Supporting patients to get the best from their osteoporosis treatment; what works for whom, why and in what circumstance: a rapid realist review

Supplementary Data File

Figure 1: Background conceptual models: systems approach to enhance adherence. Reproduced with permission[1]

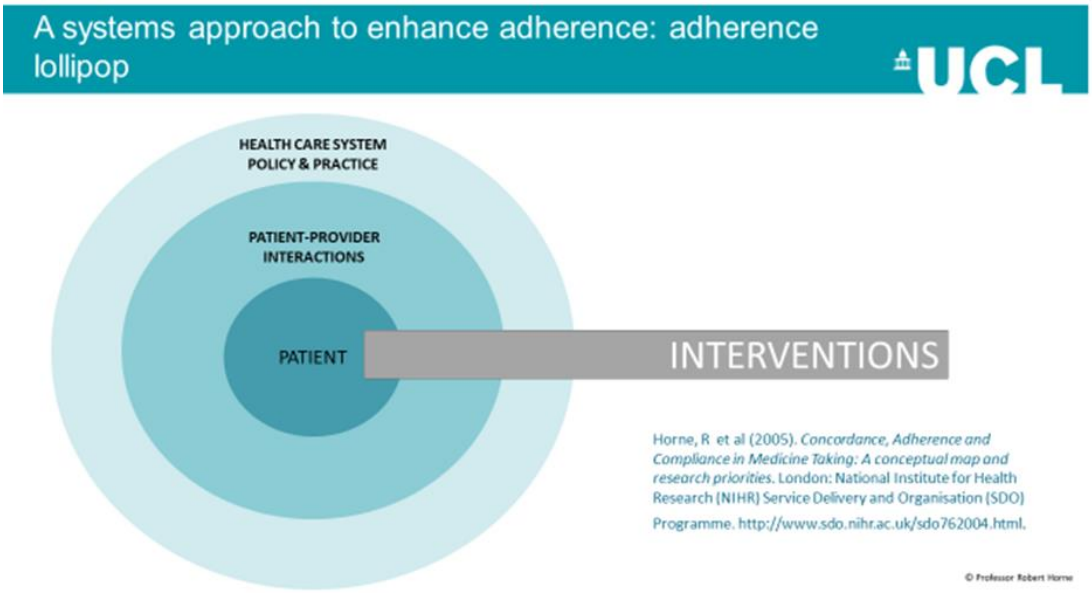
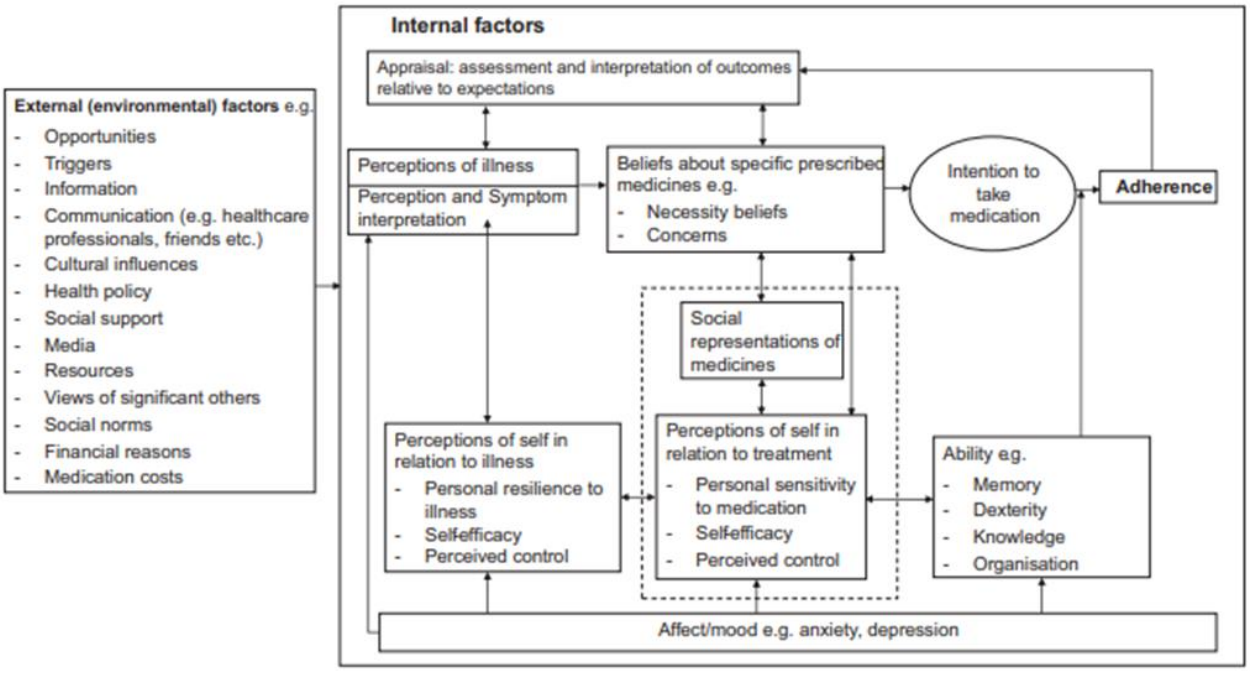


Figure 2: Background conceptual models: Perceptions and Practicalities approach conceptual model of adherence. Reproduced with permision[2]



[1] Horne R et al 2005 Concordance, adherence and compliance in medicine taking Report for the National Co-ordinating Centre for NHS Service Delivery and Organisation R & D (NCCSDO) Available at https://njl-admin.nihr.ac.uk/document/download/2027234

[2] Horne R, Cooper V, Wileman V, Chan A. Supporting adherence to medicines for long-term conditions. European Psychologist. 2019 Feb 11

Supplementary Data 1: determinants of non-adherence derived from background literature, (derived from Paskins et al, 2020[3], except items with *, derived from Cornellison et al, 2020[4])

Intrinsic	**Extrinsic**
<u>Patient context</u> • Competing priorities eg multi-morbid, life events, work*, polypharmacy* • Preceding Fall or fracture*, Hospitalisation*, <u>Low perceived need</u> • patient perceives self as 'healthy' • patient does not view OP as serious • patient does not consider self to have OP (nb gender relevant)/or be at risk or consider OP a problem (absence of symptoms) *interventional trigger eg bone density scan may mediate this belief* • patient considers OP inevitable/normal for age/treatment futile • Doubt or uncertainty about perceived effectiveness of treatments, and why Rx duration limited • Preference for other treatment/approach eg reduce falls <u>High concerns/fear</u> • About medicines in general, or aversion to pharmaceutical companies • Specific concerns about bisphosphonate rare side effects • Concerns about 'acid' • Concerns about 'special instructions' • Concerns about limited duration of use • Mistrust in clinician <u>Self-efficacy and confidence</u> • Difficulty remembering and developing routines • Difficulty understanding and taking in all information • Socio-economic status*	<u>Healthcare context:</u> • Capacity to follow up • Access to drugs, restrictions on prescribing • Access to investigations to monitor • Electronic records and primary-secondary care communication • Uncertainty about roles and responsibilities of different healthcare providers • Lack of incentivisation <u>Social/ environmental network</u> • Experience and perceptions of family and friends • Media reports <u>Patient-Provider interaction</u> • Clinician Attitudes - reinforces patient health beliefs • Clinician Knowledge • Trust • Consultation time <u>Treatment related</u> • Complexity/frequency of treatment regime offered

[3] Paskins, Zoe, et al. Acceptability of bisphosphonates among patients, clinicians and managers: a systematic review and framework synthesis. *BMJ open* 10.11 (2020): e040634.

[4] Cornelissen D et al. Interventions to improve adherence to anti-osteoporosis medications: an updated systematic review. Osteoporos Int. 2020 Sep;31(9):1645-1669. doi: 10.1007/s00198-020-05378-0

• Education level* Treatment expectations not met • **no evidence** of effectiveness or 'proof' medicine is working – lack of follow-up • perceived **evidence of no effect** eg fracture, symptoms, no change in bone density results • uncertainty/ambivalence about whether treatment is working Experienced side effects • Gastrointestinal Practical issues • cost, travel, Lower insurance coverage* • Need for increased dental check ups	

From this background literature, we identified the following possible initial (candidate) Programme Theories:

> **A person with osteoporosis and prescribed bisphosphonates**, informed about their condition, its progress and treatment options, engaged in decisions about treatment, and followed up with regular or timely support and reviews, and who understands and feels the benefit of taking bisphosphonates, is more likely to adhere to the prescribed medication.
>
> **Practitioners** prescribing, monitoring and supporting people with osteoporosis, in ways that are individualised, responsive and timely, and who share decision making, are more likely to enable the person with osteoporosis to adhere to their medication.

Supplementary Data 2: Search strategy

As per Cornelissen D, de Kunder S, Si L, Reginster JY, Evers S, Boonen A, Hiligsmann M; European Society for Clinical and Economic Aspect of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO). Interventions to improve adherence to anti-osteoporosis medications: an updated systematic review. Osteoporos Int. 2020 Sep;31(9):1645-1669. doi: 10.1007/s00198-020-05378-0. Epub 2020 May 1. PMID: 32358684; PMCID: PMC7423788. https://pubmed.ncbi.nlm.nih.gov/32358684/

Pubmed

"Osteoporosis"[Mesh] OR Osteoporosis [tiab] OR "Bone Diseases, Metabolic"[Mesh] OR Metabolic Bone Disease*[tiab] OR "Bone Demineralization, Pathologic"[Mesh] OR Bone Demineralization[tiab] OR "Decalcification, pathologic"[MeSH Terms] OR Patholog* Decalcification*[tiab] OR "Bone Density"[Mesh] OR Bone Densit*[Tiab]

AND

"Guideline adherence"[MeSH Terms] OR Guideline adherence*[tiab] OR "Patient Satisfaction"[Mesh] OR Patient Satisfaction[tiab] OR "Patient Preference"[Mesh] OR Patient Preference*[tiab] OR "Attitude to Health"[Mesh] OR Health attitude*[tiab] OR "Health Knowledge, Attitudes Practice"[Mesh] OR "Treatment Adherence and Compliance"[Mesh] OR Treatment Adherence [tiab] OR Therapeutic adherence [tiab] OR “Treatment compliance”[tiab] OR “Therapeutic compliance”[tiab] OR "Patient Acceptance of Health Care"[Mesh] OR "Patient Acceptance of Health Care"[tiab] OR "Patient Dropouts"[Mesh] OR "Patient dropout*"[tiab] OR "Patient Participation"[Mesh] OR "Patient Participation"[tiab] OR "Patient Compliance"[Mesh] OR Patient Compliance [tiab] OR Patient engagement [tiab] OR Patient Acceptance [tiab] OR Patient involvement [tiab] OR Medication adherence [tiab] OR Medication persistence [tiab] OR Medication compliance [tiab]

Embase

*metabolic bone disease/ or *bone disease/ or *bone demineralization/ or *osteoporosis/ or *bone demineralization/

AND

*disease management/ or patient attitude/ or *attitude/ or *health care quality/ or *human relation/ or *patient attendance/ or *patient compliance/ or *patient dropout/ or *patient

participation/ or *patient preference/ or *patient satisfaction/ or *refusal to participate/ or *treatment interruption/ or *treatment refusal/ or *protocol compliance/ or *attitude to health/ or *attitude/ or *health behavior/ or *knowledge/ or *attitude to illness/ or *health behavior/ or *behavior/ or *medication compliance/ or *patient education/ or *health education/

PSYCHINFO

(MM "Treatment Compliance" OR (MM "Compliance" OR MM "Treatment Compliance" OR MM "Client Attitudes" OR MM "Health Attitudes" OR MM "Health Behavior" OR MM "Health Care Utilization" OR MM "Health Education" OR MM "Health Knowledge" OR MM "Health Literacy" OR MM "Client Education" OR MM "Client Satisfaction" OR MM "Client Participation" OR MM "Client Attitudes" OR MM "Treatment Refusal")

AND

(MM "Osteoporosis") OR (MM "Bone Disorders")

Cinahl

(MM "Guideline Adherence") OR (MM "Medication Compliance") OR (MM "Patient Compliance") OR (MM "Compliance with Medication Regimen (Saba CCC)") OR (MM "Compliance with Therapeutic Regimen (Saba CCC)") OR (MM "Compliance with Medical Regimen (Saba CCC)") OR (MM "Patient Satisfaction") OR (MM "Attitude to Illness") OR (MM "Attitude to Medical Treatment") OR (MM "Attitude to Health") OR (MM "Patient Attitudes") OR (MM "Knowledge: Health Behaviors (Iowa NOC)") OR (MM "Knowledge") OR (MM "Health Knowledge") OR (MM "Acceptance and Commitment Therapy") OR (MM "Patient Dropouts")
AND
(MM "Osteoporosis")

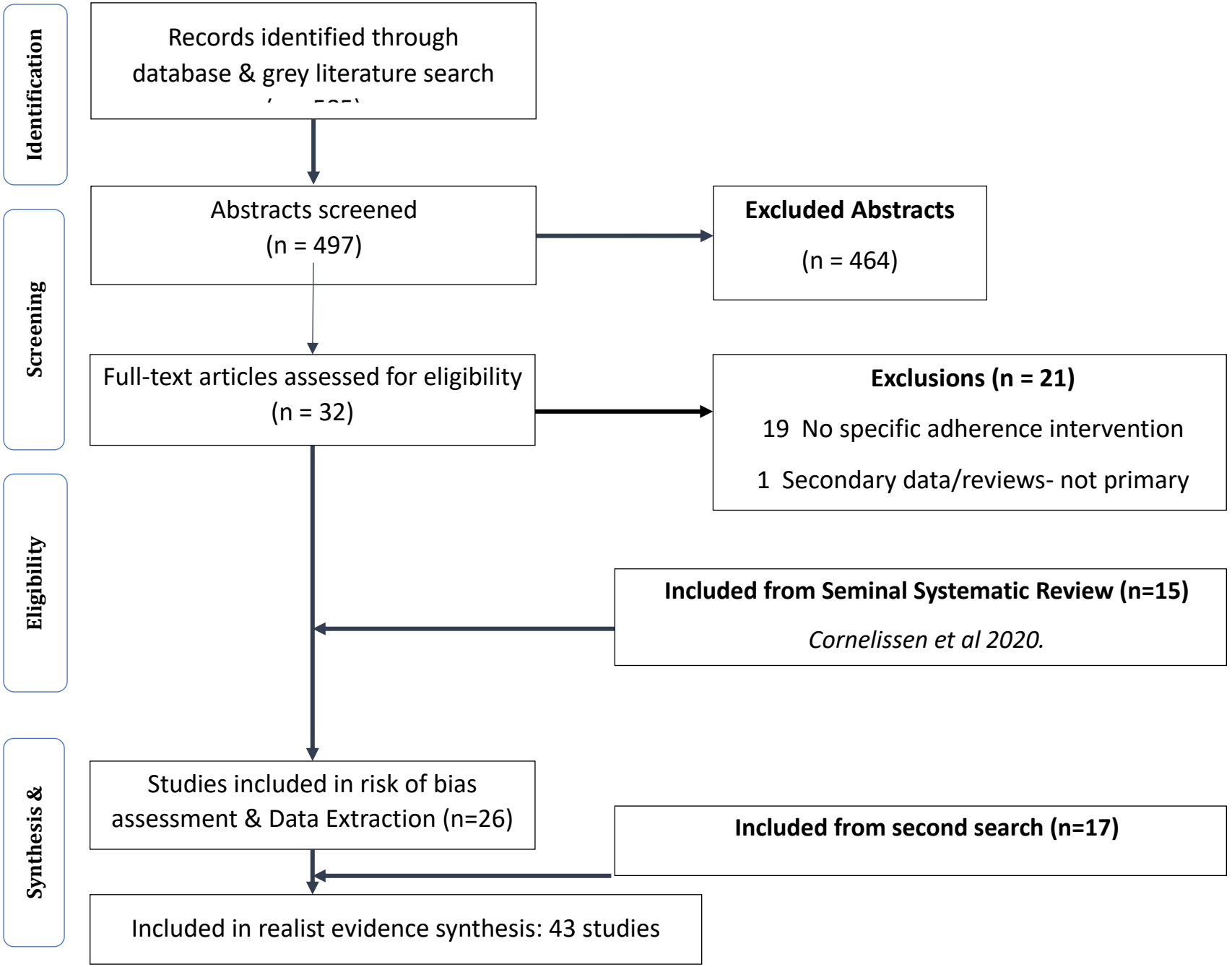
Supplementary Data 3: Data Extraction form headings

		Notes
Reviewer		
Study Characteristics		First Author /Year of publication
		Country (where study was conducted)
		Brief study aim(s)
		Study designs (NB: Drop downs)
		Study settings ***(NB: Drop downs***)
		Duration of follow up
		Total sample of participants if specified NB: Ok to estimate across studies .
		Additional notes / General comments on study/population characteristics
Medication support and adherence interventions. Use new row per intervention in the study.	**Intervention (brief name)**	Included type of management interventions (NB: only use one row for each type if the review presents separate analyses for different types)
Control/comparison intervention where relevant only		Examples: usual care / self-management / other active control
Context	**Individual**	Age/gender
		OP experience: Primary or Secondary prevention
		Illness beliefs/concerns or perceptions at baseline
		Factors that might impact understanding or adherence (health literacy; SES)
		Multi-morbidity/comorbidity/depression
	Patient-clinician	Nature of clinician –patient interactions (consider where, when, how often, what, who, how, tailoring)
	Healthcare setting	Primary vs secondary care setting and integration
		Resources/training/ support
Mechanism	**Treatment or illness beliefs**	
	Practical issues	
	Others	
OUTCOMES	**Patient - Individual**	Experience outcomes: Satisfaction
		Empowerment/enablement/self-efficacy
		Beliefs/illness perceptions/concerns
		Health outcomes – BMD/fracture/side effects
		Adherence initiation (when the patient takes the first dose of a prescribed medication)
		Adherence implementation (the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen, from initiation until the last dose)
		Adherence - discontinuation (when the patient stops taking the prescribed medication, for whatever reason(s)).
		Adherence - Persistence (length of time between initiation and the last dose, which immediately precedes discontinuation)
	Patient-clinician	Shared decision making

		Participation/involvement
	Healthcare setting	Costs
		Guideline adherence
		Referrals
Additional notes/ General comments/ Any other findings relevant to supporting patients for osteoporosis treatment?		
Further relevant papers		

Supplementary Data 4:

Primary and Secondary search findings



Supplementary Data 5: Details of secondary search

Paper from primary search or mechanism which prompted secondary search	Method of search	Number of articles screened	Identified new papers
Liu et al	Discussion with experts	1	Bagir et al
Parsons et al	References	29	Salter et al; Shepstone et al
Sagalla et al	Discussion with experts	1	Cizmic et al
	References	19	Nho et al
	Citation	0	
Stuurman bieze et al	Citation	55	Job et al Spence et al
Leblanc et al	References	19	Montori et al
	Citations	55	
Senay et al	References	44	Senay et al
Cram et al	Citations	23	Billington et al;
Van der berg et al	Citations	5	Hui et al
McAlister et al	Citations	13	Majumdar et al
Monitoring	Google scholar	20	Silverman et al; Fontalis et al; Delmas et al; Clowes et al
Burden	Google scholar	20	Iglay et al

Supplementary Table 1: Findings from included studies

First Author /Yr of publication	Brief study aim(s)	Medication support and adherence Intervention	Study findings/ comments
Beaton et al. 2017	to evaluate the impact of the implementation of the Fracture Clinic Screening Program on bone mineral density (BMD) testing, medication initiation, and medication persistence in the year after a fragility fracture.	Intervention A: several different reminders. Intervention B: same as group A, plus regular phone calls, and meetings.	Medication persistence declined from 59.9% pre-intervention to 56.4% postintervention and from 45.8% to 40.01% (at PDC50, PDC 80 respectively). NB: similar declines in control hospitals too. PDC is Proportion days covered. Effects of the intervention appeared to tailor off and didn't report how adherence could be effectively improved among possibly high-risk patients.
Bianchi et al. 2015	To evaluate efficacy of interventions for improving adherence and persistence through greater patient involvement, compared with standard clinical practice.	Tailored patient-activation BMD test result letter accompanied by a bone health brochure (postal mailed)	Starting women (adherence initiation) were 84.7 % of those prescribed a once-a-month drug, 65.4 % of those prescribed a once-a-week drug, and 75.4 % of those prescribed a once-a-day drug Full adherence (all doses taken) in only a minority of patients, 34.1 % (114/334) of the whole sample or 53 % (114/215) of the fully persistent women (drug taken for the whole period of 12 months). there were no significant differences in full adherence in the three groups. 88.7% of women who started were persistent (taking therapy for ≥10 months) but there was no statistically significant difference between intervention and control groups. Full persistence (taking therapy for 12 months) was observed in 215 women (87.0 % of starters). Additional interventions during the follow-up, including costly interventions such as phone calls and educational meetings, did not provide significant advantages.
Cram et al. 2016	To test if usual care augmented by a tailored patient-activation DXA result letter accompanied by an	Provision of detailed individual fracture risk at the point of initiation by physician.	There were no differences in adherence rates (75.1 % in the intervention group vs. 75.0 % in the usual care group at 12 weeks post-DXA) among those who reported having been prescribed osteoporosis medications based on their study DXA.

	educational brochure would improve guideline-concordant pharmacological treatment compared to usual care only.		
Danila et al. 2018	to improve rates of osteoporosis treatment among a high-risk population who previously reported a fracture but currently were not using osteoporosis therapies	SMA vs usual care. SMA included interaction with specialist, individual fracture risk info and education on fracture consequences	significantly lower proportion of participants in the pre-contemplative stage in the intervention compared to control group (860 [64.1%] vs. 923 [68.8%], OR=0.90 [0.82, 0.99]). at 18 months: 131 (11.5%) women in the intervention group and 136 (10.5%) women in the control group started osteoporosis medications (p=0.47). 157 (11.7%) and 153 (11.4%) women self-reported use of osteoporosis prescription medication in the intervention and control groups, respectively (p=0.83). In Intervention grp, 64.6% were considered adherent compared to (32.9%) in the control group. risk of discontinuation was 3.65-fold greater among patients who did not have the telephone follow-up (OR, 3.65; 95% CI, 1.92-6.92). {+ve] At 1 year follow-up, 57 out of 72 in intervention group were taking treatment (72.6%) compared to (50.6%) in the control group. no significant differences in rates of self-reported initiation of osteoporosis treatment, or BMD testing between groups at 6- and 18-months. NB: perception of a low personal susceptibility to future fracture, concordant with reluctance to acknowledge personal susceptibility to health problems.
Ducoulombier et al. 2015	to evaluate the contribution of phone follow-up to improve adherence to oral antiosteoporosis treatment among post-menopausal women presenting with	Fixed or flexible dosing regimen	reasons for discontinuation were: lack of motivation (n = 22), nonrenewal of prescription (n = 13), fear of potential adverse effects (n = 9), and multiple medications (n = 5).

	osteoporosis- related fractures.		
Ganda et al. 2014	to determine whether management by a secondary fracture prevention (SFP) program results in better compliance and persistence to OP medication than follow-up by the primary care physician, after initiation within an SFP program.	MIN intervention- education of patient on osteoporosis, BMD, fractures, treatment and encouraged to discuss with doctor. Doctor provided with suggested investigation and empirical treatment, reminders. INT intervention same as MIN with addition of blood test for patients, BMD treatments. Doctor sent results and individual advice to doctors more frequent follow up	compared to control (−2.8 vs. −1.6 nmol/mmol cr, p=0.04), neither persistence nor compliance was associated with change in uDPD/cr after adjusting for patient group, baseline uDPD/cr, co-morbidity count and BMI. {nil} 49% (22/45) and 47% (23/49) of patients were compliant in intervention and control groups respectively (p=0.85). When analysed by 6-monthly intervals, MPR was similar at all time points across 24months. Patients in intervention group were not more likely to have an MPR≥0.80 than those in control group. patients in intervention group were not more likely to have a longer time to non-persistence than those in control group. HR 0.90 (0.47–1.76) vs 0.83 (0.42–1.67) @24 months for intervention and control groups respectively. Persistence over 24 months was not significantly different between the two study groups. At the 2-year time point, persistence was 64 % in intervention group vs. 61 % in control group (p=0.75). There was no correlation between compliance and persistence as assessed by pharmaceutical claims data and self-reported compliance. Majority of patients reported excellent compliance to their medications (i.e., “never missing”). However, 84-85 % of participants with an MPR <0.8 (classified as non-compliant/non-persistent reported “never missing” their medications.
Gonnelli et al. 2016	(1) Analyse persistence and compliance with oral OP meds and (2) evaluate whether individualised information on fracture risk improves compliance and adherence	text message reminder weekly to take AOM	Older age, males, smoking, co-morbidities and obesity were associated with lower adherence Daily treatment resulted in lower adherence
Hitz 2021	(1) to compare treatment by GPs Vs OP	education intervention by nurses on BMD results, calcium and	Study did not demonstrate statistical significance for compliance and persistence

	specialists on adherence to OP meds	vit d, NOF brochures written, BMD scan and one follow up at 12 months	
LeBlanc et al. 2016	Analyse effects of the osteoporosis choice decision aid compared to usual care with and without FRAX risk calculator on knowledge, involvement in decision making process, initiation and adherence to oral bisphosphonates (OB).	patients on oral glucocorticoids and weekly alendronate 35 mg or risedronate 17.5 mg were randomly assigned either to switch to minodronate 50 mg every 4 weeks or to continue the currently taking weekly bisphosphonate for 52 weeks after a 24-week run-in period	Higher proportion initiated medicines in the GP group (69.2% V 65.6%). However, specialist were more likley to prescribed meds other than OB Odds of adherence to OB 1.7 higher in GP setting than specialist Longer term adherence at 12 and 24 months did not differ between populations. Nb: Fracture risk higher in GP group for patients over 70 years HRGPP/SP = 1.76, 95% CI 1.14–2.73, p = 0.01. BUT lower in patients 60-70 years (HRGPP/SP = 0.44, 95% CI 0.23–0.84, p = 0.01) Improved patient knowledge and satisfaction, but no evidence of improved short/long term adherence to Obs
Leslie 2019	Comparison of regular BMD monitoring on adherence and fracture outcomes		Satisfaction high in both arms, higher with the DA but not stat significant Improved patient knowledge with DA No difference between arms Increased BMD monitoring can reduce both fracture risk and adherence to medicine, particularly longer-term adherence.
Liu 2021	Comparison of SMA Vs usual care in decision to initiate treatment	Education with targeted communication with patient and providers	BMD monitoring reduced fracture risk Adherence was higher in BMD monitoring group. Stat significant but higher in years 3-5 SMAs represent a time effective means of delivering medical care and in an OP context do not negatively influence treatment initiation decisions…. No evidence of follow up SMA benefits
Makras 2020	Participation rates in FLS in Greece following fracture.	regular telephone follow-up	No difference between arms

			Poorly described study, difficult to draw any conclusions other than FLS engagement in Greece is poor compared to other settings and may be due to many localised factors
McAlister 2019	Compare patient/physician educational intervention Vs nurse led case manager	specialist management/follow-up after treatment initiation	Significantly more initiated treatment in the control (Nurse) arm compared to intervention (28% vs 48%) No stat difference in adherence and persistence between groups but higher persistence rates in intervention arm at 24 months. Case manager resulted in initially higher uptake of treatment, but long-term adherence is similar between groups. The case manager group were not followed up after 12 months which perhaps shows decline in adherence compared to intervention arm where patients were followed until year 2.
Oral et al. 2015	examine the compliance, persistence and preference between a fixed or flexible dosing regimen of daily risedronate in patients with postmenopausal OP	Participation in FLS	patient preference flexible dosing persistence better with flexible dosing, no difference in compliance, no difference in NTX in both groups. Other findings in fixed dosing preference for bedtimie regimen, suspect that providing NTX monitoring doesn't improve persistency/compliance
Parsons 2020	Investigated effect of screening intervention (FRAX) on osteoporosis meds adherence	Patient education on OP	FRAX screening also increase initiation of AOM Of those participants identified at high fracture risk in the screening group, 38.2% of those on treatment at 6 months were still treated at 60 months; whereas the corresponding figure for the control group was 21.6%. Older age was associated with poorer adherence [OR per year increase in age 0.96 (95%CI: 0.93, 0.99), p=0.01], whereas history of parental hip fracture was associated with greater rates adherence [OR 1.67 (95%CI: 1.23, 2.26), p<0.01].
Roux et al. 2013	Evaluate 2 types of education intervention designed to increase initiation of treatment	bone health evaluation, med history, blood test, BMD by FLS	Among patients who initially were untreated, 18.8% in the SC group, 40.4% in the MIN, and 53.2% in the INT groups were treated at 12 months. Change in treatment rates (adjusted for age and initial treatment) increased significantly after both MIN and INT 90% of patients treated at inclusion remained treated at 12 months. Nb: provides some evidence communication between patient, 1st and 2nd, non-specialised follow up, shared decision making, education can help increase and maintain osteoporosis treatment.

Sagalla 2021	To evaluate the extent of and reasons for non-adherence to oral bisphosphonates among veterans and to assess the acceptability and feasibility of a pilot text message reminder application.	patient identified, investigated, initiated therapy, longitudinal and systematic follow up 3,6,12,18,24 months	misconception of disease and treatment reasons for poor adherence, reminders possibly help. misconception they felt well, forgetting to take meds, bones not weak, worried of taking them forever, side effects, inconvenient to take, ran out of meds, busy, expensive, interacting with other meds, with friends and family, veterans said reminder system did very well
ScholtenDJ 2020	To assess the effects of implementation of a fracture liaison service at a tertiary care academic medical centre on osteoporosis treatment adherence and secondary fracture rates.	phone calls	Of the 1840 patients who were initially prescribed medication, 1416 (76.96%) initiated their treatment, and Fifteen patients (1.05%) on treatment sustained a secondary fracture after initiation of therapy. 1156 (81.64%) remained adherent to treatment. follow up with physicians helps initiation and initiation
Senay 2019	aimed to assess patterns of drug use in a high-level intervention FLS.	behavioural using patient activation approaches	Out of 332 subjects with complete drug insurance coverage, 297 (89.5%) were prescribed osteoporosis therapy by the FLS, and 275 (92.6%) were dispensed. Two hundred sixty participants (86.9% female; mean age 65.6 years) were selected for having filled a prescription inside 3 months after baseline. The 1- and 2-year persistence rates were 66.4% and 55.6%, respectively. Treatment re-initiation was observed in 56%of non-persistent patients. PDC was > 80%in 64.2%for 1 year and 62.5%for 2 years. Follow-up in this case was less successful.
Seuffert et al. 2016	assess whether education and referral by a nurse practitioner could improve treatment adherence in	GP care not well defined and individual variation documented. In specialist setting patients had a compliance visit or	Significantly more patients began calcium and vitamin D after education (p= 0.04); significantly more patients were taking or were recommended for an active treatment after education (p = 0.03) Approximately 50 % of patients with osteoporosis were not taking an FDA-approved pharmacologic agent for osteoporosis treatment, despite education

	patients with low bone mineral density.	phone call…not explained clearly when this happened.	Thirty percent of patients neither did not follow up or refused active treatment for osteoporosis. Didn't empower patient about medication. Not very successful. Follow up was also to collect outcome rather than to empower patients. Study highlights need to address negative attitude towards meds
Stuurman-Bieze et al. 2014	provide proactive pharmaceutical care	osteoporosis Choice decision aid	27.8 % usual care patients discontinued therapy, compared to 78 (15.8 %) patients in the intervention group (P<0.001). About 93 % of the respondents were (very) satisfied with the pharmacies' services that were provided. NB: adherence didn't change but discontinuation did – maybe explained by a large proportion stopped the drug legitimately because of steroids
Tamechika et al. 2018	To compare the usefulness and efficacy of monthly minodronate and weekly alendronate or risedronate for GIOP	Regular BMD monitoring	Adherence rates to bisphosphonate therapies weeks 48, and 76 were 99.8, and 99.4%, respectively, in the switching group and 99.4, and 99.5%, respectively, in the continuing group. No significant differences were observed between the two groups. Patients' satisfaction higher for Monthly minodronate compared to weekly alendronate or risedronate.
Tüzün et al. 2013	to assess the impact of active patient training on treatment compliance and persistence in patients with postmenopausal osteoporosis.	FRAX screening	Most satisfied with treatment' (63-75%) Adherence -no different between groups Forgetfulness described as main reason for missing medication. Authors suggests monitoring (regular follow up) may have masked effect on adherence.
van den Berg et al. 2018	Compare the effect of phone calls vs no phone calls on adherence	counselling of administration, effectiveness and side effects, incudes addressing concerns, at start 2 weeks and ad hoc if non adherent	More patients in intervention arm identified with GI side effects. BTMs correlated with adherence data about 75% both arms Adherence >75% is higher than in 'real-world'. Suggestions that the effect of being in trial itself (follow up, blood tests) promotes adherence.
vanMaren 2019	effect of educational and motivational support programme on adherence	Education - 'active training' including attendance at group education meetings and 4 telephone calls. During the	78.4 vs 71.5% persistent at 2 years NB: Baseline adherence high. Authors conjecture that that patient selection, full reimbursement of the medication and an organised follow-up system attribute to treatment persistence. Important

		telephone calls, patients were reminded to read the booklets, informed of the topic to be covered in the next educational meeting	imitation of this study is not reporting the outcomes in the people who received the additional visits (42 additional home visits or calls) to confirm if this was the mechanism for the differences observed.
Wilton-Clark 2020	evaluating the impact of autonomous treatment decisions after group consultations on adherence	assessment of motivation to continue using 'adherence tool' and then targetted additional phone call or home visit if problems with knowledge or motivation identified	75 (74.2%) participants indicate that they felt confident in their treatment intent. Of 94 participants who responded to a 3-month questionnaire, 80 (85.1%) reported being confident in their final treatment decision, and 85/89 (95.5%) respondents reported confidence at 12 months ($p < 0.0001$ for trend) 21/23 intending to take treatment at 3 months remained persistent. Nb: People with priori fracture and high fracture risk more likely to intend and persist. Small numbers

Supplementary Table 2: C-M-O configurations and summary of underpinning evidence

Context, Mechanisms and outcomes	Supporting Evidence from included papers
When a person with osteoporosis is identifying the problem – Step 1 (C) interventions **to support patient-informed decision making (M)** lead to Increases in patient knowledge, understanding of fracture risk, patient participation in consultations, increased intentions to change behaviour (O)	*Decision aids:* Use of Osteoporosis Choice (decision aid) compared to using FRAX (fracture risk assessment) increased patient knowledge (median score 6 vs. 4, p = .01), improved understanding of fracture risk and risk reduction with bisphosphonates (p = .01 and p<.0001, respectively), had no effect on decision conflict, and increased patient engagement in the decision making process (OPTION scores 57% vs. 43%, p = .001) but no difference in adherence was seen at 6 months. Initiation rates showed a tendency to be increased in the decision aid arm but numbers were small (10 (83%) vs. 4(40%), p = .07. [42] *Mailed brochures and educational materials:* A 'patient activation letter' which contained the patient's DXA result, their 10-year risk of a major osteoporotic fracture, description of osteoporosis, and five steps to better bone health (although did not explicitly discuss medicines), did not result in any difference in the proportion of patients on treatment at 12 or 52 weeks compared with usual care (n=7749). Possibly not successful as content of the letter were not directly related to actions which the patient can take to improve adherence.[23] A direct-to-patient personalised educational intervention which comprised a video (online or postal DVD) that provided general osteoporosis information, and included video vignettes from patients real life experiences, positively influenced participants' readiness for behaviour change at 6-months, but no difference was seen in self-reported use of osteoporosis prescription medication in the intervention and control groups, respectively (p=0.83) at 18 months or other outcomes including starting calcium; starting vitamin D; and BMD testing (n=2684).[40] *Factors informing evaluation of personal susceptibility to fracture:* In a small observational study, women who attended a group medical consultation for bone health with an emphasis on autonomous decision making were 'truly prepared to implement' with 90% persisting with medicine at 12 months, without any clinical follow up.[32] Participants were support to calculate FRAX themselves, thereby understanding their personal risk factors and guided through personal reflection exercises on perception of risk The SCOOP trial which investigated primary screening using FRAX showed a clear increase in treatment uptake in the treatment arm, but the intervention included bone density scans in 45% of those in the intervention arm.[44] Participants who had a DXA scan or a family history were more likely to adhere. A linked qualitative study reported patients to frequently question their fracture risk, and although women were observed to move from 'questionning' to 'accepting' they still became non-adherent, and others reported 'significant confusion about the nature and importance of risk'.[50] Senay et al examined predictors of persistence in their observational study within Fracture Liaison Services. Osteoporotic spine BMD predicted compliance: with an osteoporotic spine BMD [Tscore < − 2.5, aOR = 0.39, 95% CI (0.15–0.98)].[38]
When a primary care clinician is making diagnosis and/or giving treatment recommendations – Step 2 (C) interventions **to support clinician decision making (M)** lead to Increased rates of investigation,	*Treatment recommendations to primary care practitioners:* Practitioner coordinator to enact case identification, provision of recommendations to patients, and primary care providers about osteoporosis and suggested investigations and interventions was successful in a minor increase in investigations requested (20.9 vs 17.0%) and initiation rates (24.0% vs 21.6%).[32] In a three arm RCT by Roux et al. two interventions were compared which supported both patient and clinician. PCP support in the minimal intervention arm consisted of a letter making recommendations about treatment and investigations and reminder letters at 6 months if the patient was untreated and in the intensive intervention arm, PCPs also received individualized counselling in writing

treatment initiation and treatment persistence (O)	and direct team access for advice and guidance. Both interventions increased initiation – the intensive intervention tripled the number of treated patients and led to significantly more treated patients that the more minimal intervention at 12 months (53.2% vs 40.4%, $p < 0.05$).[27] In the SCOOP trial, participants in the intervention arm had a fracture risk score calculated, bone density scan as appropriate and treatment recommendation to the PCP – meaning that identification, investigation and treatment recommendations were enacted by the study team.[44,50] This intervention led to an increase in initiation and adherence at 60 months (high risk patients - 75.8% vs 2.0% at 6 months and 34.9% self-reported adherence compared with 21.6% at 60 months).
When a person with osteoporosis is starting medication – Step 3 (C) interventions **to reduce treatment burden and patient workload (M)** lead to Increased initiation rates(O)	Automated phone calls targeted at non-starters were effective in increasing initiation in a RCT and potentially increasing adherence over a short term 6-month period (62/127, 48.8 % initiated in intervention vs 36/118, 30.5 %) with a suggestion that this intervention also increased adherence over a short term 6-month period. (69 % (95 % CI 61–77) versus 60 % (95 % CI 49–71). This intervention was also designed to remind and increase motivation.[52] FLSs where the first prescriptions were issued directly meaning the patient did not have to visit their Primary Care Provider (PCP) – and found these were associated with increased likelihood of initiating treatment within 3 months.[38]
When a person with osteoporosis is starting medication – Step 3 (C) interventions **to support patient-informed decision making (M)** lead to increased adherence (persistence) (O)	In a RCT of a FLS intervention, authors noted a small selection of patients who had an appointment early with primary care (i.e. 3 months) after treatment initiation tended to have improved compliance over 24 months.[34] Among new users of osteoporosis medicines, those receiving an additional pharmacy appointment offered to new starters, compared to usual care were significantly more likely to be medication adherent at 6 months compared to the usual care group (OR = 1.23; 95% CI 1.05 – 1.44; p =0.012).[54] The appointment included: 1) benefits of treatment to prevent fractures and improve bone strength, 2) proper use of prescribed medications and importance of adherence, 3) the need to refill the prescription in a timely manner before running out, 4) importance of daily intake of calcium and vitamin D, including a proper diet, 5) benefit of regular weight-bearing and muscle-building exercise, 6) smoking cessation, and 7) home hazard proofing to minimize fracture risks 8) eliciting and addressing potential common barriers and signposting on to further support as needed.
When a person with osteoporosis is continuing medication – Step 4 (C) interventions **to support patient-informed decision making (M)** lead to increase adherence (persistence) (O)	*Follow up appointments to reiterate importance and address barriers:* Nurses who conducted additional telephone calls and home visits with patients who expressed doubts about their treatment, with the aim of improving knowledge and reinforcing the importance of treatment resulted in increased persistence to teriparatide injections.[47] Medical secretaries called intervention grp patients every 2 months (~10minutes). Subject of the call was to: i) motivate patients to maintain good adherence to treatment, ii) detect any difficulties in compliance with the prescription, iii) recall importance of continuing treatment as prescribed, rather than just assessing adherence alone. If poor adherence was detected, the secretary encouraged the patient to consult her primary care physician. Risk of discontinuation was 3.65-fold greater among patients who did not have the telephone follow-up (OR, 3.65; 95% CI, 1.92-6.92).[33] Ad hoc 'proactive pharmaceutical care' targeted to those who were not filling prescriptions, involved consultations to explore patients' experiences, fears and drug administration problems and resulted in reduced discontinuation rates.[45] *Treatment monitoring approaches:* Monitoring Bone Density scans: Monitored women had significantly better fracture-free survival for major osteoporotic fracture ($p = 0.040$; 10-year cumulative risk 1.9% lower, 95% confidence interval [CI] 0.3–3.6%) and hip fracture ($p = 0.001$; 10-year cumulative risk 1.8% lower, 95% CI 0.7–2.8%) compared with women who were not monitored. Hazard ratios (HRs) were significantly lower in monitored versus not monitored women for major osteoporotic fracture (HR = 0.89, 95% CI

	0.80–0.98) and hip fracture (HR = 0.74, 95% CI 0.63–0.87). Days of medication use, medication persistence ratio, and treatment switching over 5 years were greater in monitored versus not monitored women.[43] A randomised trial comparing the reporting of bone turnover marker results, education about osteoporosis, or a combination of both on persistence rates found no significant effect, although 29% of women said the bone turnover markers influenced their decision making, and the authors suggested the study may have been underpowered due to large numbers of patients discontinuing treatment before the bone turnover markers could be measured.[57]
When a person with osteoporosis is continuing medication – Step 4 (C) interventions **to support routinisation and memory (M)** lead to increased patient satisfaction (O)	*Follow up phone calls to remind:* Regular telephone calls to remind people to read educational materials and invite them to educational meetings did not affect persistence.[46] *Reminder materials:* A package of resources including education booklets, memo stickers (for calendars) and alarm clocks increased initiation rates but not persistence over 12 months in a 3 arm RCT of 334 patients.[22] *Text message reminders:* 12/29 patients declined text message reminders. Of 12 who accepted, 10 completed a survey. 9/10 reported that the text message reminders (a once weekly customisable automated text message reminder to take their oral bisphosphonate) did "very well" at reminding them to take their medication and would recommend the application to other patients/family/friends. The effect on persistence was not reported.[28]
When a person with osteoporosis is continuing medication – Step 4 (C) interventions **to reduce treatment burden and patient workload (M)** lead to increase rates of medicine persistence (O)	*Medication frequency* The proportion of people taking daily medication (vs weekly) was higher in patients with low therapeutic persistence with respect to those with better persistence (27.4 vs. 13.2%; p \ 0.001).[24]
When a clinician is reviewing medication – Step 5 (C) interventions **to support clinician decision making (M)** lead to increased identification of side effects increased rates of decisions to stop or switch medicines (O)	In a randomised trial in a FLS setting, regular phone calls with the aim of reminding patients about medicine and sharing experience about side effects did not increase adherence but did result in more patients in the intervention arm having their treatment appropriately stopped because of side effects.[39] Stuurman- Bieze et al studied a model of 'proactive pharmaceutical care' which resulted in more patients in the intervention arm being identified as having stopped glucocorticoids (57/495 vs 13/442), resulting in appropriate discontinuation of osteoporosis therapy.[45]
When a clinician is reviewing medication – Step 5 (C) interventions **to offer targeted support (M)** lead to reduced rates of treatment discontinuation lower healthcare costs improved adherence (O)	Ad hoc 'proactive pharmaceutical care' targeted to those who were not filling prescriptions, involved consultations to explore patients' experiences, fears and drug administration problems and resulted in reduced discontinuation rates. [46] In this MeMO study employed a process whereby patients' therapy adherence was monitored on a monthly basis, using standardized search algorithms in the pharmacy database. When the algorithm detected a patient's discontinuation of therapy, tailored interventions were offered to improve adherence and optimize pharmacotherapy. In a secondary care-based study, Van Maren et al used an 'adherence scoring tool' which was a questionnaire administered to patients, asking if treatment had been omitted, if people had 'lost interest' in their treatment and if people were clear on the benefits. Those who had indicated non-adherence or doubts were selected for home visits by nurses. In both studies, the intervention involved a clinician-patient consultation to explore problems, reiterate treatment importance.[47]

	Self report as a means to identify patients for targeted interventions The majority of patients reported excellent compliance to their medications (i.e. “never missing”); However, 84-85 % of participants with an MPR <0.8 (classified as non-compliant/non-persistent reported “never missing” their medications. [34]
When a clinician is reviewing medication – Step 5 (C) interventions **to offer integrated sustainable support (M)** lead to Improved adherence (O)	Before-after study evaluating the effect of implementation of a Fracture Clinic Screening programme which involved case identification, provision of recommendations to patients, and primary care providers about osteoporosis and suggested investigations and interventions was successful in a minor increase in investigations requested (20.9 vs 17.0%) and initiation rates (24.0% vs 21.6%) but did not impact persistence at one year; the authors themselves conclude that ‘much of the OP-related action needs to be taken by the PCP and the patients themselves’ inferring that the model of care placed increased workload on the patient and PCP which might have explained why it was not successful in impacting long-term outcomes. [32] Makras et al who reported an evaluation of FLS in Greece reported that when the PCP is involved in the FLS structure, patients were more likely to engage with follow up and receive anti-osteoporotic treatment.[35] One study which aimed to follow up those discharged from FLS, with self-reported adherence being high (74%) in those contacted 12 months after discharge. However, despite FLS providing a primary care management plan on discharge, one third of patients contacted after discharge from FLS required bone health advice who had not managed to source this from their PCP.[60]