SIGN Osteoporosis Consultation v.7

COMMENTS RECEIVED FROM EXTERNAL REFEREES AND OTHERS

All reviewers submitted declarations of interests which were viewed prior to the addressing of comments.

Invited reviewers			**Type of response and declared interests**
AG	Dr Andrew Gallagher	Consultant Endocrinologist, Honorary Clinical Associate Professor, Queen Elizabeth University Hospital, Glasgow	*Individual response.* Nothing declared.
EB	Professor Eamonn Brankin	Clinical Director, Primary Care, NHS Lanarkshire	*Individual response.* Shares and securities - I hold a small number of shares in Stirling Anglian Pharmaceuticals. Also I believe, in GSK and possibly Pfizer as part of a managed investment portfolio on the Fidelity Investment platform. As this is a diversified portfolio managed by fund managers I do not have details of these individual shareholdings. Remuneration for consultancy - Unrestricted educational grant of £602.73($750) from Kyowa Kirin Ltd on 13/07/18 to my research fund to help with costs of attending the ASBMR annual scientific meeting in Sept 18.
JH	Dr John Harvie	Consultant Rheumatologist, NHS Highland, Inverness	*Individual response.* Nothing declared.
PS	Professor Peter Selby	Consultant Physician and Professor of Metabolic Bone Disease, Manchester Royal Infirmary, Manchester	*Individual response.* Remuneration as holder of paid office - Vice Chair NICE technology appraisal committee Remuneration as a partner in a firm - Manchester Royal Infirmary Oxford Road

			Non-financial interests - Clinical and Scientific Fellow Royal Osteoporosis Society Non-personal support from commercial healthcare companies - Manchester Royal Infirmary Oxford Road
Open consultation			**Type of response and declared interests**
AC	Dr Andrew Colman	Physician, Computer Scientist and Honorary Research Associate, Institute of Cellular Medicine, Faculty of Medical Sciences, Newcastle University, Newcastle	*Individual response.* Nothing declared.
KF	Mrs Karen Forteza	Osteoporosis Specialist Nurse, NHS Fife	*Individual response.* Nothing declared.
RCPE		Dr Scott Jamieson, Executive Officer (Quality Improvement) commenting on behalf of Royal College of General Practitioners Scotland	*Group response.* Nature and purpose of your group or organisation - Professional group representing GPs in Scotland. How might statements and recommendations in the draft SIGN guideline impact on your organisation's functions/status productivity? - Change of clinical practice for GPs.
ROS		Alison Doyle, Head of Operations and Clinical Practice commenting on behalf of Royal Osteoporosis Society	*Group response.* Nature and purpose of your group or organisation – charity – Voluntary Organisation. How might statements and recommendations in the draft SIGN guideline impact on your organisation's functions/status productivity? - "Draft recommendations in this SIGN guideline will

			have no discernible impact on the function or productivity of our organisation.”
SB	Mrs Sandra Brown	Edinburgh	*Individual response.* Nothing declared.
SMC		Christine Hepburn, Principal Pharmaceutical Analyst, Scottish Medicine Consortium	*Group response.* Nature and purpose of your group or organisation – Heath technology assessment. How might statements and recommendations in the draft SIGN guideline impact on your organisation’s functions/status productivity? – SMC and SIGN advice should align.

Section	Comments received		Development group response
General	AC	Dear Guideline Group I am providing feedback solely on the revised version of the clinical flow chart, Figure 3 (*https://www.sign.ac.uk/assets/sign-142-update-fig-3-peer-review.pdf*) of the SIGN 142 Guideline Pathway "From risk factors to pharmacological treatment selection in postmenopausal women". (This feedback should be read in conjunction with two, illustrated pdf files, AWC_August_2019_Flow_chart_1 and AWC_August_2019_Flow_chart_2, I have emailed to your office. These are best appreciated printed in colour.) My comments are on the logic of the data flow and decision-making in this algorithm. I have not altered its information content, just the data arrangement. Introduction Since 1973 there has been an industry-standard for flowchart symbols developed by the British Standards Institute (BSI), namely BSI 4058: 1973, revision 1978 [1]. Although such symbols are widely used in engineering design and technology, they are still not used very much in medicine at present. These BSI flowchart symbols are now covered by the GCSE Computer Science curriculum and are illustrated in this BBC revision aid [2]. The most important take-home message regarding the design of clinical algorithms is that decisions should be displayed in diamond or hexagon-shaped boxes and processes (doing something) and statements which are not questions, in rectangular boxes.	Thank you, this advice was very helpful. The algorithm has been updated, taking these points and suggestions into account.

		I have identified over twenty different types of logic error in published medical papers covering most specialties that could put patient safety at risk [3]. There are several points relating to the original flow chart I have annotated in Chart_1.pdf and presented below. 1. The two dotted vertical, dotted lines with arrows pointing downwards and accompanied by the caption “DEXA unavailable or not feasible” on the middle, left-hand side of the flow chart are not standard flow chart notation and are open to misinterpretation. One of the worst clinical flow charts I have ever seen had five different styles of data flow arrows. This problem is addressed by incorporating this logic in the flow chart as illustrated by the light-blue hexagonal decision boxes of the revised flow chart in Chart_2.pdf 2. The “10 year hip fracture risk > 5%” is in the wrong place in the flow chart. It does not belong to the T-score results interpretation section of the flow chart as it is a different Data Entity Type. See part 2.3 of my 2014 paper on Data Entity Types for a detailed explanation [3]. The above logic and the logic below is presented in the yellow text and hexagonal boxes of the revised flow chart in Chart_2.pdf “In the USA, the National Osteoporosis Foundation (NOF) recommend that treatment should be initiated for any patient with DXA-proven osteoporosis or for patients with osteopenia (T-score between -1.0 and -2.5) with a 10-year fracture risk of 20% or greater.” 3. In the bottom, left-hand corner of the revised flow chart (Chart_2.pdf), I have presented more detailed information of medical decision making regarding the particular drug selected for treatment. May I suggest that each anti-osteoporosis drug could be accompanied by a	The purpose of the algorithm is to provide an overview of how each drug fits into the treatment pathway. A separate pathway on use of each drug would be too detailed for the guideline.

		short flow chart on its use and possible progression to other drugs in the pharmacological line-up. Medics have a habit of including masses of footnotes at the bottom of a flow chart when this information should be included in the flow chart itself. Relevant to this clinical topic are two e-letters I have had recently published in the BMJ about clinical flow charts that do not make sense [4.5]. Producing a satisfactory clinical algorithm is not easy and is a matter of balancing design aesthetics with logically correct decision-making to keep patients and doctors safe. Clinical flow charts I am currently working on and their "correct" versions are published on my website :- Tracheostomy Flow Chart *http://www.acolman.co.uk/nonsense_flow_charts/chart_1.pdf* (accessed August 2019) The revised Opioid Chronic Pain Flow Chart for SIGN 136 I have recently submitted and not heard about yet. *http://www.acolman.co.uk/nonsense_flow_charts/chart_2.pdf* (accessed August 2019) Provenance of my scientific and technical expertise in this field As well as being medically qualified, I hold a research MSc and PhD in Information Systems Engineering from the University of Manchester's Institute of Science and Technology (UMIST) in the field of computer-assisted instruction which I undertook through a SERC (Science and Engineering Research Council) Scholarship. For the last 25 years I have had a	

research interest in identifying and classifying logic errors in clinical flowcharts published in the medical literature [3].

Five years ago I discovered several major logic errors in Public Health England's (PHE) algorithm for the Clinical Management of Ebola Fever. I contacted PHE through the UK Government e-portal and the algorithm was immediately changed.

References

[1] BS 4058:1973 - Specification for data processing flow chart symbols ...

https://shop.bsigroup.com/ProductDetail/?pid=000000000010077532 (accessed August 2019)

[2] Introducing algorithms - Revision 5 - GCSE Computer Science - BBC Bitesize

https://www.bbc.com/bitesize/guides/z22wwmn/revision/5

(accessed August 2019)

[3] Colman A, Richards B.

Clinical Algorithms: purpose, content, rules, and benefits. International Journal on Biomedicine and Healthcare. 2014 (2), 28 –40.

http://www.ijbh.org/ijbh2014-2.pdf

(accessed August 2019)

This paper is also available from my website to avoid downloading the whole IJBH Journal Volume.

http://www.acolman.co.uk/my_clinical_flow_chart_paper/ijbh2014_awc.pdf (accessed August 2019)

[4] Colman A.

The two "No" responses to the

		"Treatable cause identified?" question in the thrombocytosis diagnostic algorithm figure are ambiguous. *British Medical Journal [eLetter], 11 July 2019.* *https://www.bmj.com/content/366/bmj.l4183/rr-2* *(accessed August 2019)* *[5] Colman A.* *Some questions in the patient algorithm on adverse drug reactions (ADRs) use inconsistent binary logic as four of them lack "No" responses. [e-letter]* *British Medical Journal [eLetter], 23 July 2019.* *https://www.bmj.com/content/363/bmj.k4051/rr-1* *(accessed August 2019)* Kind regards Yours faithfully Andrew Colman Newcastle upon Tyne UK. August 10th 2019	
3.4.6	AG	A sensible analysis of the latest data regarding HIV as increasing the risk of fracture. A timely inclusion with the accruing evidence.	*Thank you.*
	RCGP	I think we must be very careful in 3.4.6's recommendation. In this meta-analysis there were only 131 people in entire study from the UK on cART therapy (all from 1 cross sectional study using self-reporting https://doi.org/10.1177%2F0956462413492714) Given the treatment quality of HIV across the world and those affected varies so massively we cannot say with the confidence we are that in a UK population the problem is of a significant magnetite, nor if we should be actively doing anything about it. This is an ideal study for the CPRD	*The purpose of this recommendation is to raise awareness of a potential risk factor. The recommendation is only that it should be considered as a an additional risk, and 'particularly where other risk fractures are present'.*

		network to look at real life UK wide data to try to correlate. I fear in this recommendation we might be going beyond where the evidence actually holds for a UK population under treatment. We must be clearer on the caveats and limits of the evidence.	
	SB	Usually before SIGN documents are put on websites someone takes the trouble to proof the content. Why has this not happened on this occasion for the whole document and not just this question? The figures throughout the document need to be double checked as well. A number of references are also wrong! I don't see why you are relying on individuals to point out basic mistakes when this should of been picked up at the start. I'm embarrassed for the organisation here.	*This is a draft document. Prior to full publication it will go through editorial and the final version will be checked and proofed.* *The figures and references have been checked. The confusion here may be that some of the references cited are in the original version of SIGN 142, into which this revision will be incorporated. This will be clear in the published guideline.*
	JH	No comments to make	*No action required.*
	EB	This is perhaps taken out of context in what I was sent but paragraph 2 refers to HR, which I assume refers to hazards ratio, but is not explicitly detailed before.	*The first use of hazard ratio is in section 3.2.3 and this new section will replace section 3.4.6 in SIGN 142.*
	PS	There is a lack of clarity regarding what is the result of HIV infection and what is a consequence of ART and how these might influence treatment decisions. Any discussion of osteoporosis in patient with HRT should not be undertaken without clear signposting of other issues such as ART induced hypophosphataemia which can masquerade as osteoporosis and needs to be considered before a diagnosis of osteoporosis is made.	*There is insufficient evidence available to tease this out, and this discussed in the evidence statement.* *There was nothing in the studies re hypophosphatemia.* *This is too detailed for inclusion and may detract from the main message. If hypophosphatemia is seen in clinics it is dealt with so it is unlikely to have an impact.*
5.1	AG	Nothing new. Had no problems with the text first time round and likewise now.	*Thank you*
	RCGP	"Drug therapy should only be offered to patients who are likely to benefit from any intervention". What do we mean by this? It's not really true is it? I like the word offered but we must be very clear these are population level drugs. An individual patient is	*This has been removed and an additional paragraph around discussion with patients on treatment options, risks and benefits, has been included.*

		unlikely to benefit no matter how high their risk. We need to give it to lots of people for 1 to benefit. I don't get a sense of realistic medicine/shared decision making here. QFracture risk of 30%, only 135/1000 have a radiologically detected vertebral fracture and 100 will not get a hip fracture as a result of bisphosphonates. The majority by far don't benefit even in the highest risk so we cannot really say a person is likely to benefit. That sadly is unlikely.	
	SB	Hard to follow and seems confused.	*Further text has been added to clarify and in response to comments from RCGP.*
	ROS	It is disappointing that treatment in men is not given greater emphasis, in line with treatment licences.	*A cross-reference to section 7.3 (pharmacological management of osteoporosis in men) has been added to section 5.7*
	PS	No comment	*No action required*
5.2	AG	Happy with the conclusion regarding the need for both fracture risk assessment and BMD being required.	*Thank you*
	RCGP	I really like this recommendation. Absolutely. Too often I still see BMD alone being taken as the standard by which treatment is indicated and as GPs we are posted default letters recommending starting of treatment based upon BMD result alone. We must share the decision and likelihood of benefit of treatment with the patient and let them choose. We should not assume what level of benefit a patient would regard as suitable to start treatment.	*Agree*
	SB	Why are you using that risk analysis tool? The figures from the studies also need checked.	*Evidence for risk analysis tools is discussed in section 4 of SIGN 142 and will be published in the update.* *The figures have been checked and are correct.*
	EB	5.3. 'unless they are shown to have low bone density on DXA examination. Perhaps should detail low bone density (T score <2.5) on DXA.....	*This section and good practice point were removed as it was felt that the advice on who should be targeted for treatment is adequately covered by the other sections.*
	ROS	In the flow chart it states 10 year risk on FRAX above 10% should have DXA. It should make clear whether or not this is major osteoporotic fracture or hip fracture risk (the main	*'Major osteoporotic fracture' has been added.*

		guidance does make this clear that this is major osteoporotic fracture) Other fractures seem to be given less importance, we would suggest that forearm fractures should be considered important given they carry a significant increased risk of hip and vertebral fractures in both genders.	*Other fractures are included in the algorithm.*
5.4	PS	Whilst I would reach different conclusions from the data reviewed I believe that for the most part the evidence has been fairly presented. In the section on vertebral fractures there is a glaring error: " People who have suffered a vertebral fracture are considered to have osteoporosis, even in the absence of a BMD value in the diagnostic range and are eligible for pharmacological therapy to reduce risk of further fracture" - Is simply not true as it stands. It needs to exclude the very real possibility that any such fracture was traumatic (especially important in men) before it could be considered as reasonable basis for guidance.	*This section has been renumbered 5.3.* *The text has been amended to "People who have had a low-trauma vertebral fracture…"*
5.6	AG	No concerns with the conclusions drawn from the COSHIBA study and useful to have this info in our guideline.	*Thank you.*
	RCGP	I really liked the importance of this outcome as 'clinical fracture'. Remember many studies found the reductions based upon serial lumbar spine XRs. Given vertebral fractures are commonly found coincidentally, it is important to find a reduction in clinical fractures, not just ones on serial x-rays.	*Noted. No change required.*
	SB	You have not looked at enough studies for this and are drawing flawed conclusions.	*The study was identified through a systematic search of the literature, from which SIGN present the highest quality evidence available. This is a large, robust study conducted in a population similar to that of Scotland.* *Details of the search strategy will be published alongside the guideline.* *It is unclear from the comment what is considered to be flawed in the conclusions.*

	PS	This seems inappropriate to include unless you offer guidance on the basis of this section	*A sentence has been added to say there is insufficient evidence to support a screening programme based on height loss.*
5.7	AG	Phew, thank goodness for the conclusions drawn here!!	*No action required.*
	RCGP	Yup agree, no place for screening based on current evidence. I am a little confused though over the last sentence: " Further evidence is required to inform implementation and delivery of a national screening programme for osteoporosis." No not at all. There is no evidence to support any national screening programme so why would we need to inform any evidence to support the implementation and delivery of a national screening programme. There was no evidence provided at all to support the need. So far as we say "population-based screening programmes... are not effective at preventing major osteoporotic fractures." So why scope anything...? Yes we can seek more evidence to affirm or refute current evidence but we are going beyond our scope and the evidence to suggest we should now scope how to inform any national delivery.	*Agree, the statement has been removed.*
	SB	Some excellent studies here which have been written up poorly.	*The studies have been written up as succinctly as possible whilst ensuring the key details are captured.*
	PS	I believe that the authors have incorrectly interpreted this data and that have written these paragraphs in such a way as to recommend a negative conclusion. This is in direct contradiction to the conclusion of the NICE guidelines group. Whilst I understand the fact that we are dealing with different health economies it seems strange that this particular document which is widely used in other parts of the UK is not referred to in this section, even if only to highlight that authors of this guideline have reached a different conclusion. However they don't even reach a conclusion and again it seems bizarre that so much space is spent developing an evidence review and then no recommendation follows	*This section has been updated with the advice from MHRA in July 2019 which has superseded the NICE advice.* *The SIGN advice is in line with National Screening Programme (reference added).* *A recommendation not to use population-based screening has been added.*

	AG	OK with this however remove Romosozumab from severe osteoporosis arm, as rejected by EMA.	*Romosozumab removed.*
	RCGP	I do not like at the bottom where there is the assumption that all people will want to be on treatment if they have mild/moderate or severe osteoporosis. Being on treatment is a choice. We should be using the language consistent with CMO policy in Realistic Medicine to 'offer treatment' in context of shared decision making. It is due to algorithms like this, we struggle to get people to use guidelines as 'guidelines' and not rules to follow. Can I check we are clear that even though QFracture/FRAX etc do take previous fractures into account we feel there is no place at all to calculate the ongoing risk using these tools if the patient has a fracture. I think they support shared decision making to quantify the risk for the patient and would consider inclusion.	*The flowchart is for pharmacological treatment (should the patient wish to have pharmacological treatment). Advice on discussing treatment options has been added to section 5.1.* *Agree, it can be useful for shared decision-making. While this is too much to include in the algorithm, a sentence has been added in the introduction to section 5.1 to state discussion with patients* *"should include a discussion of the risks of fracture with and without treatment, using tools such as Qfracture and FRAX, the risks and benefits of treatment and the option not to have drug treatment."*
	EB	In my comments on this revised guideline I'm aiming to respond to this as a GP/generalist rather than someone with a specific interest in osteoporosis. In the text box T score -1 to -2.5 at hip or spine with an arrow to zoledronic acid (section 6.4.3) I'd be looking for much more clarity and ideally a clear idea of what to do on the actual one page flow chart, not a reference to another section to have to read through and interpret. GPs only have 10 mins per appointment after all! It needs to be clear and simple in my opinion. Should this not detail T score -1 to -2.5 + 10 year risk > 20% (NOF guideline) and is this risk of MOF or # NOF?? ... and/or if the guideline is suggesting following the Reid et al paper instead rather than the US one should this be osteopenia + risk of MOF >12% and >2.3% risk of #NOF if over 65? I feel this needs to be clearer for a generalist and be easier to follow. also note box on TPD or romosozumab, this has obviously now not been approved by the EMA.	*The algorithm has been revised to be clearer.*

6.4.3	AG	The advice, coming on the back of the New Zealand trial, looking at treatment for osteopaenia in the context of risk factor calculation is an important new development but likely to create extra work for those of us reporting DXA. So be it.....	*No action required.*
	JH	"In women over 65 years of age with osteopenia (by t-score) and baseline 10- year osteoporotic fracture risk of ≥12% (or hip fracture risk of ≥2.3%), zoledronic acid may be considered to reduce risk of vertebral and non-vertebral fractures." The Reid IR et al NEJM study recruited patients with osteopaenia at either total hip or femoral neck and not vertebral osteopaenia so perhaps the SIGN guidelines will recruit patients who were not covered in the original study. The same paper also stated that the presence of osteoporosis (T score<-2.5 at one hip site or T score <-3.0 in spine) was not a reason for exclusion from study as long as they were osteopaenic in femoral neck or total hip. As such the phrasing may exclude patients who were included in the original study. You have based treatment on achieving certain levels of fracture risk, however although the quoted figures were the median risk in the study I am not aware of sub-analysis which states that it is not as effective in patients with lower fracture risks. However it is not far away from criteria for requiring a DXA scan in the first place (10%).	*The recommendation has been changed to 'women over 65 who have osteopenia at hip or femoral neck on DXA'.* *When these patients were excluded from analysis HR was still significant.* *The levels of fracture risk have been removed from the recommendation.*
	EB	Do you need to mention something about the Reid et al paper not using ca/ vit D in comparison to most other studies?	*The sentence 'The use of calcium supplementation was minimal (2%), although dietary calcium intake was calculated to be adequate (average of ~880 mg/day).' has been added.*
	ROS	The algorithm in figure 3 seems paradoxical to me in that a postmenopausal woman with a fracture who is osteopaenic can receive ZOL as first line treatment but if she is osteoporotic, ALN or RIS are first-line and ZOL is second-line. It is also perhaps confusing to	*The algorithm has been changed so if patient preference is for zolendronic acid then it can be offered as first line.*

		suggest that 10-year hip fracture risk >5% represents a different cohort to either osteopenia or osteoporosis. Consideration on zoledronate in osteopaenic people showing significant reduction in fracture rates. The guidance seems inconsistent as at one point it says that zoledronate could not be recommended in men but later it does recommend it.	*The SMC advice has been removed.*
	PS	The recommendation regarding use in over 65s with osteopenia does not really seem to be flow readily from the evidence review. Also on what basis was this recommendation made? Later on the document uses ICERs = why not here?	*There is no cost-effectiveness data available. However, NICE concluded that the therapy was cost effective above 10% fracture risk. The recommendation is based on clinical efficacy from the Reid study which used median 12% fracture risk with treatment every 18 months, so it could be considered to be cost effective.*
6.4.6	AG	Nothing new save for more info on uveitis/episcleritis and the reassurance of no lasting damage.	*No action required.*
	SB	Again poorly written.	*With the exception of the final paragraph, this is text from SIGN 142. It has now been revised with additional evidence for gastrointestinal adverse effects, osteonecrosis and uveitis (now section 6.4.5).*
	PS	It is bizarre that the comments AE - GI intolerance is not mentioned other than with in a consideration of upper GI cancer	*GI adverse effects are discussed in the sections for individual therapies. More general advice has now been added (now section 6.4.5).*
6.4.8	JH	Phrasing somewhat difficult to follow when describing the trial. VERO study phrased it better - postmenopausal women with at least two moderate or one severe vertebral fracture AND a BMD T score less than or equal to -1.5. I think the SIGN guidance is just missing a comma	*Agree, the sentence has been restructured.*
	EB	Do you need to have some more detail in the recommendation on when to use TPD eg based on the NICE TA or is this deliberately vague?? ie •who are 65 years or older and have a T-score of –4.0 SD or below, or a T-score of –3.5 SD or below plus more than two fractures, or who are aged 55–64 years and have a T-score of –4 SD or below plus more	*The recommendation is based on evidence from the VERO study which is more recent than the NICE TA.* *The recommendation has been revised to include more detail.*

		than two fractures. *(https://www.nice.org.uk/guidance/ta161/chapter/1-Guidance)*	
	ROS	Although the proposed section on ROMO recommends follow-on treatment with an anti-resorptive treatment, this recommendation is not made in relation to TPD treatment. We believe that equity of treatment for both men and women is important.	*Follow-on treatment with an anti-resorptive has been added to the TPD section.* *Recommendations for men have been made where evidence and SMC advice allows.*
	PS	The recommendation of use over bisphosphonate in patients with severe spinal OP needs clarification: 1. What is the definition of "severe spinal OP" it certainly doesn't fit, say, WHO classification 2. What is the basis the recommendation? The authors say that there has been no new cost effectiveness studies so how can they justify their conclusion?	*The wording of the recommendation has been revised to 'with at least two moderate or one severe low trauma vertebral fractures' to be more specific. It reflects the patient group in the study.* *The recommendation is based on the results of the clinical trials. The cost of teriparatide has reduced now that biosimilars are available.*
6.4.9	AG	Rejected by EMA. Appeal going in but unlikely to be heard in foreseeable future.	*This has been reassessed and accepted so a description of the trials has been included. The recommendation is pending SMC advice.*
	JH	Comments noted on marketing authorisation	*See above.*
	EB	In Recommendation, ... women with severe osteoporosis (define/ clarify) who are at high risk (again define, how high is high?) Note recent EMA recommendation	*The wording of the recommendation will be revisited once SMC advice is available.*
	SMC	As advised earlier by e-mail, romosozumab received a negative CHMP opinion so is not licensed and is unlikely to be licensed in the near future.	*See above*
	ROS	We note Romosozumab is included due to recent EMA decision this may need to change.	*See above*
	PS	I presume this will not be included.	*See above*

6.4.10	AG	Should guidance be given as to what bisphosphonate therapy should be considered to reduce or prevent the rebound increase in bone turnover?	*This section has been renumbered to 6.4.7* *No evidence was identified to advise on this.* *Usual practice is to try switching to a different bisphosphonate.* *Further advice, based on other guidance, and a recommendation has been added.*
	EB	Again in original text what is 'severe' osteoporosis ? defined here as T score <4.0 - different from more normal definition of <-2.5 + #.	*The word 'severe' has been removed.*
	KF	Serum calcium should be checked two weeks before denosumab treatment is due, for all patients. I feel that 2 weeks prior to each injection would be very difficult to manage in primary care as clinic appointments are usually made 6 weeks in advance. Patients with renal impairment should have serum calcium checked again two weeks after therapy. I would like clarification at what level of renal impairment this relates to and is if after every injection? These measure will greatly increase the workload for those prescribing Denosumab. In Fife we have @ 700 patients who are prescribed Denosumab.	*This advice follows the Summary of Product Characteristics that serum calcium should be monitored. This is good practice.* https://www.medicines.org.uk/emc/product/4675/smpc *The renal impairment cut off has been added to the good practice point.*
	ROS	The description of the Denosumab extension studies does not make it clear that the median follow-up after discontinuation of Denosumab was only 6 months and that a significant proportion (14.5% Denosumab and 42% placebo) of participants received other osteoporosis treatment on discontinuation of Denosumab even prior to the occurrence of VFX. Taking these factors into consideration, the studies do not provide much reassurance with regard to the rebound effect. We do agree with the recommendation made to switch	*Further advice on treatment for rebound and a recommendation has been added.*

		treatment on discontinuation but wonder if this should be strengthened.	
6.4.14	AG	No issues and should hopefully allay much of the 'scaremongering concern' circulating over recent years re calcium/vitamin D.	*This section has been renumbered to 6.4.13* *No action required.*
	RCGP	This recommendation is not consistent with the CMO (Scotland) advice and we are making a noose for ourselves here and stretching beyond the evidence. CMO was clear in her letter to clinicians that she recommends Vitamin D for at risk groups all year round and "We are not currently in a position to extend universal provision of vitamin supplements to the whole of the Scottish population or to additional at risk groups including the elderly, women in the pre-conception period, infants or young children." https://www.cps.scot/media/1987/cmo-unnumbered-letter-issued-on-24-november-2017-final-new-recommed.pdf By going further and adding calcium to this, you have made it a medicine and not a public health supplement. Calcium/vitamin D are PoM and not OTC supplements. As you say, "There is inconsistency in the results of benefits in fracture outcome measures" and so we must be cautious and careful in the wording of our recommendations, otherwise you have just recommended we prescribe this rather than as is the current CMO advice it is a public health supplement. I would have the recommendation to this to align to CMO's current advice, otherwise I suggest we take it up with them prior to publication as we do not have the resource (or evidence) to justify to prescribe to all as calcium/vitamin D.	*Calcium/vit D is a pharmacy medicine (P) and is treated as such in this analysis. The wording has been strengthened to make this clearer, and the title of the section changed to 'Vit D and calcium treatment'.* *Section 6.3.3 addresses dietary supplementation and has been updated to reflect the most recent CMO advice.* *The recommendations in 6.4.14 (new 6.4.13) are that it is NOT recommended in the general public and may be considered in frail elderly people who are at high risk. This does not contradict the advice from the CMO.* *The CMO advice is based on SACN advice which states:* *SACN found insufficient evidence to draw firm conclusions on the impact of low vitamin D levels for non-musculoskeletal health outcomes. Therefore this is considering different outcomes. We are specifically looking at fragility fracture outcomes rather than non-musculoskeletal health outcomes. If we then look at the later advice that at present we cannot afford to prescribe vitamin D to all at risk groups this refers to ALL those over aged 65 years. However the recommendation is for a much narrower population - frail older people. This is a much smaller, restricted group who do not have the easy access to OTC, supermarket vitamin D. They are by their nature often housebound or nursing home residents. Therefore many would not have the access to obtain vitamin D. While some may have relatives who could provide this for them, there could be an unmet need here.*

	EB	Note out of the blue there are now details of references 277, 278/279. how does this fit in with the new guideline? Are these still accurate? Does this make sense in the overall document?	*These references are from the original text from SIGN 142, so they will make sense in the overall document.*
	ROS	We have concerns about it saying that routine supplementation with calcium and vitamin D is not necessary in Scotland. Given the lack of the right UV radiation for much of the years especially in more northerly parts of Scotland like Aberdeen rates of vitamin D insufficiency or deficiency might be quite high.	*See comments above.* *Text has been added to clarify that this section addresses 'therapeutic vit D/calc' and cross references to section 6.3.3 for public health supplementation.*
	PS	This seems to be ignoring the joint statements of the CMOs suggesting adults supplement with vit D over the winter.	*See responses above.*
6.4.15	AG	Happy with this and goes hand in hand with section 6.4.8	*No action required.*
6.5.4	AG	Fine regarding this. The 6 year data for a select patient group a useful adjunct.	*Thank you. In light of response from other peer reviewers the recommendation on further treatment has been removed, as the evidence is inconclusive.*
	RCGP	I don't think we have address the elephant in the room here. As you'll be aware, NICE are saying in their multimorbidity guide: "Tell a person who has been taking bisphosphonate for osteoporosis for at least 3 years that there is no consistent evidence of further benefit from continuing a bisphosphonate for another 3 years, or harms from stopping a bisphosphonate after 3 years of treatment. Discuss stopping bisphosphonate after 3 years and include patient choice, fracture risk and life expectancy in the discussion." We haven't addressed this different nor justified not revising 6.5.2 onwards. The statement above from a NICE guideline is a great example of realistic medicine - a concept found in Scotland. For the inconsistencies and uncertainties in this area of prescribing, we must be bold and empower clinicians. Currently we say "Alendronic acid may be continued for up to 10 years in postmenopausal women with	*The recommendation has been changed to: 'Zoledronic acid 5 mg intravenously annually for three years is recommended in postmenopausal women with osteoporosis. The clinical benefit of annual zoledronic acid in preventing fractures beyond three years is uncertain.'* *Section 5.1 now has a paragraph regarding discussion of treatment options with patients.*

		osteoporosis, especially those that are at high risk of vertebral fracture." I think the statement above from NICE is far more forward thinking that what we have written and we need to be ambitious in supporting Realistic Medicine in SIGN guidelines. We are not far off but must make the necessary tweaks to language. Uncertainly is OK to express in a guideline...	
	EB	Recommendations: good clear advice.	*Thank you. The recommendation for further treatment has been removed in light of other peer review comments and lack of evidence.*
	PS	Perhaps this needs to be toned down because it is almost completely evidence free and this needs to be reflected in a low grade of recommendation. For instance the various groups in whom continued therapy is recommended are largely based on prejudice and there is no clinical evidence to support these assertions. Of course NO|GG make exactly the same sweeping assumptions	*Recommendation has been removed.*
6.5.6	AG	Happy with this section and the updated guidance re the use of therapy for up to 10 years. As before, guidance as to what to lock in density accrual with (in terms of bisphosphonate/duration) may be helpful to include.	*Advice on rebound therapy has been added to section 6.4.7 (denosumab)* *There is no evidence to determine duration of rebound therapy. It has been added to the list of research recommendations.*
	EB	Recommendations: good clear advice.	*Thank you. The advice on rebound has been removed in light of other peer review comments. Further detail and a recommendation on rebound has been added to section 6.4.7*
	PS	As I recall the evidence suggests that treatment with bisphosphonates does not ameliorate the rebound fracture risk with denosumab cessation. So why do you recommend it?	*Advice on rebound removed from this section. While there is little evidence for rebound or which bisphosphonate to use, the European Calcified Tissue Society and the Endocrine Society advise using an alternative anti-resorptive treatment. Other reviewers have also expressed a need for this. Further detail and a recommendation has been added to section 6.4.7.*
7.3.2	SMC	The reference to the SMC not recommended advice in the paragraph immediately above the recommendation appears contradictory. Please could this	*The reference to advice from SMC in sections 7.3.2 and 10.4 has been removed.*

		paragraph be removed from the text. Please also remove reference to the SMC advice for risedronate in men from section 10.4 of the guideline.	
7.3.3	AG	No issues.	*No action required.*
	SMC	The reference to the SMC not recommended advice in the paragraph immediately above the recommendation appears contradictory. Please remove reference to the SMC not recommended advice in the text. Please also remove reference to the SMC advice for zoledronic acid in men from section 10.4 of the guideline.	*The advice from SMC has been removed.*
9.2	AG	Comprehensive, as always.	*Thank you.*
	RCGP	I think we should say: All treatment options should be discussed with the patient, including not wishing treatment, and consideration should be given to the patient's ability and motivation to adhere to treatment recommendations. Also: Possible benefits and adverse effects of any treatment should be shared with the patient in order to help support an informed decision. Utilising shared decision aids can support this conversation. Reassurance should be given that other options to reduce fracture risk are available if the patient does not wish or tolerate therapy.	*These points have been added in.*
	SB	Very useful part of the document, it makes sense in most parts.	*No action required.*
	PS	How was this developed? What was the user involvement?	*It was developed by the previous guideline development group, including two patient representatives. Further advice was added by the patient representatives on the guideline development group producing this update. Both iterations have been peer reviewed.*
11.2	AG	As before comprehensive and now including HIV and population screening.	*No action required.*
	RCGP	"a feasibility study on the introduction of a screening programme in NHS Scotland, including who should be targeted, frequency of screening and resource impact"	*The screening recommendation has been removed.*

		Can we be clear on the aims of this. Screening in the UK is the responsibility of the UKNSC. Is this SIGN's responsibility to take on? We must be clear that with the lack of evidence to support why should we be investing in this? The current evidence doesn't support population screening so why do a study to scope feasibility to roll out? We have already said "population-based screening programmes... are not effective at preventing major osteoporotic fractures." This is clearly beyond the remit of SIGN nor the cited evidence within the guideline	
	SB	Should have a part here to have a recommendation for someone to start over again than present this flawed guideline. Could it not just be written to the standard of other SIGN guidelines?	*The draft sections are written in the same style as SIGN 142, into which they will be incorporated. It has been developed using the same methodology and to the same standard as other SIGN guidelines.*
	ROS	Treatment in men is not given greater emphasis, in line with treatment licences, especially as this is not highlighted as an area for further research.	*Agree. A recommendation for RCTs on pharmacological treatments in men has been added.*
	PS	This seems to be a random list of things plucked out of the air and probably reflecting the interests of those sat around the table. There needs to be much greater justification of these in terms of symptom burden, health impact and possible sot benefit before they are included like Holy Writ in a document like this	*The recommendations are based on gaps in the research identified when the systematic reviews were conducted for each of the key questions used for the original SIGN 142, or this update.*
12.4.1	SB	Even this question in the survey is confusing. I don't get how you ever expect anyone to put this guideline into practice if it is not written correctly. If this goes out in its current form then I'm going to complain to whoever in Scottish Government will listen that SIGN is out of control and using up valuable NHS money to produce poorly worded guidelines like this. Why is there no any other questions box? You clearly do not want anyone to actually comment on this and are trying to hide the consultation and	*The draft is written to the standard SIGN style and will be incorporated into SIGN 142.* *The consultation form is set out by section to encourage open feedback and avoid use of potentially leading questions. The form is the standard format for consulting on SIGN guidelines and the context for the consultation was set out on the webpage.*

		rush it out quickly. These survey questions are also lazy as just putting down headings rather than actually taking the time to come up with proper questions. I cannot stress enough how even poorly worded this survey is. I've never answered one before where it is so lazy that you do not even put down proper questions. You owe it to patients and professionals to look again at the guideline and put in a new team to coordinate it, as it is truly appalling!	
	EB	Re my details. as well as being detailed as CD, primary care, NHSL I now also affiliated to two universities, U of G and GCU. Can this be included please? (just trying to give both due reference and keep all politics happy!) Re my colleague Robin Munro in NHSL, the correct nomenclature for Wishaw is now University Hospital Wishaw, not WGH. Re our colleague Prof Dawn Skelton, she is not Prof of Physiotherapy but rather Professor in Ageing & Health.	*Universities added.*
	ROS	Thank you for the opportunity to submit a response to the consultation. SIGN 142 continues to be an important standard in the management of osteoporosis and the prevention of fragility fractures.	*Thank you.*
	PS	There do not appear to be any patients or carers represented here.	*Two patient representatives participated in the guideline development group. Two further patient representatives were invited to comment on the draft, along with the Royal Osteoporosis Society.*