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## Review

# Goal-directed Treatment for Osteoporosis: A Progress Report from the ASBMR-NOF Working Group on Goal-directed Treatment for Osteoporosis†

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## Abstract

The American Society for Bone and Mineral Research and the United States National Osteoporosis Foundation (NOF) formed a working group to develop principles of goal-directed treatment and identify gaps that need to be filled to implement this approach. With goal-directed treatment, a treatment goal would first be established choice of treatment determined by the probability of achieving that goal. Goals of treatment would be freedom from fracture, a T-score  $> -2.5$ , which is above the NOF threshold for initiating treatment, or achievement of an estimated risk level below the threshold for initiating treatment. Progress toward reaching the patient's goal would be periodically and systematically assessed by estimating the patient's compliance with treatment, reviewing fracture history, repeating vertebral imaging when indicated, and repeating measurement of bone mineral density (BMD). Using these data, a decision would be made to stop, continue, or change therapy.

Some of these approaches can now be applied to clinical practice. However, the application of goal-directed treatment cannot be fully achieved until medications are available that provide greater increases in BMD and greater reduction in fracture risk than those that are currently approved; only then can patients with very high fracture risk and very low BMD achieve such goals. Furthermore, assessing future fracture risk in patients on treatment requires a new assessment tool that accurately captures the change in fracture risk associated with treatment and should also be sensitive to the importance of recent fractures as predictors of imminent fracture risk. Lastly, evidence is needed to confirm that selecting and switching treatments to achieve goals reduces fracture risk more effectively than current standard care. This article is protected by copyright. All rights reserved

**Keywords:** osteoporosis, treatment, goal, target, treat-to-target, treat-to-goal

## Background

It has been proposed that the goal of treatment for osteoporosis should be an acceptably low risk of fracture and that treatment decisions should be guided by maximizing the probability that a patient will achieve the goal.(1,2) The American Society for Bone and Mineral Research (ASBMR) and the United States National Osteoporosis Foundation (NOF) established the Working Group on ‘Goal-directed Treatment for Osteoporosis’ to consider setting goals to guide therapeutic decisions. The Working Group members were selected for their expertise and clinical experience in the management of osteoporosis. They represent a broad array of primary care and specialist clinicians and experts in epidemiology and ethics from the United States, Canada, Europe, Australia/New Zealand, and Japan. Many are also members or leaders of other societies that focus on osteoporosis. The Working Group includes no representatives and received no funding from the pharmaceutical industry. Some members of the Working Group have received funds from pharmaceutical companies as described in the disclosures.

After several discussions of draft principles, the Working Group concluded that setting treatment goals with patients and making therapeutic decisions based on the likelihood of achieving those goals is an ideal strategy for treatment of osteoporosis. Some parts of this approach can be recommended for use in clinical practice now. Other components have limitations that need to be addressed before implementation in clinical practice. In particular, there is a need for new treatments that have more potent effects on fracture risk and bone mineral density (BMD) that would enable patients to achieve goals that may not be reachable with current therapies. Ideally, additional agents that act to maintain treatment targets (beyond intermittent bisphosphonates) are also needed to optimize the goal- directed treatment paradigm.

There is limited evidence on which to base principles of goal-directed treatment. This report describes principles based on interpretation of evidence that reflects a consensus of expert opinion of

members of the Working Group. The report represents the first step of an iterative process that warrants continued discussion. Gaps in evidence need to be filled so that treatment decisions based on goals are grounded in sufficient data.

### **Differences between standard treatment and goal-directed treatment**

With current guidelines for managing osteoporosis, once a decision has been made to treat a patient with a pharmacologic agent, a “first line” drug, usually an oral bisphosphonate, is prescribed. BMD is often repeated 1-2 years later to evaluate for response to therapy. Stabilization or improvement of BMD is usually accepted as validation that the patient is responding appropriately to treatment. The same treatment is then continued; after 3-5 years of oral or intravenous bisphosphonate therapy, a bisphosphonate “holiday” may be considered.<sup>(3)</sup> If there is a statistically significant decline in BMD 1-2 years after starting therapy, clinicians may evaluate for factors contributing to a suboptimal response to therapy and consider switching to a different agent. Sometimes bone turnover markers are used to monitor response to therapy, with a significant change in the expected direction (decreased with antiresorptive agents, increased with osteoanabolic agents) taken as an acceptable response.

In contrast, goal-directed treatment is a strategy where (a) a goal of treatment is established for a patient, (b) the initial choice of treatment is based on the probability of reaching the goal, and (c) progress toward reaching the patient’s goal is reassessed periodically, with decisions to stop, continue, or change treatment based on achievement of the goal or progress toward achievement of the goal. Goal-directed treatment differs from standard practice in a fundamental way. As with all treatment, the overriding goal of treatment is to achieve freedom from fracture or at least a low risk of fracture. If a fracture, including a morphometric vertebral fracture, occurs during treatment, despite evidence of response to treatment by improvement in BMD and markers of bone turnover, then the patient has an increased risk of a recurrent fracture for at least several years (4-6), warranting consideration of

switching to a more potent treatment or combination of treatments or, at a minimum, continuing an effective therapy.

## **Principles of Goal-directed treatment**

### **1. Establishing treatment goals**

The principles of goal-directed treatment are founded on the identification of a target BMD or fracture risk to guide decisions about initial treatment and treatment decisions during the course of therapy. Currently, the NOF suggests initiating treatment in patients with hip or vertebral fractures, patients with a T-score in the lumbar spine, total hip or femoral neck  $\leq -2.5$ , and those with a 10-year probability of hip fracture  $\geq 3\%$  or 10-year probability of major osteoporotic fracture  $\geq 20\%$ , using the US-adapted World Health Organization (WHO) absolute fracture risk model (FRAX<sup>®</sup>).<sup>(7)</sup>

Osteoporosis treatment goals parallel indications for initiating treatment; logical treatment goals are BMD levels above and fracture risk levels below those for which treatment is usually recommended. In a patient with an incident fracture while on osteoporosis medication, treatment should be continued regardless of the T-score, since the risk of another fracture in the next few years is very high.<sup>(4-6)</sup> Once a fracture-free interval of 3-5 years has been documented, other treatment targets can be considered, as follows.

**T-score as a goal.** If the primary reason for starting treatment is a T-score  $\leq -2.5$  at the femoral neck, total hip, or lumbar spine by dual-energy X-ray absorptiometry (DXA), then the goal of treatment is a T-score  $> -2.5$  at that skeletal site. Although absolute BMD (in  $\text{g}/\text{cm}^2$ ) is used for quantitative comparison of serial BMD measurements by DXA, T-score is preferred as a goal because T-scores mitigate much of the BMD variability associated with different skeletal sites, regions of interest, and

DXA make and model. This approach is feasible in clinical practice. A T-score goal is attractive because it is measurable and improved by treatments.

There is limited evidence that, for an individual patient, greater increases in BMD are associated with greater reductions in fracture risk. Previous meta-analyses(8) and a preliminary report from a meta-analysis of almost all trials of anti-resorptive drugs done up to 2015(9) found that for individual patients, there was only weak correlations between change in femoral neck BMD on treatment and change in risk of nonvertebral fracture. In contrast, decreases in spine BMD during treatment with alendronate has been associated with a higher risk of vertebral fracture than in those whose spine BMD improved(10) Changes in femoral neck BMD in individual patients during 3 years of treatment with denosumab were correlated with reductions in risk of nonvertebral fracture.(11) On the other hand, for the purpose of predicting of the results of clinical trials of antiresorptive drugs, greater increases in mean vertebral and femoral neck BMD in trials of antiresorptives are significantly associated with greater of reductions in the risk of vertebral and hip fractures, respectively, in those trials.(8) (12) (9)

Of greater importance than the association between BMD gain and fracture risk reduction, however, is identification of a T-score value above which there is an acceptably low risk of future fracture. Evidence from the Fracture Intervention Trial Long-term Extension (FLEX) trial of alendronate and the HORIZON Extension trial of zoledronic acid indicate that a persistently low femoral neck T-score  $\leq -2.5$  in women who had received 5 years of treatment with alendronate or 3 years of zoledronic acid was associated with a high risk of future vertebral fracture.(4,13,14).

Furthermore, in a post hoc analysis of a high risk subset of subjects in the FLEX trial, continuing alendronate beyond 5 years reduced the risk of nonvertebral fractures in women with femoral neck T-score  $\leq -2.5$ , but not in those with a femoral neck T-score  $> -2.5$ .(15) With continued zoledronic acid treatment beyond 3 years, there was a suggestion that continued vertebral fracture risk reduction was limited to those with T-score  $\leq -2.5$ , with the absolute risk of fracture very low in those patients who

attained BMD above that level.(4) Similarly, data from the FREEDOM Extension study of denosumab also suggest that fracture risk while on denosumab treatment is a function of the hip T-score achieved during treatment.(16) A target T-score  $> -2.5$  is also consistent with the recommendations of the ASBMR Working Group on Long-term Bisphosphonate Treatment,(3) which state that after treatment for 5 years with alendronate or 3 years with zoledronic acid, postmenopausal women with low fracture risk (hip T-score  $> -2.5$ ) may be considered for discontinuation of bisphosphonate therapy, with reassessment of fracture risk 2 to 3 years after discontinuation.

There are a number of limitations to the use of T-score as a target for osteoporosis treatment. For some skeletal sites, such as the femoral neck, achieving a goal T-score  $> -2.5$  might be unlikely or impossible with current medications. There are no data about continued benefits of treatment or risk of future fracture for lumbar spine BMD. A clinician might decide to set a goal of T-score  $> -2.5$  at the lumbar spine because of discordance in BMD between the lumbar spine and hip, with a lower spine BMD indicating a greater risk of vertebral fracture.(17,18) A lumbar spine T-score goal may be particularly important when the treatment being considered, such as teriparatide, improves spine BMD substantially more than hip BMD. Measurement of BMD, as with any measurement, has inherent variability due to factors that include instrument calibration, patient positioning, and analysis. Furthermore, lumbar spine BMD in the elderly may increase due to degenerative changes that are not associated with improvement in bone strength. For individual patients, serial BMD measurements by DXA typically have a “least significant change” in the range of 3-5% (about 0.3 to 0.5 T-score units) with a 95% level of confidence.(4) Therefore, reaching a T-score  $> -2.0$  on a single measurement provides a very high degree of confidence that the T-score is truly  $> -2.5$ . Confidence that the goal T-score  $> -2.5$  has been achieved is also enhanced when the T-score at a skeletal site is  $> -2.5$  on more than one measurement. In consideration of technical differences with DXA systems of different manufacturers and sources of measurement variability, measurements should ideally be made on the

same device at the same facility, using the same reference databases to calculate T-scores, provided there is adherence to well-established quality standards(19) and DXA Best Practices.(20) With future advances in knowledge, other methods for assessing bone strength, such as finite element analysis, may someday play a role in determining treatment targets.

**Fracture risk as a goal.** If the primary reason for starting treatment is a high absolute risk of fracture, then the goal is a level of fracture risk below the risk threshold for initiating treatment. For example, if the treatment threshold were a 10-year risk of major osteoporotic fractures (hip, humerus, wrist, and clinical spine fractures)  $\geq 20\%$ , then the treatment goal would be a 10-year risk below 20%. A patient's risk of fracture will, on average, decrease by the amount observed in clinical trials in a patient who is adherent to therapy. For example, a patient with a 5% 10-year risk of hip fracture will reduce that risk to about 3% by treatment with an agent that reduces hip fracture risk by 40%. However, using fracture risk as a goal of therapy for individual patients is limited by the absence of a validated approach for estimating the risk of fractures in individual patients who are receiving treatment.(21) Observational studies have found that the World Health Organization fracture risk assessment tool (FRAX) is not sensitive enough to the changes in BMD and fracture risk with treatment, with fracture probabilities tending to increase because of increasing age during treatment.(22,23). In addition, FRAX fracture risk calculations do not take into account how recently a fracture occurred. Recent clinical trial and observational data in individuals treated for osteoporosis suggest that a history of recent fracture during treatment is associated with an increased risk of another fracture during treatment.(4-6) Despite its logical appeal as a treatment goal, fracture risk is currently not feasible for clinical practice. Better methods for assessing fracture risk for patients on treatment are needed in order to enable use of fracture risk goals to guide therapeutic decisions.

## 2. Goal-directed selection of initial therapy

The Working Group recognizes that selection of treatment is often based on, or constrained by, local policies and payer reimbursement practices. Furthermore, selection of therapy must consider patient age, stage of life, comorbidities, concomitant medications, falling risk and frailty, in addition to severity of osteoporosis.

For patients with recent fractures, it is critical to prevent fractures during the next several years, when the risk of another fracture is substantially elevated.(24-31) Therapeutic agents that reduce fracture risk rapidly are desirable for these patients.

For patients with a T-score substantially below -2.5, treatments having the potential to achieve a greater increase in BMD should be considered. The acceptable probability of achieving the treatment goal and the time to achieve it has not been established. Defining this probability requires analyses of the costs and benefits of alternative approaches. In the absence of such evidence, the Working Group judged that it was intuitively reasonable to expect that initial treatment should offer at least a 50% chance of achieving the treatment goal within 3 to 5 years of starting therapy. This level of probability has not been generated from trials of approved drugs and should be revised if evidence suggests that an alternative probability is more appropriate.

If initial treatment with an oral bisphosphonate offers a low probability of reaching the target T-score of  $> -2.5$ , then an agent with substantially greater effect on BMD, if available, should be considered for initial therapy. Similarly, if initial treatment with an oral bisphosphonate offers a low probability that the patient will reach a goal of reduction in fracture risk, an agent or sequence or combination of agents with greater effect on fracture risk should be considered for initial therapy. Choice of initial therapy should also consider the balance of expected benefits and potential risks, patient preference, and cost. This approach is feasible to apply to clinical practice currently.

**Screening for vertebral fracture.** Patients who have sufficiently high risk of fracture or low BMD to warrant starting treatment should have DXA-based vertebral fracture assessment (VFA), or a lateral thoracolumbar spine radiograph to determine whether vertebral fractures are present. This principle is based on the recommendation from the NOF and the International Society for Clinical Densitometry which state that women age  $\geq 70$  years and men age  $\geq 80$  years should have a screening vertebral imaging test if the T-score is  $\leq -1.0$  at the lumbar spine, femoral neck, or total hip; women age 65-69 years and men age 70-79 years should have vertebral imaging if the T-score is  $\leq -1.5$  at any of these skeletal sites.(7,19) The presence of a vertebral fracture, especially one that is at least of moderate severity and/or a recent occurrence, greatly increases fracture risk and may warrant selection of an initial treatment that has the greatest efficacy for reducing the risk of vertebral fracture. Additionally, obtaining a baseline spine image allows for comparison with repeat spine imaging in the future to determine whether a vertebral fracture has occurred during therapy; this information might influence subsequent treatment decisions to intensify and/or continue treatment. The Working Group noted that the use of vertebral imaging might differ in different countries and that recommendations about vertebral imaging should consider local guidelines. Measuring body height accurately when treatment starts also allows for assessment of height change during treatment follow-up that helps inform decisions about when to obtain a follow-up VFA or spine radiograph.

### **3. Goal-directed assessments and treatment decisions during treatment**

**Assessing adherence to treatment.** Achieving a goal requires adherence to treatment. In general, taking less than 80% of prescribed oral medications is associated with a suboptimal therapeutic effect, which may be recognized by a decline in BMD, failure of bone turnover markers to respond as expected, or occurrence of a fracture. Poor adherence should prompt interventions to improve adherence.(32) The Working Group suggests that when adherence to an oral agent is inadequate,

parenteral therapy should be considered. Levels of adherence with pill taking may be difficult to estimate in practice but can be approximated from electronic pharmacy records, if available, using the history of patient refills of prescribed therapy. Comparisons of adherence with oral and injectable therapy showed that treatment with SC denosumab every 6 months (33) and IV ibandronate every 3 months (34) produced better adherence than did weekly oral bisphosphonate.

**Monitoring response to therapy.** A treatment goal cannot be achieved unless the patient is responding to therapy, although response to therapy is not a guarantee that the goal will be reached. A fracture occurring while on therapy warrants further evaluation to confirm no hidden underlying secondary causes of osteoporosis. Patients who have had fractures on treatment should not be considered to have achieved treatment goals until they have remained free of fracture for at least 3-5 years past the fracture. Guidelines recommend repeating a DXA study 1 to 2 years after starting therapy, and/or measuring a bone turnover marker(7,35) to assure that there is a treatment response. However, a patient may be a good responder with improvement in BMD or an appropriate change in bone turnover marker, yet still have an unacceptably high level of fracture risk. This could be because BMD remains very low, the patient had a recent fracture or there are underlying comorbidities or medications that increase fracture risk substantially. With the goal-directed approach, despite a treatment response being confirmed, consideration should be given to modifying therapy to help achieve treatment goals.

Patients whose BMD does not improve on treatment cannot achieve a T-score goal. Loss of BMD during treatment warrants evaluation of adherence and other causes of inadequate response to treatment.(7,19,35) Treatment monitoring should also include assessment of possible adverse effects of therapy, interval fracture history, assessment of back pain, and body height measurement to determine whether VFA should be repeated.(36)

There have been no analyses of the best frequency for reassessing fracture history, re-screening

for vertebral fractures, or measuring height. Furthermore, the ideal interval for assessing BMD has not been studied and would depend on the difference between the patient's T-score and T-score goal and expected effects of the treatment. However, the Working Group judged that, in general, it would be reasonable to reassess patients yearly for assessment of adherence, interval medical history and height measurement, and at least every 2 to 3 years to determine whether the goal has been achieved or if there is a high likelihood that it will be achieved soon. Timely achievement of the treatment goal is desirable, although there is no analysis indicating an acceptable duration of treatment to achieve the goal. It is rational to utilize the medication most likely to achieve the BMD goal quickly in patients at highest risk for fracture.

Assessment of treated patients should include several elements:

Assessment for occurrence of new vertebral fracture. If a new vertebral fracture occurs, whether it be a clinically apparent or radiographic fracture found by proactive vertebral imaging, continuation of treatment for up to 5 additional years should be considered, after appropriate evaluation for factors contributing to skeletal fragility, regardless of evidence of achievement of a T-score goal. The patient should be treated with an agent that maximizes the prevention of another vertebral fracture. Occurrence of back pain consistent with an acute vertebral fracture warrants clinical evaluation and imaging. If height was measured at baseline, then it should be measured again at follow-up visits at least after 3-5 years of treatment to screen for asymptomatic new vertebral fracture. More than a 2 cm ( $> \frac{3}{4}$  inch) decrease in measured height indicates an increased probability that a new vertebral fracture has occurred and warrants spine imaging with repeat VFA or radiography.(36,37) For the same reasons, if height and spine imaging were not obtained at baseline, they should be considered early during treatment. These principles are based primarily on expert opinion and warrant additional analysis of the cost and benefits of this approach.

Occurrence of nonvertebral fracture during treatment. With a recent nonvertebral fracture, continuation of treatment or changing to one with greater efficacy for reducing nonvertebral fracture risk should be considered, after appropriate evaluation for factors contributing to skeletal fragility, regardless of achievement of a T-score goal. Current treatments typically reduce the risk of nonvertebral fractures by about 20-35% during 1.5-5 years of treatment.(38) It is not clear that switching treatment will offer additional reduction in risk of nonvertebral fracture. (4,39-44) Based on studies from patients who are not receiving treatment, the increase in risk of fracture associated with an incident nonvertebral fracture may be greatest in the first 5 years after the fracture occurs and then wane with time.(24-31) Furthermore, in patients receiving zoledronic acid, incident nonvertebral fracture is an important risk factor for future nonvertebral fractures over the next three years if therapy is discontinued.(4) Therefore, it is the opinion of the Working Group that the occurrence of a nonvertebral fracture during treatment, even if the T-score goal has been reached, should prompt continuation, change or addition of therapy, at least until the patient has been fracture-free for 3 to 5 years. Evidence is needed to confirm that this approach will reduce the risk of subsequent nonvertebral fractures.

Change in other risk factors for fracture risk on treatment. Besides occurrence of fracture on treatment, changes in other risk factors for fracture, such as change in medications, weight loss, or development of a diagnosis that influences fracture risk suggests a change in risk of fracture during treatment. These changes may influence the decision to continue or switch to a more potent agent. This view is based on expert opinion and requires the development of models that accurately estimate risk of fracture during treatment.

Achievement of a T-score goal. Other groups have made recommendations about stopping or continuing treatment after achieving T-score levels.(3,45) If a decision is made to stop treatment, goal-directed treatment suggests that BMD should be maintained above the goal (i.e., generally a T-score > -

2.5). Based on randomized trials comparing the benefits of continuing alendronate or zoledronic acid versus stopping treatment, the benefits of continuing treatment appear to be very small when the patient has achieved a femoral neck T-score  $> -2.5$ . (45). However, the concept of a “drug holiday” applies only to patients taking bisphosphonates because of a transient residual antiresorptive effect after discontinuation due to skeletal retention of drug. For non-bisphosphonates, a drug holiday is not appropriate, since BMD declines rapidly after treatment is stopped.(46,47) Therefore, after a T-score goal is achieved with a non-bisphosphonate, treatment should generally be continued with an agent that maintains BMD, possibly a bisphosphonate (at least short-term).(33) Additional medications that can maintain treatment effects after achieving treatment goals would enhance the goal-directed treatment strategy. Although there are no data about the efficacy of this strategy, the Working Group judged that it is reasonable to consider restarting treatment if a fracture occurs, a patient’s BMD at the hip or spine decreases, or risk of fracture increases to a level that would warrant initiation of treatment (e.g., the use of glucocorticoids or new parental history of hip fracture). A patient’s risk of fracture rises with age and may reach a level that warrants resumption of pharmacologic therapy even in the absence of other factors. The best interval for repeating measurements of BMD has not been determined. Measurement of markers of bone turnover might aid decisions about resuming treatment, but the Working Group did not address targets for bone turnover markers due to limited evidence and uncertainties with these measurements.

### **Limitations of goal-directed treatment**

Although several principles of goal-directed therapy could be applied to clinical practice, the concept has limitations.(48) In particular, it may not be feasible for patients with a very high risk of fracture or very low BMD to achieve goals with current treatments; more potent treatments are needed. For example, with current treatments it may not be possible for a patient with a very high baseline risk of

fracture, such as a 10% ten-year probability of hip fracture, to reduce that risk to  $< 3\%$ , or for a patient with a baseline femoral neck T-score of  $-3.5$  to achieve a T-score  $> -2.5$ . For these patients, treatment with the most potent agents should be considered. Optimal treatment sequences, such as anabolic therapy followed by a potent antiresorptive drug, could potentially achieve BMD goals (even in patients who start with very low BMD). This highlights the importance of selecting the most appropriate initial therapy in patients who are far below the ultimate T-score goal.

A goal of T-score  $> -2.5$  (or higher if measurement variability is considered) does not apply to patients who initiate treatment because of high fracture risk with baseline T-scores  $> -2.5$ . A more aggressive treatment goal (T-score  $> -2.0$  instead of  $> -2.5$ ) may be desirable for patients with a very high baseline risk of fracture, such as those with a recent vertebral fracture or those over age 70 years of age.<sup>(49)</sup> Applying goal-directed treatment for these patients requires development of methods for assessing fracture risk in patients receiving drug treatments.

Evidence and recommendations regarding the use of BMD for making clinical decisions to continue or withhold treatment with alendronate or zoledronic acid and the value of BMD for predicting fractures while on treatment are based on femoral neck or total hip BMD. There are no such data for lumbar spine BMD or other measurement sites. Nevertheless, including lumbar spine T-score as a goal of treatment is consistent with recommendations that the diagnosis of 'osteoporosis' be made when the T-score is  $\leq -2.5$  at the femoral neck, total hip, or lumbar spine.<sup>(7,50)</sup> Maintaining treatment goals attained with non-bisphosphonate agents requires continuing the agent or switching to a bisphosphonate. Additional data are needed about the relative merits and safety continuing treatment or switching to a different agent. .

There are important caveats to these principles. Clinician judgment and patient preference may sometimes override numerical goals. These proposed recommendations are not intended to describe comprehensive care for patients, which should also include regular physical activity, assurance of

adequate nutrition, avoidance of smoking and excessive alcohol intake. Patients with a history of falls warrant assessment of risk of future falls and, perhaps, a program of fall prevention that includes regular weight-bearing exercise.(51) (52) Importantly, the establishment of goals should not be interpreted to deny insurance coverage or reimbursement for further treatment if a patient has achieved a goal.

### **Research needs**

The evidence supporting some of the recommendations is limited. The choice of treatments should ideally be based on randomized trials that compare alternative strategies. Further study is needed to fully validate the clinical application of all aspects of goal-directed treatment (Table). In particular, evidence and analyses are needed to determine levels of risk or T-score that warrant selection of more potent agents instead of a first-line bisphosphonate. We encourage those who sponsor trials of therapeutic agents to conduct comparative studies and analyses that would be valuable to defining goals of treatment and support choices of initial and follow-up treatment to reach those goals.

The Working Group recommends that studies be done to compare the probability of reaching a T-score goal with alternative treatments based on a patient's BMD and other characteristics; these could be done with existing data from clinical trials. It would be ideal to have trials that compare the anti-fracture efficacy of first-line therapies, such as alendronate, to more potent drugs in patients who have low probability of reaching a T-score goal. Fracture risk data are needed on the probability of achieving T-score goals based on the patient's starting T-score and other characteristics. These estimates should be generated from previous trials of current treatments in a form that is easy for clinicians to use.

As noted, the evidence for the potential benefit of switching treatment is limited to a few small short-term trials.(4,39-44) The Working Group recommends that trials be conducted comparing

continuing bisphosphonate therapy versus switching to presumably more potent treatments for patients who have not reached a goal, or who continue to have high fracture risk. These trials should continue for at least 3 years to provide data about the probability that switching treatment will achieve a T-score goal with longer therapy. Ideally trials comparing continuing or switching treatment would have sufficient power to determine whether switching reduces the risk of fracture.

Models to estimate risk of fracture in patients who are receiving treatment are needed; these could be developed from existing data from clinical trials of approved drug treatments. In addition, analyses of associations between change in BMD and change in risk of fracture during treatment are needed across all trials for vertebral, nonvertebral, and hip fractures and should be done for new treatments that have anti-fracture efficacy.

Patient's views about the value of setting goals would be valuable; further studies are needed to elucidate these. A recent study suggested that the threshold risk of fractures at which patients report they would be willing to take fracture prevention medication is quite variable.<sup>(53)</sup> Trials should compare the effect of setting goals to standard practice on patient's persistence and adherence with treatments.

## **Conclusions**

This Working Group interim report supports the potential value of goal-directed treatment and sets out several principles to guide this approach to selecting and monitoring treatments. Some of these general principles, such as considering a more potent initial treatment in those with high risk of fracture, use of parenteral therapy for persistent non-adherence, measurement of height and vertebral imaging before and during treatment, and continuation or intensification of treatment when a vertebral fracture occurs on therapy, could be put into practice now. Others, such as estimating the probability of achieving goals with specific initial treatments, and deciding, based on risk, to continue or switch agents during

treatment, lack evidence or assessment tools. These principles are based primarily on the judgment of experts who comprised the Working Group. Achievement of treatment goals presented here is not possible for all patients due to limited efficacy of medications that are currently available. This may change with the development and approval of new agents or combinations of medications that provide more robust effects on fracture risk and BMD than current agents. Finally, these preliminary principles should be revisited when relevant new data and analyses become available and when new treatments with substantially greater effects on BMD and fracture risk are approved.

Accepted Article

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