

**A Report from the Federal Partners Meeting of the National Institutes of Health
Pathways to Prevention Workshop: Appropriate Use of Drug Therapies for
Osteoporotic Fracture Prevention**

July 22, 2019

Sponsored by:

National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institute on Aging
National Institutes of Health Office of Disease Prevention

Introduction

The Pathways to Prevention (P2P) program of the National Institutes of Health (NIH) Office of Disease Prevention (ODP) promotes the use of evidence-based practices to address complex public health issues by identifying research gaps and needs in specific topic areas. The goals of the P2P workshops are to synthesize and interpret the current evidence, identify research gaps, shape a research agenda, and develop an action plan. On October 30–31, 2018, the NIH convened the P2P Workshop: Appropriate Use of Drug Therapies for Osteoporotic Fracture Prevention. This workshop was cosponsored by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the National Institute on Aging (NIA), and the ODP.

This P2P workshop assessed the available scientific evidence through a systematic evidence review, invited numerous speakers to present their research, and provided opportunities for public discussion and comment to better understand the appropriate use of drug therapy for osteoporosis fracture prevention. An independent panel made recommendations for moving the field forward. In April 2019, the [systematic evidence review](#),¹ [P2P workshop panel report](#),² and an invited [commentary](#)³ were published in the *Annals of Internal Medicine* and posted on the ODP website.

As the final step in the P2P program process, the ODP convened a meeting on July 22, 2019, with representatives from federal government agencies (the Federal Partners) to identify strategies to address the recommendations in the P2P workshop panel report. This document summarizes the discussions and next steps identified at the Federal Partners Meeting.

Background

More than 10 million people in the United States have osteoporosis,⁴ a skeletal disorder that causes bones to become weak and fragile as a result of low bone mass. The condition makes people more susceptible to fractures, which can impair their ability to live independently and even threaten their lives.⁵ The social and economic burden of osteoporotic fractures is substantial.⁶ Reducing osteoporosis prevalence and hip fracture incidence are among the major objectives of [Healthy People 2020](#),⁷ the U.S. Department of Health and Human Services' (HHS) national health promotion and disease prevention initiative.

Lifestyle changes—including getting adequate nutrition and regular exercise, quitting tobacco use, limiting alcohol use, and preventing falls—can help reduce a person's risk of osteoporotic fractures.⁸ However, medications may be prescribed to prevent fractures if a person has very low bone mineral density or has experienced a prior fragility fracture.

The U.S. Food and Drug Administration (FDA) has approved several types of drugs to treat osteoporosis and prevent osteoporotic fractures. These drugs are unequivocally effective for high-risk patients. Clinical guidelines by various medical organizations recommend bisphosphonates (BPs) as a first line of treatment for most people who have osteoporosis.^{9,10} BPs are effective for short-term use (up to 3–5 years) by people who are at high risk of fracture. However, the benefits and risks of longer-term treatment are less clear. Reports of rare but serious adverse events such as atypical femoral fractures and osteonecrosis (death of bone cells) of the jaw have raised questions about the safety of osteoporosis drug use, especially in people who use the drugs for more than 3–5 years or who had a low risk of fracture when they began treatment.

There are gaps in scientific knowledge about appropriate long-term use of many osteoporosis drugs, and uncertainties about the optimal duration of treatment and which people will benefit or may be harmed if they take the drugs long-term. These unanswered questions and public concern about the drugs' rare but serious adverse events have coincided with a significant decrease in use of osteoporosis drugs and a leveling off in what had been a promising decline in the incidence of osteoporotic fractures.^{11,12} These changes have raised concerns within medical and scientific communities that many people who might need the drugs are not being prescribed or taking them. In addition, evidence is limited regarding the initiation and length of "drug holidays" (a medical practice in which a patient stops taking medications and then resumes treatment again after a specified period if the patient or their doctor believes it could be in their best interests), whether stopping treatment reduces the risk of serious adverse events while maintaining fracture prevention benefit, and which individuals should change treatments instead of simply taking a drug holiday from their current medication.

Innovative research strategies are needed to address these knowledge gaps and to help better inform individuals and physicians in their decision making about osteoporosis treatment.

P2P Workshop Key Questions

As its title indicates, the workshop assessed the available scientific evidence to better understand the appropriate use of drugs for osteoporotic fracture prevention. Specifically, the workshop sought to address the following four questions:

1. What are the benefits and risks (including major adverse events) of osteoporotic drugs with *short-term* use (from first use up to 3–5 years of treatment) and what factors influence outcomes?
2. What are the benefits and risks of osteoporotic drugs over the *longer term* (for treatment periods longer than 3–5 years) and what factors influence outcomes?
3. Do drug holidays improve outcomes and what factors influence outcomes?
4. What patient and clinician factors impact the use of and adherence to osteoporotic drugs?

Systematic Evidence Review

A [systematic evidence review of the scientific literature](#),¹³ focusing on key questions 2 and 3, was conducted by the Minnesota Evidence-based Practice Center through a contract with the Agency for Healthcare Research and Quality (AHRQ) to facilitate the workshop discussion and was published in the [Annals of Internal Medicine](#).¹ The purpose of the systematic evidence review was to provide an evidence-based synthesis of the research base and suggest areas where future research is needed to advance the scientific field and the clinical practice of osteoporotic fracture prevention. Key findings from the review are included in [Appendix A](#).

P2P Workshop Panel Report

A unique feature of every P2P workshop is the involvement of a multidisciplinary, independent panel comprised of non-federal representatives who have certified that they hold no scientific or personal conflicts with the subject matter of the P2P workshop for which they have volunteered their service. Workshop panel members are vetted for potential conflicts of interest. Panel members are charged with writing the P2P workshop panel report that (1) summarizes the key findings and research needs outlined in the systematic evidence review and discussion at the workshop, and (2) provides a set of recommendations to move the field forward. As noted above, the [Workshop Panel Report for the P2P Workshop: Appropriate Use of Drug Therapies for Osteoporotic Fracture Prevention](#)² was published in the Annals of Internal Medicine; a summary of the recommendations is provided in [Appendix B](#).

Federal Partners Meeting and Discussion

This meeting was convened on July 22, 2019, with representatives from federal government agencies (the Federal Partners), to review and discuss the findings and recommendations outlined in the P2P workshop panel report (see [Appendix C](#) for the list of attendees and [Appendix D](#) for a list of Federal Partner initiatives and resources). Meeting objectives were to identify next steps for implementing the recommendations from the P2P workshop, prioritize action items, and set the stage for future collaborations.

The discussions and action items identified at the P2P Federal Partners Meeting on Appropriate Use of Drug Therapies for Osteoporotic Fracture Prevention are summarized below.

1. Discussion of P2P Workshop Panel Report [Recommendation 1](#): In assessing both existing and potential treatments and optimizing duration, researchers should make use of innovative designs and approaches (e.g., modeling studies; clinical trials; observational studies in additional populations).

1a. Background: Randomized controlled trials (RCTs) are often designed to exclude participants with comorbidities.¹⁴ This creates knowledge gaps in how the medication will perform when taken by the general patient population, many of whom have more than one health condition. The workshop panel recommended taking advantage of innovative study designs, like modeling studies, so the long-term effects of osteoporosis drug therapies can be discerned for more diverse patients who already take these medications or individuals at risk for osteoporotic fractures who could benefit from treatment.

The Federal Partners discussed populations that are not being adequately addressed in research studies on preventing osteoporotic fractures. For example, of special interest to the U.S. Department of Veterans Affairs (VA), men are not included in most studies of osteoporosis, even though they experience worse outcomes after a hip fracture and are less likely to be treated afterwards. Other patient populations that will benefit from more research include patients on long-term glucocorticoids, aromatase inhibitors, and androgen deprivation therapy (ADT). No standard of care exists for osteoporosis management in populations with spinal cord injury (SCI) and many other patients with mobility disorders are not included in research studies. Rural residence lowers a person's likelihood of being properly diagnosed and treated for osteoporosis, but local fracture liaison services (FLS) offer signs of improvement for secondary fracture prevention in rural populations. FLS and other team-based care can also improve care in places where primary care is overburdened. Review of the NIH portfolio in the past 10 years identified more than two dozen projects examining osteoporosis treatment among patients with other health conditions (e.g., cancer, anorexia nervosa, frail elderly, Parkinson's) and a few projects that were exploring the use of innovative methods, such as the development of prediction tools, that will further scientific knowledge in preventing osteoporotic fractures. Participants also discussed how guidelines on screening for osteoporosis vary by organization and which population is

being screened. The U.S. Preventive Services Task Force (USPSTF) recommends screening for women aged 65 years and older, as well as for postmenopausal women younger than 65 who are at increased risk (B recommendation).¹⁵ However, the USPSTF issued an “insufficient evidence” statement regarding osteoporosis screening for men. In contrast, the VA guideline is to do targeted screening for men at high risk. VA-sponsored studies are finding that targeted screening reduces fractures in men; however, routine screening with dual-energy x-ray absorptiometry (DXA) scans was not associated with a reduction in fractures, primarily due to poor medication adherence despite the lack of financial barriers among veterans in the VA health care system. In a high-risk group of veterans, men were much less likely than women to receive DXA testing, calcium/vitamin D supplements, or BP treatment.¹⁶

1b. Specific Areas of Research Focus: Because standard RCTs can be very expensive, innovative methods and designs will be needed to address many of the recommendations. The Federal Partners discussed the use of existing databases as an efficient way to move forward. The research community could take advantage of observational study designs incorporating causal methods, especially with subjects not eligible for standard RCTs or who have been underrepresented in these studies and include outcome measures that go beyond fracture numbers. Researchers should consider including different racial/ethnic populations (taking into account countries of origin), men, adults with comorbid conditions, and other populations such as women aged 80 years or older in their studies. There could be utility in taking a life-course approach that builds bone density among women before menopause that might reduce the number of women who need treatment for osteoporosis and decrease the amount of time women who require drug therapy are treated with these agents. Other special populations that could benefit from attention from the research community include individuals with mobility disorders, such as those resulting from SCI, stroke, or Parkinson’s disease, and patients on medications that increase their risk for fractures, such as long-term use of glucocorticoids, aromatase inhibitors, or ADT. The Centers for Medicare and Medicaid Services (CMS) is required to address the needs of the beneficiary population the Agency serves, therefore studies that provide evidence on the understudied beneficiary population is critical for CMS-authorized program and policy decisions.

Other research gaps include studies that compare comprehensive osteoporosis treatment (e.g., drug therapy combined with nutrition and exercise interventions) with monotherapy osteoporosis drug treatment. There have been few comparative effectiveness research (CER) studies on the different osteoporosis drug therapies. A network meta-analysis to compare different osteoporosis drug therapies might be valuable, but these studies would need to limit comparisons to the same class of osteoporosis drugs due to the significant cost differences between the classes of drugs. To address the issue of cost differences, CER studies, in combination with cost-effectiveness analyses, may be particularly informative.

More studies that include outcome measures that go beyond fractures—such as hospitalization, pain, death, cost, functional status, nursing home placement, and other measurements of quality of life changes—are also needed. These outcomes are important for patients and physicians to use in their decision making for initiating, pausing, or discontinuing treatment to prevent osteoporotic fractures.

The panel recommendation includes a call for pragmatic trials. The Federal Partners expressed the view that large-scale pragmatic trials to assess long-term osteoporosis treatment and discern optimal durations of drug therapies are helpful for clinical decision making. The Federal Partners also discussed the value of pilot studies, modeling studies, and smaller implementation science studies to inform later pragmatic trials. Of note, pragmatic trials are not always less expensive than standard RCTs to conduct. Making use of electronic medical/health records (EHRs) by designing EHR-embedded trials, such as those supported by the [NIH Health Care Systems Research Collaboratory \(NIH Collaboratory\)](#),¹⁷ may help reduce costs of either type of study.

The research community should know that CMS can provide payment for routine services and care that is reasonable and necessary when delivered to Medicare beneficiaries as part of their participation in a clinical trial as detailed in the CMS [Medicare Clinical Trial Policies](#).¹⁸

Because modeling requires a very specialized expertise that most medical researchers do not have or have limited exposure to, efforts to promote collaboration with and provide access to such expertise for the osteoporosis research community should be explored.

1c. Opportunities for Collaboration Among Federal Agencies, Resources, and Next Steps: The Federal Partners identified the following opportunities and available resources:

- Opportunities to leverage existing resources with data collected on relevant primary outcomes:
 - The FDA’s [Sentinel Initiative](#).¹⁹ Sentinel is the FDA’s national electronic system, which has transformed the way the safety of FDA-regulated medical products are monitored, including drugs, vaccines, biologics, and medical devices. The research community could explore whether opportunities exist to collaborate with the FDA to study the use of osteoporosis drug therapies and the adverse events associated with them, potentially including the more uncommon adverse events for which other data systems may not have adequate numbers of patients.
 - CMS has several resources to assist the research community in gaining access to various sets of administrative data collected on beneficiaries (e.g., Medicare Parts A, B, and D claims data), and also quality data on health care providers and facilities across the care continuum that includes measures of interest to patients, such as functional status, cognitive function, and changes in function and cognitive function.²⁰ Osteoporosis researchers should consider utilizing these expansive and rich data sources to address the workshop panel recommendations with these resources, and the Federal Partners could hold joint webinars to promote their use:
 - [Blue Button 2.0](#).²¹ Blue Button 2.0 from CMS is an application programming interface (API) that contains four years of Medicare Parts A, B, and D data for 53 million Medicare beneficiaries. These data reveal a variety of information about a beneficiary’s health, including type of Medicare coverage, drug prescriptions, primary care treatment, and cost.
 - [Research Data Assistance Center \(ResDAC\)](#).²² Established in 1996, ResDAC is a CMS contractor that provides free assistance to academic, non-profit, for-profit, and government researchers interested in CMS data.
 - [CMS Virtual Research Data Center \(VRDC\)](#).²³ Through ResDAC, CMS offers researchers a secure way of accessing its program data through virtual access to the CMS VRDC. The CMS VRDC is a virtual research environment that provides timelier access to Medicare and Medicaid program data in an efficient and cost-effective manner.
 - [CMS Data Element Library \(DEL\)](#).²⁴ The CMS DEL is the centralized resource for CMS assessment instrument data elements (e.g., questions and responses) and their associated health information technology (IT) standards. The standardized patient assessment data elements are:
 - Function (e.g., self-care, mobility)
 - Cognitive function (e.g., express and understand ideas; mental status, such as depression and dementia)
 - Special services, treatments, and interventions (e.g., need for ventilator, dialysis, chemotherapy, and total parenteral nutrition)

- Medical conditions and co-morbidities (e.g., diabetes, heart failure, and pressure ulcers)
 - Impairments (e.g., incontinence; impaired ability to hear, see, or swallow)
 - Other categories
 - Of special note, approximately 50% of veterans are also Medicare beneficiaries, so there are opportunities to learn about osteoporosis treatment in this population from Medicare claims data.
- Partnership opportunities may exist with the VA as it converts to the Cerner EHR system beginning in 2020.²⁵ Before this occurs, researchers have the opportunity to use VistA/CPRS (i.e., Veterans Health Information Systems and Technology Architecture/Computerized Patient Record System), VA's legacy EHR system, to investigate populations who are at high risk for osteoporotic fractures, such as glucocorticoid and ADT users. The new EHR system may provide opportunities to acquire longitudinal data on evaluation and treatment of osteoporosis.
- Kaiser Permanente and other health maintenance organization (HMO) health systems have established large databases with their members' health care records, and these represent rich data sources for the types of modeling and observational research studies the workshop panel recommended pursuing.
 - The [Health Care Systems Research Network \(HCSRN\)](#)²⁶ is a collaboration among research centers of large health care systems in the United States. HCSRN's [Virtual Data Warehouse \(VDW\)](#)²⁷ facilitates multi-site research as a distributed data-sharing model based on electronic clinical claims and administrative health care data. AHRQ can use Interagency Agreements (IAA) through the [Accelerating Change and Transformation in Organizations and Networks III \(ACTION III\)](#)²⁸ contract mechanism to collaborate with HCSRN on this resource. Care for people with multiple chronic conditions is an AHRQ priority, so there could be opportunities for collaboration specifically in this area.
- The National Heart, Lung, and Blood Institute (NHLBI) has funded multiple ongoing cohort studies that may have relevant data for ancillary studies on osteoporosis prevalence and the race/ethnicity and health profiles of women with osteoporosis (e.g., Women's Health Initiative).
 - [Women's Health Initiative \(WHI\)](#)²⁹ WHI is a long-term national health study that has focused on strategies for preventing the major causes of death, disability, and frailty in older women, specifically heart disease, cancer, and osteoporotic fractures. This multi-million dollar, 20+ year project, sponsored by the NIH through the NHLBI, originally enrolled 161,808 women aged 50-79 between 1993 and 1998.
- The [National Patient-Centered Clinical Research Network \(PCORnet®\)](#)³⁰ PCORnet was developed as a large, highly representative network for conducting clinical outcomes research, including comparative effectiveness research and pragmatic clinical trials. PCORnet offers standardized data across participating health systems.
- [ADVANCE Data Warehouse](#)³¹ OCHIN, a nonprofit health care innovation center comprised of members that include community health centers and other safety net health care providers in the United States, leads the ADVANCE Clinical Research Network, one of the PCORnet clinical data research networks. Its ADVANCE Data Warehouse contains care and health outcomes data on over 5 million safety net patients in the United States.
- [The National Health and Nutrition Examination Survey \(NHANES\)](#)³² NHANES is a program of studies designed to assess the health and nutritional status of adults and children in the United States. The survey is unique in that it combines interviews and physical examinations.

Opportunities exist to collaborate with NHANES to sponsor new questions or tests in future surveys.

- The Foundation for the National Institutes of Health (FNIH) Biomarkers Consortium’s [Bone Quality Project](#).³³ The FNIH manages the Biomarkers Consortium, a public-private biomedical research collaboration that supports studies to identify new biomarkers for clinical practice. The Bone Quality Project was a study funded by this consortium that created a dataset of more than 170,000 patients from 50 RCTs to discover biomarkers of bone strength and to use as surrogate markers for fracture outcome. However, it remains to be seen whether access can be expanded to other researchers in the future.
- The [NIH Collaboratory](#)¹⁷ is an NIH Common Fund program to engage health care delivery organizations (e.g., clinics, hospitals) as research partners in the conduct of pragmatic clinical trials. The NIH Collaboratory has developed [best practices for conducting pragmatic clinical trials](#)³⁴ that would be a valuable resource when addressing the workshop panel’s recommendation related to embedded pragmatic trials.
- For research modeling expertise, the Federal Partners discussed the benefits of using existing expertise outside the field of osteoporosis that is available among NIH staff and the extramural community. For example, the [Cancer Intervention and Surveillance Modeling Network \(CISNET\)](#)³⁵ consortium might serve as a template for the infrastructure that may spur the types of modeling studies on osteoporosis drug therapies the workshop panel recommended. CISNET is a consortium of National Cancer Institute (NCI)-sponsored investigators who use statistical modeling to improve the research community’s understanding of cancer control interventions in prevention, screening, and treatment and their effects on population trends in incidence and mortality.

2. Discussion of P2P Workshop Panel Report [Recommendation 2](#): Future clinical trials should evaluate new agents or multicomponent interventions (e.g., oral care, FLS) that potentially lack the side effects of current antiresorptive treatments and may have greater efficacy.

2a. Background: The workshop panel summarized the need for future clinical research so new treatment options that have improved efficacy and side effect profiles can be developed. Related to this recommendation, a large portion of NIH-funded basic/translational osteoporosis studies can lead to knowledge that may inform developing new therapies with greater efficacy and fewer side effects. In addition, NIH has funded more than two dozen clinical research projects between fiscal year (FY) 2010 and FY 2019 that are focused on developing new or multicomponent osteoporosis treatment modalities or other management strategies related to this recommendation. Examples of the types of interventions being developed with NIH support include dietary supplements, lifestyle interventions, mechanical stimulation devices, new drugs, FLS, and the combination of exercise and therapeutic agents.

2b. Specific Areas of Research Focus: The Federal Partners discussed whether the perceived cost of FLS or other patient navigator services in hospitals where patients are undergoing treatment for osteoporotic fractures is a barrier to implementation. The Geisinger health system has shown the cost-effectiveness of FLS, but more studies may be needed in other health care settings to help reduce this barrier. One effort underway to increase the use of FLS among hospitals and other health care institutions is the American Orthopaedic Association’s [Own the Bone](#) program.³⁶

2c. Opportunities for Collaboration Among Federal Agencies, Resources, and Next Steps: The Federal Partners identified the following opportunities and available resources:

- Datasets described above under P2P Workshop Panel Report Recommendation 1 are also applicable to this recommendation.
- The National Center for Advancing Translational Sciences (NCATS) has infrastructure that may be useful in addressing the P2P workshop panel’s recommendations relevant to implementing clinical trials for new drug therapies and other interventions to prevent osteoporotic fractures—the [Trial Innovation Network \(TIN\)](#)^{37,38} is a collaborative initiative within NCATS’ Clinical and Translational Science Awards (CTSA) Program:
 - Along with the CTSA-funded academic medical centers (i.e., hubs), the NCATS TIN includes two types of centers that are funded through 2022:
 - Three Trial Innovation Centers (TICs) were funded to help investigators with study design issues.
 - One Recruitment Innovation Center (RIC) was funded to help researchers engage and recruit diverse populations into clinical trials.
 - There is the potential to leverage the more than 50 CTSA-funded hubs across the United States to recruit patients for RCTs and pragmatic trials, and opportunities exist to gain support for trial planning and participant recruitment for these studies through TIN.
 - The NIH HEAL (Helping to End Addiction Long-termSM) Initiative’s [Pain Management Effectiveness Research Network](#)³⁹ consists of a set of comparative effectiveness trials that are using the TIN resources on study design and recruitment and can serve as a model for how to leverage this NCATS-supported infrastructure.
- To increase the adoption of FLS programs, one approach is to propose its inclusion as part of the CMS [Bundled Payments for Care Improvement \(BPCI\) Initiative](#).⁴⁰ Through the Center for Medicare and Medicaid Innovation (CMMI) authorized by the Affordable Care Act, and through state demonstration authorities, CMS tests care and payment models that link payments for the multiple services beneficiaries receive during an episode of care. Under the initiative, organizations enter into payment arrangements that include financial and performance accountability for episodes of care. These models may lead to higher quality and more coordinated care at a lower cost to Medicare.

3. Discussion of P2P Workshop Panel Report [Recommendation 3](#): More research is needed to prevent and characterize atypical femoral fracture (AFF) and osteonecrosis of the jaw (ONJ) as rare serious adverse events are associated with long-term bisphosphonate or denosumab use.

3a. Background: In the past 10 years, NIAMS has funded a handful of clinical research projects focused on AFF that address this workshop panel recommendation. Additionally, in the past 13 years, the National Institute of Dental and Craniofacial Research (NIDCR) has funded more than three dozen ONJ research projects on topics such as wound healing, biodistribution of osteoporosis drugs, and risk factors for ONJ. Just over a third of these funded projects on ONJ were submitted to a series of funding opportunity announcements (FOAs) that NIDCR published between 2006 and 2014 that solicited basic, translational, exploratory, and developmental research projects to better understand ONJ.

Several barriers make it challenging to conduct research on AFF and ONJ. For example, for AFF, in addition to the lack of a common definition, there are no specific International Classification of Diseases, Tenth Revision (ICD-10) codes to capture these rare adverse events. For ONJ, care coordination and collaboration between dentists and primary care providers is usually absent or limited. As an example, among Medicare beneficiaries, CMS cannot require physicians to collaborate with non-Medicare paid professionals like dentists. This limits the number of patients who receive a dental pre-screening before initiating osteoporosis drug therapy.

3b. Specific Areas of Research Focus: The pathophysiology and mechanisms of AFF are understudied. NIDCR has made investments in supporting research on ONJ, but the exact pathophysiology is not completely known and therefore could benefit from additional studies. The research community could advance from data and tools for modeling studies to assess risk, incidence, and prevalence of AFF and ONJ. Most patients who experience an AFF require surgery, so the osteoporosis research community could benefit from the establishment of a related surgical network and protocols that would allow for AFF sample collection with relevant patient information. Research studies could confirm the utility of extended DXA femoral scans for early detection for AFF. Furthermore, the extent to which AFFs occur in people who have not been exposed to bisphosphonates is unclear; case-control studies in collaboration with a large health system may be useful here.

3c. Opportunities for Collaboration Among Federal Agencies, Resources, and Next Steps: The Federal Partners identified the following opportunities and available resources:

- An opportunity exists to add AFF to NHANES data collection for the 2021 or 2022 surveys, and it might be possible to expand existing NHANES DXA measurements to include extended femoral scans, but such additions would be expensive.
- The [WHI study](#)²⁹ (described above) captured observational data that could be used to examine research gaps related to ONJ, but WHI does not contain data on AFF.
- The NIH, VA, and Department of Defense (DOD) could consider collaborating on research to advance the science related to the pathophysiology and mechanisms involved in developing AFF and ONJ.

4. Discussion of P2P Workshop Panel Report [Recommendation 4](#): More evidence and research are needed to determine which patients are optimal candidates for drug holidays and sequential therapies, and possible strategies for mitigating serious adverse events associated with long-term bisphosphonate or denosumab use (i.e., AFF and ONJ).

4a. Background: “Drug holidays” and sequential/combo therapy are two treatment approaches that attempt to maximize the beneficial effects while decreasing the chance of rare but serious adverse events such as AFF or ONJ for patients taking osteoporosis drug therapies. Drug holidays are periods of time when a patient temporarily discontinues taking bisphosphonates or denosumab to minimize their chances of developing an AFF or ONJ. Sequential therapy is when a patient takes one class of osteoporosis drug therapy when initiating treatment for a period of time before switching to a medication belonging to a different class of osteoporosis drug therapy. Some patients combine drug holidays with sequential therapy. In the NIH portfolio, there were approximately 10 clinical projects over the past decade that address the P2P workshop panel’s recommendation on osteoporosis drug holidays and sequential therapy.

4b. Specific Areas of Research Focus: The Federal Partners agreed with the workshop panel that the bone health field would benefit from having a consensus definition of drug holiday. However, more data on how drug holidays are being implemented in clinical practice are needed to inform the development of a consensus definition. The Federal Partners asked whether other terms should be used that convey more accurate information so that patient-provider communications regarding drug therapy options are more effective. For example, the term holiday implies the absence of treatment, but bisphosphonates are deposited in bone where they have a long half-life. This means that a patient who stops taking a bisphosphonate will continue to receive some osteoporotic fracture prevention benefit from the medication they already took, although this benefit will wane as the medication deposited in their bones is depleted.

Research studies on drug holidays will need very large sample sizes to determine whether periods of temporary medication discontinuation can retain the fracture prevention benefit and reduce the incidence of AFF and ONJ. The variable length of these holidays in clinical practice further adds to the complexity of this research question. A good platform may be modeling studies utilizing data available in EHRs to mine patient records for DXA measures, fractures, treatment duration, and the medication drop off period. Modeling studies are only as good as the data that is available to go into the model, so the research community would benefit from harmonizing across disease registries (e.g., orthopaedic or dental data sources) to ensure needed endpoints are collected with common data elements. The Federal Partners also discussed the need to use real world evidence and conduct observational studies and secondary data analysis that capture drug holidays; a collaboration with the [HCSRN](#)^{26,27} might provide a good match for this research. Social media data mining tools could provide information in the aggregate on important factors that inform patients' decisions on whether to take a drug holiday from social media posts; this could supplement the data captured in EHRs.

In addition to osteoporosis drug therapies that are associated with rare serious adverse events, researchers should consider looking more comprehensively at other types of interventions that could help prevent osteoporotic fractures like those related to falls prevention and adequate nutrition. In terms of considering whether patients can benefit from a combination of lifestyle changes (e.g., increasing exercise) and drug therapy, research studies could help determine what the best balance is and how this fluctuates during a drug holiday. For patients who have not yet started treatment with osteoporosis drug therapy or are taking a drug holiday, there is also an opportunity for studies to collect information on what else patients are doing to prevent osteoporotic fractures (e.g., falls prevention activities).

Researchers could consider partnering with pharmacies on improving adherence and on studies focused on the long-term use of osteoporosis drug therapies and drug holidays; for example, pharmacies can send prescription reminders to patients to help increase medication adherence rates or help with the transition back onto a drug therapy at the conclusion of a drug holiday.

4c. Opportunities for Collaboration Among Federal Agencies, Resources, and Next Steps: The Federal Partners identified the following opportunities and available resources:

- CMS Part D data may be useful in identifying treatment uptake and gaps in prescriptions filled.
- Pharmacy-based patient reminders to improve medication adherence and for patients at the conclusion of drug holidays is a research opportunity.
- There was interest among the NIH Federal Partners to hold webinars on research needs related to panel recommendation and the resources available to the research community:
 - NCATS could cover the CTSA program and public-private partnerships.
 - The National Center for Complementary and Integrative Health (NCCIH) could cover the NIH Collaboratory.
 - NIH Institutes and Centers (ICs) could reach out to their trainees to encourage them to tap into existing datasets.

5. Discussion of P2P Workshop Panel Report [Recommendation 5](#): More research on barriers to osteoporotic drug therapy is needed.

5a. Background: The FDA has granted approval to a range of drugs that are effective in decreasing fracture incidence in osteoporosis patients. Available data show low uptake of these drugs by individuals with osteoporosis for both primary and secondary fracture prevention. The Federal Partners agreed with the panel recommendation that more research should be devoted to investigating barriers on osteoporosis therapies and ways to overcome these barriers.

The [P2P workshop panel report](#)² summarizes the identified barriers that were presented at the workshop and that may contribute to low prescription and uptake of osteoporosis drug therapies among people at risk for osteoporotic fractures, as well as low adherence rates. The Federal Partners discussed the impact of perceptions of rare serious adverse events, such as AFF and ONJ, on therapy uptake for patients who are at risk of fracture. In addition, osteoporosis is asymptomatic until a fracture occurs, so some patients do not start pharmaceutical treatment, while others start but then stop taking medications, because the pharmaceutical regimen does not improve how they feel. Patients with other health conditions face similar challenges; examples include patients with a history of myocardial infarction who discontinue statin therapy because they experience no perceived benefit. The osteoporosis field may benefit from lessons learned and successful strategies from other fields.

For patients at risk of osteoporotic fracture, drug therapies come with other, more common side effects that can discourage uptake or lead to medication cessation. For example, patients can experience gastroesophageal reflux from taking oral bisphosphonate tablets or have temporary flu-like symptoms following IV bisphosphonate infusions. However, some of these more common side effects can usually be well controlled if brought to medical attention. Out-of-pocket costs of the drugs (and, if applicable, hospital facility fees to administer them) can be a barrier that limits the uptake of some osteoporosis drug therapies or constrains patients' choices based on which medications they can afford to take; however, cost is less of a barrier for some patient populations, like veterans who receive care within the VA health care system.

5b. Specific Areas of Research Focus: Psychosocial and behavioral health and dissemination and implementation (D&I) research, which seeks to understand how evidence-based practices, interventions, and policies are effectively translated to and used in real-world settings, will be important for addressing this panel recommendation. The Federal Partners perceive a need for more researchers from these disciplines in the osteoporosis field, based in part on NIH portfolio analyses conducted for the Federal Partners meeting. The portfolio analysis showed a paucity of clinical research projects in the past 10 years that aim to understand the barriers limiting the uptake of osteoporosis drug therapies and explore various approaches to mitigate them. More research is needed to identify where the barriers are—with providers, patients, or both—that limit the uptake of osteoporosis drug therapy. Research on dissemination, implementation, and communication practices could be particularly beneficial for this P2P workshop panel recommendation and research into social and behavioral determinants of health should be considered when addressing these barriers. The Federal Partners discussed the importance of studies that include outcome measures other than just fractures that are important to patients, such as quality metrics, which are also important to CMS. Studies to better understand the incidence of AFF and how to predict and mitigate AFF risk could help to ease patients' fear of the association of some osteoporosis drugs with this rare but serious adverse event. As noted above, the Federal Partners felt that before the osteoporosis research field conducts large-scale pragmatic trials, smaller studies could provide a better understanding of the barriers to treatment adherence and prescribing practices. The Federal Partners identified an opportunity for researchers to partner with community-based organizations to study the benefits of chronic-disease self-management and falls prevention programs that assist patients with osteoporosis in staying compliant with their treatment goals to prevent fractures.

Testing models of care could improve appropriate uptake of pharmaceutical treatments. Team-based care may provide a good model, but more information is needed on the role of other health professionals and support personnel (e.g., physical therapists, nutritionists). Studies on shared decision making and patient attitudes could determine which factors are important for effective shared decision making. Research into clinical decision support tools that build prompts into the EHR and help alert clinicians to the need to discuss fracture prevention medication with appropriate patients is an

understudied area. More user-friendly clinical decision support tools could be beneficial; an example is the VA's use of expert e-consults that use telehealth to help with clinical decision making among primary care providers and their patients.

5c. Opportunities for Collaboration Among Federal Agencies, Resources, and Next Steps: The Federal Partners identified the following opportunities and available resources:

- Several partners have interest in collaborating in D&I research, as well as in studies of patient/provider knowledge, attitudes, beliefs, and barriers to osteoporosis therapy uptake.
 - AHRQ has interest in collaborating with NIH on D&I efforts: one possibility is to develop a series of workshops in various formats on identifying and addressing barriers that could be shared with other professional societies.
 - Existing active trans-NIH FOAs (and possible reissuances) could be used to support D&I research. For example:
 - PAR-19-274: [Dissemination and Implementation Research in Health \(R01 Clinical Trial Optional\)](#)⁴¹
 - PAR-19-275: [Dissemination and Implementation Research in Health \(R21 Clinical Trial Optional\)](#)⁴²
 - PAR-19-276: [Dissemination and Implementation Research in Health \(R03 Clinical Trial Not Allowed\)](#)⁴³
- Effective decision support tools and models from other organizations and/or fields could be adapted for osteoporotic fracture prevention:
 - One example of a decision aid is the [Prostate Cancer Screening: Should I Have a PSA Test?](#)⁴⁴ tool from the [Dartmouth Center for Shared Decision Making](#).⁴⁵
 - AHRQ developed the [SHARE Approach](#),⁴⁶ which is a five-step process for shared decision making that includes exploring and comparing the benefits, harms, and risks of each option through meaningful dialogue about what matters most to the patient. Training materials and other resources for health professionals are available on the AHRQ website.
 - AHRQ also created the [Clinical Decision Support \(CDS\) Connect Repository](#),⁴⁷ which is a project that demonstrates a web-based repository service to enable the CDS community to identify evidence-based standards of care, translate and codify information into an interoperable standard, and leverage tooling to promote a collaborative model of CDS development.
 - AHRQ has several D&I efforts underway that could inform the D&I science on osteoporosis:
 - Cardiac rehabilitation has an established evidence base demonstrating the benefits of using this multicomponent treatment model and AHRQ is collaborating with the American Hospital Association to increase the uptake of cardiac rehabilitation nation-wide.
 - Opioid use by older adults is a topic where the evidence base is much more limited, so AHRQ is conducting an environmental scan through the [ACTION III](#)²⁸ network to learn about the innovative approaches health systems are implementing, which will inform future efforts to advance the science in this field.
- Dissemination could be a trans-agency effort to communicate research results:
 - The Administration on Aging/Administration on Community Living has a number of public-facing resources relevant to osteoporosis, such as materials on falls prevention,

and could help with public education and outreach activities through the [Aging and Disability Resource Centers \(ADRC\)](#)⁴⁸ it supports with the Council on Aging.

- The U.S. HHS [Office on Women's Health \(OWH\)](#)⁴⁹ can assist with communication, messaging, and other dissemination efforts via the OWH website and helpline.
- The [NIH Osteoporosis and Related Bone Diseases National Resource Center website](#)⁸ could be used to promote relevant information.
- Opportunities to collaborate with the [Health Resources and Services Administration \(HRSA\)](#)⁵⁰ and HRSA-funded Federally Qualified Health Centers should be explored.
- NCATS has developed [template agreements](#)⁵¹ for Memorandum of Understanding, Confidential Disclosure Agreements, and Collaborative Research Agreements that could be helpful when establishing public-private partnerships with industry.
- [NCATS patient engagement days](#)⁵² could be used as a model for obtaining the perspectives of patients with osteoporosis or at risk for osteoporotic fractures when developing research initiatives.

Next Steps

While the Federal Partners Meeting represents the conclusion of formal P2P program activities related to the appropriate long-term use of drug therapies for osteoporotic fracture prevention, efforts are underway to address the research gaps identified from this workshop. This includes the convening of special sessions at relevant scientific meetings to disseminate findings from the workshop. On September 22, 2019, a special session was held at the [2019 American Society for Bone and Mineral Research \(ASBMR\) Annual Meeting](#)⁵³ titled, National Institutes of Health Pathways to Prevention Workshop: Research Gaps for Long-Term Drug Therapies for Osteoporotic Fracture Prevention. A similar session was held at the [Gerontological Society of America \(GSA\) Annual Meeting](#) in November 2019.⁵⁴

The Federal Partners ended their meeting by categorizing next steps for research activities related to appropriate use of osteoporosis drug therapy based on the prioritization and readiness for action of each activity:

- Immediate Steps:
 - Explore opportunities to encourage studies on identifying patient/provider knowledge, attitudes, beliefs, and barriers to therapy uptake, as well as strategies to foster shared decision making related to appropriate drug use (including drug holidays).
 - Encourage research into understudied aspects of AFF and ONJ.
 - Host workshops and webinars on available resources for studies of existing osteoporosis drug therapies.
 - Explore opportunities to collaborate with Federal Partners on communication and dissemination efforts.
 - Explore opportunities to encourage studies that use available large datasets described above, including modeling studies (this can be intermediate steps depending on availability of resources and expertise).
- Intermediate Steps:
 - Explore opportunities to encourage studies on different care management strategies, such as FLS and other team-based case-management models.
 - Explore opportunities to promote research on addressing barriers to the appropriate use of drug therapies.
- Long-Term Steps:
 - Promote collaboration with researchers from other fields.

- Promote collaboration among Federal Partners on areas of mutual interest related to communication and dissemination efforts as well as research efforts.
- Explore opportunities to encourage pragmatic trials and other strategies to address the workshop panel recommendations.

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Appendix A: Systematic Evidence Review Key Findings

A [systematic evidence review of the scientific literature](#),¹³ guided by the key questions, was conducted by the Minnesota Evidence-based Practice Center through a contract with AHRQ to facilitate the workshop discussion and [was published in the *Annals of Internal Medicine*](#).¹ The purpose of the systematic evidence review was to provide an evidence-based synthesis of the research base and suggest areas where future research is needed to advance the clinical practice of osteoporotic fracture prevention.

- Evidence on the effects of long-term osteoporosis drug treatment and drug continuation versus discontinuation is mostly limited to white, healthy, postmenopausal women.
- Long-term alendronate reduces radiographic vertebral and nonvertebral fractures in women with osteoporosis; long-term zoledronate reduces vertebral and nonvertebral fractures in women with osteopenia or osteoporosis.
- Long-term bisphosphonates may increase atypical femoral fractures (AFFs) and osteonecrosis of the jaw (ONJ), although both are rare.
- In women with osteoporosis, long-term raloxifene reduces vertebral fractures, but not hip or nonvertebral fractures, and increases venous thromboembolism.
- Long-term oral hormone therapies reduce hip and clinical fractures but increase multiple serious harms.
- Evidence is insufficient about the effects of long-term denosumab, risedronate, ibandronate, teriparatide, and abaloparatide on fractures and harms.
- Continuing bisphosphonates after 3–5 years versus discontinuation reduces some measures of vertebral fractures, but not nonvertebral fractures.

The [systematic evidence review](#)¹³ identified the following recommendations¹³ for future research that, if addressed, would further the scientific knowledge on the benefits and risks of longer-term osteoporosis treatment to prevent fractures:

- Future long-term osteoporosis treatment trials that compare drug holidays to continued treatment should be devised with the required statistical power to examine risks of fracture endpoints like hip fractures, which have the greatest negative impact on morbidity and mortality.
- Research studies need more diverse study samples that include men, racial, and ethnic minority women, patients with comorbidities, and adults aged 80 years and older so results are more generalizable.
- Sequential osteoporosis drug treatment trials are needed that compare continuous long-term antiresorptive therapy to both anabolic-then-antiresorptive therapy and denosumab-then-bisphosphonate therapy.
- Trials are needed that look at various drug holiday iterations in terms of duration, whether medications are restarted, and multiple treatment/drug holiday cycles; observational studies can further provide information on the benefits and harms of various durations of drug holidays and which patients benefit from these breaks and those who should forego holidays and continue drug therapy.
- Information on harms should be systematically collected, analyzed, and reported in future research studies on the long-term use of drug therapies for osteoporotic fracture prevention.
- Rare harms like AFF and ONJ will remain difficult to study in clinical trials due to inadequate statistical power, so examining these harms in observational studies is needed.

- To minimize confounding by indication and selection bias, observational studies should apply consensus case definitions, standard non-case and exposure controls, cohort designs to determine incidence rates, and appropriate statistical adjustments.
- Future research studies should examine potential effect modifiers of the benefits and harms of long-term therapy and outcomes associated with drug holidays, such as age, bone mineral density (BMD), and bone turnover markers (BTMs).
- Future osteoporosis drug therapy trials should determine how suitable BMD and BTMs are in serving as surrogate measures for new fractures.

Appendix B: Workshop Panel Report Recommendations

The [Workshop Panel Report for the P2P Workshop: Appropriate Use of Drug Therapies for Osteoporotic Fracture Prevention](#)² recommendations are:

1. In assessing both existing and potential treatments and optimizing duration, researchers should make use of innovative designs and approaches, including:
 - a. Modeling studies: Include biological and nonbiological determinants of fractures and how much of the biological pathway a treatment mitigates.
 - b. Clinical trials: Apply comparative effectiveness designs, embedded pragmatic trials, preference designs, sequential intervention designs, adaptive trial methodology, and platform trials; include fracture sequelae outcomes (functional status, mobility, hospitalizations, and nursing home placement).
 - c. Observational studies: Apply causal methods; include fracture sequelae; include diverse populations (e.g., men, racial/ethnic groups, people with multiple chronic conditions, people in various residential settings, people with high fracture risk who do not have osteoporosis); estimate drug interactions.
2. Future clinical trials should evaluate new agents or multicomponent interventions (e.g., oral care, FLS) that potentially lack the side effects of current antiresorptive treatments and may have greater efficacy.
3. More research is needed to prevent and characterize atypical femoral fractures (AFF) and osteonecrosis of the jaw (ONJ) as rare serious adverse events are associated with long-term bisphosphonate or denosumab use.
 - a. Studies should use standard case definitions for these complications.
 - b. Studies should assess incidence by race/ethnicity, risk factors, comorbidities, concurrent medication usage, pathogenesis, algorithms to predict risk, and interventions to reduce incidence.
4. More evidence and research are needed to determine which patients are optimal candidates for drug holidays and sequential therapies, and possible strategies for mitigating serious adverse events associated with long-term bisphosphonate or denosumab use (i.e., AFF and ONJ).
 - a. Studies are needed that are drug- and patient-specific, and that establish optimal timing and duration of and follow-up for drug holidays.
 - b. Concurrent study of the efficacy of lower-dose bisphosphonate therapy, as a means of delaying or preventing the need for drug holidays, is needed.
 - c. Designs listed in 1a and 1b and analyses of existing data would provide a more real-world picture of drug therapy discontinuation.
 - d. A consensus definition of “drug holiday” would facilitate data collection and interpretation.
 - e. The use of other pharmacologic therapies to supplement bisphosphonate treatment or replace it during drug holidays requires evaluation.
 - f. Studies to establish the appropriate timeframe, order, medication type, and optimal patient characteristics for sequential therapy are needed.
5. More research on barriers to osteoporotic drug therapy is needed.
 - a. More empirical studies, and particularly randomized, controlled trials, are needed to provide evidence on the efficacy of different management approaches, such as hospital-based FLS and other case management models.

- b. Studies assessing who initiates treatment, who does not, and why will increase understanding of the numerous factors that influence decisions about osteoporotic drug therapy use.
- c. Studies that examine patient and provider attitudes and that identify ways of increasing long-term use of osteoporotic drug therapies are needed.
- d. Research that establishes the best context for shared decision making among patients, providers, family members, and other informal caregivers would help to mitigate many patient- and provider-related barriers.

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Note: A representative from the U.S. Food and Drug Administration participated in planning activities for this workshop but was unable to attend the Federal Partners Meeting.

Appendix D: Federal Partner Initiatives and Resources Relevant to Appropriate Use of Drug Therapies for Osteoporotic Fracture Prevention

National Institutes of Health (NIH)	
	Cancer Intervention and Surveillance Modeling Network (CISNET) ³⁵
	National Center for Advancing Translational Sciences (NCATS) Patient Engagement Day ⁵²
	NCATS Template Agreements ⁵¹
	NCATS Trial Innovation Network (TIN) ³⁸
	NIH Health Care Systems Research Collaboratory (NIH Collaboratory) ¹⁷
	NIH Collaboratory Living Textbook of Pragmatic Clinical Trials ³⁴
	NIH Osteoporosis and Related Bone Diseases National Resource Center ⁸ (for communication, dissemination, and outreach of fracture prevention messages)
	Trans-NIH Dissemination and Implementation (D&I) Funding Opportunity Announcements (FOAs):
	<ul style="list-style-type: none"> • PAR-19-274: Dissemination and Implementation Research in Health (R01 Clinical Trial Optional)⁴¹ • PAR-19-275: Dissemination and Implementation Research in Health (R21 Clinical Trial Optional)⁴² • PAR-19-276: Dissemination and Implementation Research in Health (R03 Clinical Trial Not Allowed)⁴³
	Women's Health Initiative (WHI) ²⁹
Administration for Community Living (ACL)	
	ACL Aging and Disability Resource Centers ⁴⁸
Agency for Healthcare Research and Quality (AHRQ)	
	Clinical Decision Support (CDS) Connect Repository ⁴⁷
	The SHARE Approach ⁴⁶
Centers for Disease Control and Prevention (CDC)	
	National Health and Nutrition Examination Survey ³²
Centers for Medicare and Medicaid Services (CMS)	
	Blue Button 2.0 ²¹
	CMS Bundled Payments for Care Improvement (BPCI) Initiative ⁴⁰
	CMS Data Element Library (DEL) ²⁴
	CMS Virtual Research Data Center (VRDC) ²³
	Medicare Clinical Trial Policies ¹⁸
	Research Data Assistance Center (ResDAC) ²²
Office on Women's Health (OWH)	
	OWH Helpline (1-800-994-9662) ⁴⁹ (for communication, dissemination, and outreach of fracture prevention messages)
U.S. Food and Drug Administration (FDA)	
	Sentinel Initiative ¹⁹