**
Step 18	Identify men who are on a standard dose regimen for treatment (of osteoporosis)	
Step 18a	Apply a Query using READ codes [fo41., fo42., like “alendron”, like “fosamax”, like “fosavance” AND using [like “*10*] in the field preparation	**Access Query**
Step 19	Identify patients with glucocorticoid therapy	
Step 19a	Apply Query using READ codes [fe1.., fe2.., fe3.., fe4.., fe5.., fe6.., fe9.., like “betamet*”, like “betnesol”, like “corti*”, like “dex*”, like “Hydro*”, like “methylpred*”, like “medr*”, like “pred*”, like “deltacord*”, like “deflaza*”, like “calcort”] AND using [like “*tab*”, like “*cap*”] in the field preparation	**Access Query**
Step 20	Identify patients who are on a standard dosage regimen for prevention (in osteopenia) in glucocorticoid –induced osteoporosis (alendronic acid)	**Access Query**
Step 20a	Apply a Query using READ codes [fo43., fo4z., like “alendron*”, like “fosamax”] AND “*5*” (preparation) AND using [like “*daily*”] in the field frequency	
Step 21	Identify patients who are on a standard dosage regimen for prevention (in osteopenia) in glucocorticoid –induced osteoporosis (disodium etidronate)	**Access Query**
Step 21a	Apply a Query using READ codes [fo1.., like “etidron*”, like “didronel”, AND like “cacit”, like Calcichew”, like “*500*”] AND using [like “*1*”] in the field quantity	
Step 22	Identify patients who are on a standard dosage regimen for prevention (in osteopenia) in glucocorticoid –induced osteoporosis (risedronate sodium)	**Access Query**
Step 22a	Apply Query using READ codes [fo61., fo6y., like “actonel”, like “risedron*”} AND “*5*” (preparation) AND using [like “*daily*”] in the field frequency	
Step 23	Identify patients who are on a standard dosage regimen for prevention (in osteopenia) in glucocorticoid –induced osteoporosis (alendronic acid)	
Step 23a	Apply a Query using READ codes [fo43., fo4z., like “alendron*”, like “fosamax”] AND “*5*” (preparation) AND using [like “*daily*”] in the field frequency	**Access Query**
Step 24	Identify patients who are on a standard dosage regimen for prevention (in osteopenia) in glucocorticoid –induced osteoporosis (risedronate sodium)	
Step 24a	Apply Query using READ codes [fo61., fo6y., like “actonel”, like “risedron*”} AND “*5*” (preparation) AND using [like “*daily*”] in the field frequency	**Access Query**
Step 25	Identify postmenopausal women diagnosed with osteoporosis treated with teriparatide	**Access Query**
Step 25a	Apply a query using READ codes [fu3.., 8BP1, like “terpar*”, like “forst*”] using the query from step 1 For each patient, identify the preparation and quantity Teriparatide containing preparations are the following:	

	Forsteo®	
Is prescribed a daily dose of 20 microgram as subcutaneous injection for a maximum of 18 months (standard)		
Step 4	Inclusion of those prescribed a daily dose of 20 microgram as subcutaneous for maximum of 18 months	
Step 4a	For each patient, identify the preparation (=20) and quantity (=19)	**Access Query**

Database Protocol		
Criterion 14		
A patient when started on bisphosphonate therapy *Was initiated on alendronate*		
Identify patients, who comply with qualifier as follows (qualifier):		
Identify patients when started on bisphosphonate therapy		
Step 1	Inclusion of patients when started on bisphosphonate (alendronic acid, disodium etidronate, disodium pamidronate, ibandronic acid, risedronate sodium, sodium clodronate, tiludronic acid, zoledronic acid)	
Step 1a	At least one READ code [fo.., fv1.., like “bisphos*”, like “*dronate*”, like “alendronic*”, like “fosamax”, like “fosavance”, like “didronel”, like “actonel”, like “aredia”, like “bondronate”, like “bonviva”, like “bonefos”, like “loron”, like “tiludronic*”, like “skelid” like “zoledronic*”, like “zometa”] Drugs containing bisphosphonates are the following: Alendronic acid (Fosamax®, Fosavance®), disodium etidronate (Didronel®, Didronel PMO®), ibandronic acid (Bonviva®, Bondronate®), risedronate sodium (Actonel®), sodium clodronate (Bonefos®, Loron®), tiludronic acid (Skelid®), zoledronic acid (Zometa®)	**GPASS sampling**
Was initiated on alendronate (standard)		
Step 2	Inclusion of those started on alendronate	
Step 2a	Apply a Query using READ code [fo4.., fo6.., like “alendronic”, like “alendronate”, like “fosamax”]	**Access Query**

Database Protocol		
Criterion 15		
Postmenopausal woman diagnosed with osteoporosis/osteopenia and not treated with alendronate *Is prescribed risedronate*		
Identify patients, who comply with qualifier as follows (qualifier):		
Identify postmenopausal woman diagnosed with osteoporosis/osteopenia and not treated with alendronate		
Step 1	Inclusion of patients diagnosed with osteoporosis/osteopenia	
Step 1a	At least one READ code [N330, NyuBC]	**GPASS sampling**
Step 2	Identify postmenopausal women	
Step 2a	Apply a Query using READ code [K5A1., K5A3., K59B.]	**Access Query**
Step 2b	Apply a Query identifying patients > 59 years	**Access Query**
Step 2c	Complete list of postmenopausal women	**Manually**
Step 3	Identify patients treated with alendronate	**Access Query**
Step 3a	Apply a Query using READ codes [fo4., like “alendronic*”, like “*fosamax*”, like “*fosavance*”]	
Step 3b	Exclusion of patients treated with alendronate by comparing the table from step 2c and the query from step 3a	**Manually**
Is prescribed risedronate (standard)		
Step 4	Inclusion of patients with prescribed risedronate who were not treated with alendronate	
Step 4a	Apply a Query using READ code [fo6.., like “risedronate”]	**Access Query**

Database Protocol		
Criterion 16		
Postmenopausal women with ≥ 2 vertebral fractures and NOT treated with alendronate or risedronate *Is prescribed intermittent cyclical etidronate*		
Identify patients, who comply with qualifier as follows (qualifier):		
Identify postmenopausal women with ≥ 2 vertebral fractures and NOT treated with alendronate or risedronate		
Step 1	Inclusion of postmenopausal women	
Step 1a	Apply a Query using READ code [K5A1., K5A3., K59B.]	**Access Query**
Step 1b	Apply a Query identifying patients > 59 years	**Access Query**
Step 1c	Complete list of postmenopausal women	**Manually**
Step 2	Identify postmenopausal women with vertebral fractures	**Access Query**
	Apply a Query using READ code [14G8.., S15.., N3310, N331,	

	N3318, N3319, N331A, N331C, N331D, N331E, N331F, N331G, N331H, N331J, N331K, N331L, N3746, N3741, N371.., S102.., S104.., S106.., S10B0, S10B1, S10B6, S10x, S10z]	
Step 3	Identify postmenopausal women with ≥ 2 vertebral fractures	**Manually**
Step 4	Identify postmenopausal women with ≥ 2 vertebral fractures and NOT treated with alendronate or risedronate	**Access Query**
Step 4a	Apply a Query using READ codes [fo4.., fo6.., like "*fosamax*", like "*fosavance*", like "*alendronic*", like "*risedronate*"]	
Step 4b	Apply a query using the table from step 4a and exclude those patients who were treated with alendronate and risedronate by comparing with the table from step 3	**Manually**
Is prescribed intermittent cyclical etidronate(standard)		
Step 5	Inclusion of those with prescribed cyclical etidronate	
	Apply a Query using READ code [fo1.., like "etidron*", like "didronel*"] AND like "*90*" or "*3*" (frequency) using the table from 4b Disodium etidronate containing preparations are the following: Didronel®, Didronel PMO®	**Access Query**

Database Protocol		
Criterion 17		
Patient who is on long-term glucocorticoid therapy (≥ 7.5 mg prednisolone or equivalents for ≥ 3 months) *Is prescribed a bisphosphonate*		
Identify patients, who comply with qualifier as follows (qualifier):		
Identify patients who are on long-term glucocorticoid therapy (7.5 mg prednisolone or equivalents for ≥ 3 months)		
Step 1	Inclusion of patients with glucocorticoid therapy	
Step 1a	At least one READ code [fe1.., fe2.., fe3.., fe4.., fe5.., fe6.., fe9.., like "betamet*", like "betnesol", like "corti*", like "methylpred*", like "medr*", like "pred*", like "deltacord*", like "deflaza*", like "calcort"]	**GPASS sampling**
Step 2	Identify patients who are on long-term glucocorticoids Glucocorticoid therapy are the following drugs: Betamethasone (Betnelan®, Betnesol®, Betamethasone®), cortisone acetate (Cortisone®), dexamethasone (Dexamethasone®, Dexsol®), hydrocortisone (Hydrocortisone®, Hydrocortone®), Methylprednisolone (Medrone®, Methylprednisolone®), prednisolone (Prednisolone®, Deltacortil®) deflazacort (Deflazacort®, Calcort®)	**Manually**
Is prescribed a bisphosphonate (standard)		
Step 3	Inclusion of those with prescribed bisphosphonate	
Step 3a	Apply a Query using READ code [fo.., like "bisphos*", like "didronel*", like "*dron*", like "alendron*", like "fosa*", like "actonel", like "bon*", like "*zometa*", like "*skelid*", like "*loron*"] using the table from step 2 Bisphosphonates therapy are the following drugs:	**Access Query**

	Alendronic acid (Fosamax®, Fosavance®), disodium etidronate (Didronel®, Didronel PMO®), ibandronic acid (Bonviva®, Bondronate®), risedronate sodium (Actonel®), sodium clodronate (Bonefos®, Loron®), tiludronic acid (Skelid®), zoledronic acid (Zometa®)	

Database Protocol		
Criterion 18		
A postmenopausal woman diagnosed with osteoporosis requiring treatment for primary prevention of fractures who has an identifiable reason for not being prescribed a bisphosphonate (see below) Is prescribed strontium ranelate.		
Identify patients, who comply with qualifier as follows (qualifier):		
Step 1	Inclusion of patients diagnosed with osteoporosis without a record of fractures, presenting an identifiable reason for not being prescribed a bisphosphonate	
Step 1a	At least one READ code [N330,…]	**GPASS sampling**
Identify postmenopausal women diagnosed with osteoporosis		
Step 2	Identify postmenopausal women	
Step 2a	Apply a Query identifying patients > 59 years	**Access Query**
Step 2b	Complete list of postmenopausal women	**Manually**
Step 3	Inclusion of primary prevention patients	
	Apply a query identifying patients with vertebral or non-vertebral fracture A READ code for vertebral fracture [14G8, S15.., N3310, N3311, N3318, N3319, N331A, N331C, N331D, N331E, N331F, N331G, N331H, N331J, N331K, N331L, N3946, N3741, S102.., S104.., S106.., S10B0, S10B1, S10B2, S10B6, S10x, S10z] or a READ code for non-vertebral fracture [14GA]	**GPASS sampling**
	exclude those patients by comparing with the table from step 3	
Step 4	Identify postmenopausal women with at least one osteoporotic fracture and reasons to avoid bisphosphonates	**Manually**
Demographic categorisation: reasons to avoid bisphosphonates		

Categorise sample by: contraindication to bisphosphonate (see 10) Oesophageal strictures and achalasia Inability to remain upright for > 30 min after ingestion Hypocalcaemia Osteomalacia (etidronate) Moderate renal impairment (CrCl < 35 mL/min) Pregnancy and breast feeding inability to comply with the instruction for use of bisphosphonates: (see 17) ingestion on an empty stomach washing the medication down with 250 ml water avoidance of food for 30 min avoidance of lying flat within 30 min of ingestion unsatisfactory response to bisphosphonates (another fracture occurs, decrease in BMD despite adherence to treatment) intolerance to bisphosphonates (oesophageal ulceration, erosion or stricture, severe lower GI symptoms)		
Is prescribed strontium ranelate (standard)		
Step 5	Identify postmenopausal women treated with strontium ranelate	**Access Query**
Step 5a	Apply Query using READ code [fu51., fu5z., like"*stronti*", like"*ranelat*", like"*protelo*"]	**Access Query**

Database Protocol		
Criterion 19		
A postmenopausal woman diagnosed with osteoporosis with at least one osteoporotic fracture who has an identifiable reason for not being prescribed a bisphosphonate (see below) Is prescribed strontium ranelate or raloxifene		
Identify patients, who comply with qualifier as follows (qualifier):		
Step 1	Inclusion of patients diagnosed with osteoporosis presenting at least one osteoporotic fracture and an identifiable reason for not being prescribed a bisphosphonate	
Step 1a	At least one READ code [N330,…]	**GPASS sampling**
Identify postmenopausal women diagnosed with osteoporosis		
Step 2	**Identify postmenopausal women**	
Step 2a	Apply a Query identifying patients > 59 years	**Access Query**
Step 2b	Complete list of postmenopausal women	**Manually**
Step 3	Inclusion of patients presenting an osteoporotic fracture	
Step 3a	Apply a query using READ code [14G8, S15.., N3310, N3311, N3318, N3319, N331A, N331C, N331D, N331E, N331F, N331G, N331H, N331J, N331K, N331L, N3946, N3741, S102.., S104.., S106.., S10B0, S10B1, S10B2, S10B6, S10x, S10z, 14GA]	**GPASS sampling**
Is prescribed strontium ranelate or raloxifene (standard)		
Step 4	Identify postmenopausal women treated with strontium ranelate and raloxifene	**Access Query**
Step 4a	Apply Query using READ code [fu51., fu5z., fv1.., like"*stronti*", like"*ranelat*", like"*protelo*" like "*raloxi*", like "evis*"]	**Access Query**

Database Protocol
Criterion 20
Postmenopausal woman diagnosed with osteoporosis and at least one osteoporotic fracture who has either a reason to avoid bisphosphonates (see12) a contraindication to strontium ranelate pregnancy breast feeding an intolerance to strontium ranelate persistent nausea persistent diarrhoea and who is either aged ≥ 65 years with a T-Score ≤ -4 SD aged ≥ 65 years with a T-Score ≤ -3.5 SD and has more than two fractures aged 55-64 years with a T-Score ≤ -4 SD and has more than two fractures

Is prescribed teriparatide		
Identify patients, who comply with qualifier as follows (qualifier):		
Identify postmenopausal woman diagnosed with osteoporosis		
Step 1a	Inclusion of patients diagnosed with osteoporosis	
Step 1a	At least one READ code [N330,…]	**GPASS sampling**
Inclusion of postmenopausal women diagnosed with osteoporosis		
Step 2	Identify postmenopausal women	
Step 2a	Apply a Query identifying patients > 59 years	**Access Query**
Step 2b	Complete list of postmenopausal women	**Manually**
Step 3	Inclusion of patients presenting an osteoporotic fracture	
Step 3a	Apply a query identifying postmenopausal women with vertebral or non-vertebral fracture A READ code for vertebral fracture [14G8, S15.., N3310, N3311, N3318, N3319, N331A, N331C, N331D, N331E, N331F, N331G, N331H, N331J, N331K, N331L, N3946, N3741, S102.., S104.., S106.., S10B0, S10B1, S10B2, S10B6, S10x, S10z] or a READ code for non-vertebral fracture [14GA]	**Access Query**
Step 4	Identify postmenopausal women with at least one osteoporotic fracture and reasons to avoid bisphosphonates	**Manually**
Demographic categorisation: reasons to avoid bisphosphonates		
Categorise sample by: contraindication to bisphosphonate (see 10) Oesophageal strictures and achalasia Inability to remain upright for > 30 min after ingestion Hypocalcaemia Osteomalacia (etidronate) Moderate renal impairment (CrCl < 35 mL/min) Pregnancy and breast feeding inability to comply with the instruction for use of bisphosphonates: (see 17) ingestion on an empty stomach washing the medication down with 250 ml water avoidance of food for 30 min avoidance of lying flat within 30 min of ingestion unsatisfactory response to bisphosphonates (another fracture occurs, decrease in BMD despite adherence to treatment) intolerance to bisphosphonates (oesophageal ulceration, erosion or stricture, severe lower GI symptoms)		
Step 5	Identify postmenopausal women with at least one osteoporotic fracture and a contraindication to strontium ranelate or an intolerance to strontium ranelate	
Demographic categorisation: contraindication or intolerance to strontium ranelate		
a contraindication to strontium ranelate pregnancy breast feeding an intolerance to strontium ranelate persistent nausea persistent diarrhoea		

Step 6	Identify postmenopausal women with at least one osteoporotic fracture and a contraindication to strontium ranelate or an intolerance to strontium ranelate who have a combination of age and T-Score as shown below	
	and who is either aged ≥ 65 years with a T-Score ≤ -4 SD aged ≥ 65 years with a T-Score ≤ -3.5 SD and has more than two fractures aged 55-64 years with a T-Score ≤ -4 SD and has more than two fractures	**Manually**
Is prescribed teriparatide (standard)		
Step 7	Inclusion of those with prescribed teriparatide	
Step 7a	Apply a Query using READ code [fu3.., like “teripara*”, like “forsteo”] Teriparatide containing preparations are the following: Forsteo®	**Access Query**

Database Protocol		
Criterion 21		
A postmenopausal woman diagnosed with osteoporosis and with at least one vertebral fracture NOT treated with a bisphosphonate or raloxifene, strontium ranelate *Is prescribed calcitonin.*		
Identify patients, who comply with qualifier as follows (qualifier):		
Identify postmenopausal woman diagnosed with osteoporosis/osteopenia		
Step 1	Inclusion of patients diagnosed with osteoporosis/osteopenia	
Step 1a	At least one READ code [N330.]	**GPASS sampling**
Step 2	Identify postmenopausal women	
Step 2a	Apply a Query identifying patients > 59 years	**Access Query**
Step 2b	Complete list of postmenopausal women	**Manually**
Step 3	Inclusion of postmenopausal women diagnosed with osteoporosis	
Step 3a	Apply a query using READ code [like "*n330*"] using the table from step 1c	**Access Query**
Step4	Identify postmenopausal women with vertebral fracture	
Step4a	Apply a query using READ code [14G8, S15.., N3310, N3311, N3318, N3319, N331A, N331C, N331D, N331E, N331F, N331G, N331H, N331J, N331K, N331L, N3946, N3741, S102.., S104.., S106.., S10B0, S10B1, S10B2, S10B6, S10x, S10z]	**Access Query**
Step 5	Identify postmenopausal women with at least one osteoporotic fracture treated with bisphosphonate or raloxifene	**Access Query**
Step 5a	Apply a Query using READ codes [fo.., fv1.., like "bisphos*", like "*dronate*", like "alendronic*", like "fosamax", like "fosavance", like "didronel", like "actonel", like "aredia", like "bondronate", like "bonviva", like "bonefos", like "loron", like "tiludronic*", like "skelid" like "zoledronic*", like "zometa" like "*raloxif*", like "*evista*"] Treatment options in patients with osteoporosis: Bisphosphonates: Alendronic acid (Fosamax®, Fosavance®), disodium etidronate (Didronel®, Didronel PMO®), ibandronic acid (Bonviva®, Bondronate®), risedronate sodium (Actonel®), sodium clodronate (Bonefos®, Loron®), tiludronic acid (Skelid®), zoledronic acid (Zometa®) Raloxifene: Raloxifene (Evista®)	**Access Query**
Step 6	Exclusion of patients diagnosed with osteoporosis and not treated with a bisphosphonate or raloxifene using the table from step 5a and exclude those patients by comparing with the table from step 4a	
Is prescribed calcitonin for the prevention of vertebral fractures (standard)		
Step 7	Inclusion of those with prescribed calcitonin	
Step 7a	Apply a Query using READ code [like "*calciton*", like "miacal*"] Calcitonin containing preparations are the following: Miacalcic®	**Access Query**

6.3. Appendix 3: Study Protocol

Title of the thesis

Development of a pharmaceutical care tool to guide community pharmacy interventions in Osteoporosis

Visiting Scholar Investigator	Anton Luf
Academic supervisors	Oskar Hoffmann (University of Vienna)
Co-supervisors	Steve Hudson
Collaborators	E. Past, J. Schlais
Study Site	University of Strathclyde, Glasgow, Scotland

Introduction:

Osteoporosis is a metabolic skeletal disease, characterised by low bone mineral density (BMD) and increased fragility of the bone. It is a chronic disease affecting both women and men.[1] This often under-diagnosed condition progresses exponentially with increasing age. The decrease of BMD and hence decrease in strength and stability of the bone leads to fragility fractures, the major outcome of the condition.[2] Especially at early stages the disease is asymptomatic and therefore often not detected.**Fehler! Textmarke nicht definiert.** The incidence of osteoporosis is distinctively higher in females than in males.[3] As the population is growing and people are likely to reach higher ages, the incidence of osteoporosis will rise in the future and will thereafter contribute to raising costs in health care system.[4] In addition osteoporosis is associated with pain, long term care placement, increased morbidity and premature mortality.[3] The incidence and progression of the disease is “strongly” linked to clinical risk factors like low dietary intake of calcium and vitamin D, smoking, extensive alcohol consumption, a low BMI and lack of exercise. Besides these avoidable risk factors there are circumstances that cannot be modified namely age, sex, ethnicity, reproductive factors and family history of osteoporotic fracture. In addition to the risk factors named above there is evidence that certain diseases, in

particular affecting the gastrointestinal tract and use of medication, especially long term systemic corticosteroids and anticonvulsant medication cause decrease of bone mineral content **Fehler! Textmarke nicht definiert.**[9]. Another contributor to the incidence of fractures is falling.[5] Again there are certain factors that contribute to the risk of falling e.g. physical condition or the use of drugs causing hypotension. Thus, patients with a combination of risk factors are at high risk of sustaining an osteoporotic fracture. Fall risk prevention services have been recently developed to be used in a community pharmacy setting.

According to the WHO, osteoporosis is defined based on the results of BMD measurement as > 2.5 SDs below the mean peak BMD of the young adult. Above this threshold the bone is considered normal.[1]The gold standard for the measurement of BMD is a DEXA-scan (dual energy x-ray absorptiometry) of the hip, spine or forearm.[6]

For fracture risk assessment and the diagnosis of osteoporosis it is important to take clinical risk factors in account in addition to BMD measurement results. According to recent guideline recommendations, pharmacological treatment is indicated without referring to a DEXA-scan, if the patient presents a certain combination of risk factors and age.[5]

FRAX®, a fracture risk assessment tool which has become available in 2008, predicts the 10 year-probability of sustaining an osteoporotic fracture or a hip fracture for women and men based on age, sex, CRFs and femoral neck BMD.[7] The tool uses four different algorithms to calculate fracture probability with and without femoral neck BMD.[8]

There have been studies conducted prior to the present that deal with the development of a medication assessment tool (MAT). This tool was built to audit the quality of clinical practice by assessing the adherence to the guideline recommendations regarding prevention, diagnosis, and management of osteoporosis.[9,10] The original MAT, developed by JJ McAnaw was adapted to audit guideline adherence in osteoporotic patients by E. Past in 2007 by extracting and combining recommendations of national and international guidelines.[11] In 2008 J. Schlais emphasised on designing data base protocols for the purpose of automatically applying patient data to the MAT_{osteo}. Data was acquired by accessing the GPASS® system in two different GP-practices. Additional data was collected by examining supplementary paper records in order to apply the required data to the tool. A total number of 194 patients with a diagnosis of osteoporosis were included in the survey.[12]

It has been shown in a survey conducted by J. Schlais that some criteria are likely to cause difficulties during data collection as the data could not be retrieved automatically from the GPASS® system (a Windows based computer programme to manage patient data). Furthermore technical difficulties have been reported regarding data handling and alignment during applying data to database protocols.[12]

A major objective of the present study is to create (examine the feasibility of creating) a model for primary and secondary prevention of osteoporosis for the use in a community pharmacy GP collaboration. The model will consist of a combination of the FRAX® tool for risk assessment of osteoporotic fractures and the fall reduction service that assesses the risk of falls and subsequent fractures in combination with an updated version of MAT_{osteo}.

A review will be conducted by the investigator aiming to detect critical criteria and report the findings to the research group. It will be examined if the concerning criteria can be adapted in respect of wording and structure, without harming the integrity and the reliability of the tool. Patient data of studies prior to this will be reapplied after adjusting the regarding criteria for primary prevention and implementing new guideline recommendations into the existing MAT_{osteo}. Existing risk assessment tools and the fall-prevention-model will be reviewed in respect of the feasibility of integrating them into the pharmaceutical care model named above.

Research Question, Aims and Objectives

Research question:

Aim

To review and validate components for the creation of a pharmaceutical care tool-kit for the delivery of pharmaceutical care to osteoporosis patients

Objectives

1. To conduct a literature review of osteoporosis and the evidence-base for the management of the condition
2. Screening of risk factors in primary prevention (community pharmacy opportunities model)
3. Evaluation of prescribing in secondary prevention (measure guideline adherence in those with osteoporosis diagnosis on GPASS, re-evaluation of Johanna data)
4. Integration of the above into a Model of Collaboration to reduce the risk of falls. Validation of the Model and critical review of opportunities and barriers to implementation
5. Make recommendations for the development of a toolkit to support the delivery of pharmaceutical care to (Osteopenia and) Osteoporosis patients.

Methods

1. To conduct a literature review of osteoporosis and the evidence-base for the management of the condition

For the purpose of updating the existing assessment tool, guideline recommendations of Scottish Intercollegiate Guideline Networks (SIGN), National Institute for Clinical Excellence (NICE) and the summary of the Canadian Guidelines for the Diagnosis and Management of Osteoporosis are reviewed to identify recent changes in guideline recommendations. Furthermore the online-databases Medline®, PubMed®, and Embase® are searched for relevant information. By using SFX and METALIB, resources to link search results to the original source available from journal web-pages and library catalogues, full information could be obtained from regarding sources. Further information was gathered by directly accessing journal homepages concerning the subject like Bone, Osteoporosis International and Joint Bone Spine. In addition the online resources Science Direct and Springer Link were consulted to gather background information on regarding topics.

A combination of keywords and phrases e.g. “risk assessment” and “osteoporosis” was entered into the search fields in order to obtain relevant literature. Results were specified and refined by choosing publishing-date limitation, article language and by using exclusion information e.g. not “osteopenia”.

2. Screening of risk factors in primary prevention (community pharmacy opportunities model)

Recently a tool has become available to assess a patient’s probability of sustaining an osteoporotic fracture, called FRAX®. The tool, an online questionnaire developed under the aegis of the WHO, calculates the 10 year fracture probability on the basis of age, sex, ethnicity (United States only), clinical risk factors and femoral neck BMD. Suggestions for assessment and intervention thresholds have been published by the WHO research group which allow interpreting the outcome.[13] In this study assessment tools are reviewed and linked with the medication assessment tool designed in prior studies and the fall risk reduction service, to create a pharmaceutical care tool for primary and secondary prevention of osteoporosis.

3. Evaluation of prescribing in secondary prevention (measure guideline adherence in those with osteoporosis diagnosis on GPASS, re-evaluation of Johanna data)

New criteria due to recent changes in guideline recommendations are created and integrated in the latest version of MAT_{osteo}. A review is conducted to analyse the differences in findings of previous surveys. Criteria that present statistically significant differences regarding applicability and adherence will be refined in this study. In addition criteria associated with difficulties regarding the availability of data are modified to be consistent with information stored on the GPASS® system and to improve the data processing with Microsoft Access®. Adaptation of criteria, concerning primary and secondary prevention and changes in data base protocols are conducted in this study in order to raise the sensitivity and the reliability of the tool. A secondary data analysis with patient data previously collected from the GPASS® system is conducted using the updated MAT_{osteo}.

4. To integrate the above into a Model of Collaboration to reduce the risk of falls and fractures. Validation of the Model and critical review of opportunities and barriers to implementation

In this study the revised MAT_{osteo}, FRAX®, and the fall risk reduction service to establish a pharmaceutical care tool-kit for primary and secondary prevention of osteoporosis. The aim is assisting clinicians in providing best care for patients including risk assessment, prevention and latest diagnosis methods and treatment options. A method is designed to identify those eligible for fracture risk assessment at the community pharmacy (primary prevention branch). Inclusion criteria are established e.g. chronic disease patients picking up their medicine from the community pharmacy.

The model will be validated by interviewing a group of clinicians involved in a model *similar* to the present. Pharmacists will be asked to give their opinion regarding the practicability of each stage of the model and make recommendations for redesigning concerning measures. Pharmacists will be asked to give their view on opportunities, obstacles and barriers of the use of such a model. The adherence of patients to recommendations for prevention and referral uptake could cause difficulties, as it was shown in a study conducted by Judith et al.[14]

5. Make recommendations for the development of a toolkit to support the delivery of pharmaceutical care to (Osteopenia and) Osteoporosis patients.

Recommendations for the development of a pharmaceutical care tool-kit are included in the discussion section of this study. The investigator makes suggestions on how to apply the method to patients for the prevention and management of the condition in a community pharmacy GP collaboration setting. This takes account of inclusion criteria for the study population. Also recommendations of how to integrate the model into a pharmaceutical care feedback loop (Design-Deliver-Evaluate) are put forth in this study. Suggestions for the integration of a Microsoft Access® query form (tool) created by Tobias Dreischulte that improves the process of automatically accessing patient data are made in this study.

Analysis of findings

The literature review supplies the investigator with recent updates of guideline recommendations and background information for the topic.

The review of fracture risk assessment tools provides information about the feasibility of using these methods in a model of collaboration.

Results of the secondary data analysis will be compared to the study prior to this by using Fisher's exact test and Chi-square; this will show the effect of updating and redesigning the criteria.

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