

The Voice of the Patient

OA affects more than 30 million American adults.

#1 most desired treatment outcome is pain reduction.

OA is linked to increased rates of comorbidities.

Osteoarthritis (OA) impacts everyday activities.

There is no cure.

OA is the most common articular disease of the developed world and the leading cause of chronic disability.

OA brings loss of independence and feelings of isolation.

This is a summary report resulting from the Arthritis Foundation's externally-led Patient-Focused Drug Development meeting, a parallel effort to the FDA's Patient-Focused Drug Development Initiative. This report reflects the perspectives of patients and caregivers who participated in the meeting. No source of funding was received for the meeting.

Osteoarthritis
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Introduction

On March 8, 2017, the Arthritis Foundation, FDA, osteoarthritis (OA) patients, drug developers, health care providers and academic researchers came together to discuss the serious burden of OA disease, particularly the most significant OA-related symptoms, the impact of those symptoms, currently available treatments and ideal treatments. Patients shared how OA affects their lives as well as the gaps in treatment to provide the rationale required for choosing clinical trial endpoints that are clinically meaningful to patients living with OA.

More information on externally-led PFDD meetings can be found at <https://www.fda.gov/forindustry/userfees/prescriptiondruguserfee/ucm453856.htm>

Overview of Osteoarthritis

OA is the most prevalent form of joint disease, affecting 30.8 million adults in the United States (13.4% of the civilian adult US population). This estimate is conservative as it misses those who have not yet been officially diagnosed by a doctor and may not be aware that they have OA as well as those who are institutionalized. In the US, it is the leading cause of disability amongst those 65 years of age and older. Notably, 2 million Americans under 45 years of age are currently diagnosed with knee OA. The prevalence in children are uncertain yet it is well known that among youth, sports participation is the leading cause of injury. Additionally, sports injuries are associated with a 4-fold increased risk of developing post-traumatic OA (PtOA) 12-20 years after a knee injury compared to the uninjured population. A white paper entitled "Osteoarthritis: A Serious Disease" written by Osteoarthritis Research Society International (OARSI) and provided to the US Food and Drug Administration in January 2017 provides comprehensive data demonstrating how OA meets the current definition of a serious condition, defined as "a disease or condition associated with morbidity that has substantial impact on day-to-day functioning" (21 CFR 312.300(b)(1)). OA encompasses all aspects of a serious condition including morbidity and mortality. Levels of disability can range from mild, when it may cause intermittent pain with minimal difficulty performing daily activities, to severe with constant chronic pain, progressive irreversible structural damage and progressive loss of function. Increases in pain and reduced function are associated with decline in mental and overall health; subsequently, increasing mortality when a person is no longer able to walk or live independently. Pain from arthritis is one of the key barriers to maintaining physical activity and can be considered a key factor in onset of frailty in the elderly. OA is associated with increased all-cause mortality, believed in part due to inability to perform physical activity. In fact, the more severe the walking disability, the higher the risk of death, largely due to cardiovascular disease. OA is associated with comorbidities, significantly limiting a person's ability to self-manage additional conditions such as diabetes and hypertension. The impact of OA on quality of life is complex and multi-factorial.¹

There is no cure for osteoarthritis and the plethora of treatment options which aim to reduce symptoms and improve the quality of life are lacking in one or both aspects. There are numerous non-pharmacologic and pharmacologic interventions for OA, yet there is no known proven strategy for reducing progression from early to end-stage OA. Many individuals may be in a health state that would be considered severe enough for total joint surgery, but a variety of factors are barriers to appropriate care.¹ Notably, some comorbidities constitute contraindications to using OA therapies such as non-steroidal anti-inflammatory drugs (NSAIDs). Treatment related adverse events and the paucity of effective treatment options, create an urgent need for clinical studies of new and existing agents which may intervene in the pathophysiology and progression of OA. Most importantly, therapies must improve how a patient feels, functions and survives. Clinical trials for OA must choose outcomes which are most meaningful to the patient (such as fatigue, functional status, independence, pain, etc.). It is imperative to comprehend patient preferences not merely for symptom modifying treatments; most importantly, patients' paramount priority is for structure (disease) modifying treatments which prevent disease and stop OA disease progression.

The purpose of this meeting was to gain an up to date understanding of the treatment outcomes most meaningful to patients in the current landscape of OA therapy. These results are meant to inform the design of clinical trials for OA to facilitate choices of outcomes now most meaningful to patients. Results of this meeting suggested that current patient preferences are not merely for symptom modifying treatments; most importantly, a paramount patient priority is now structure (disease) modifying treatments that prevent disease early in it's course and halt OA disease progression and onset of disability. In response to solicitation for their ideal treatment perspective, participants repeatedly emphasized they care most about treatments for disease prevention and stopping progression.

1. For more information on the Arthritis Foundation's sponsored Osteoarthritis Research Society International (OARSI) White Paper; Osteoarthritis: A Serious Disease, Submitted to the U.S. Food and Drug Administration, refer to:
https://www.oarsi.org/sites/default/files/docs/2016/oarsi_white_paper_oa_serious_disease_121416_1.pdf

Meeting overview

This meeting provided key drug development stakeholders the opportunity to hear directly from patients, caregivers, and other patient representatives about their lived experiences with osteoarthritis and its treatments. The discussion focused on two key topics: (1) disease symptoms and daily impacts of osteoarthritis which matter most to patients and (2) patients' perspectives on current approaches to treating symptoms of osteoarthritis. Stakeholders were particularly interested in hearing from patients about their fatigue, functional impairment and pain symptoms as well as what the ideal patient-centered treatment approach would be. The questions discussed are presented in Appendix 1.

For each topic, a panel of patients (Appendix 2) shared comments to begin the dialogue. Panel comments were followed by large-group facilitated discussions inviting comments from other patients and patient representatives in the audience. A PCORI-trained Arthritis Foundation staff member facilitated the discussion. Participants who joined the meeting via the live webcast (referred to in this report as web participants) were invited to contribute comments throughout the discussion. In addition, in-person and web participants were periodically invited to respond to polling questions (Appendix 3), which provided a sense of the demographic makeup of participants and how many participants shared a particular perspective on a given topic.

Approximately 50 osteoarthritis patients or patient representatives attended the meeting in-person. Approximately 81 people attended the meeting through the live webcast contributing input. According to their responses to questions, in-person and web participants represented the full spectrum of severity observed in the osteoarthritis patient population. There was a higher proportion of female versus male participants (90% female, 10% male) overall, yet the patient panel represented 40% males. The largest age group of participants also represented that which has been reported previously in the literature with the majority over age 65 and most participants overall between the ages of 61 to 70. Participants also represented a wide range in duration since time of diagnosis from less than five years ago to more than 20 years ago with approximately 78% of participants reporting a diagnosis of osteoarthritis five or more years ago and 54% of participants reporting a diagnosis more than 10 years ago.

While the participants' disease represented a broad range of osteoarthritis aetiologic phenotypes including, biomechanical, inflammatory, chronic degenerative, familial, post-traumatic, etc., more than half of the participants indicated having a family history of osteoarthritis. More than a quarter of those surveyed noted OA associated with a previous injury or accident, which coincides with prevalence reports in the PtOA literature. Participants indicated a myriad of joint locations affected by osteoarthritis including, toe, foot, ankle, knee, hip, hand, wrist, lumbar spine, elbow, thoracic spine, shoulder, cervical spine, etc. Although participants in this meeting may not fully represent the many diverse phenotypic populations living with osteoarthritis, they provided representation which coincides with patients in the OA community. To solicit comprehensive input, ensuring representation of those in rural areas and those who may not have been able to attend in person, the Arthritis Foundation conducted pre-meeting patient engagement activities including focus groups and national polls prior to the March 8th meeting. These findings are presented in Appendix 5.

Report overview and key themes

This report summarizes the input shared by patients and patient representatives during the meeting or through the webcast. To the extent possible, the terms used in this report to describe specific osteoarthritis symptoms, impacts, and treatment experiences reflect the words used by in-person or web participants. The report is not meant to be representative in any way of the views and experiences of any specific group of individuals or entities. There may be symptoms, impacts, treatments, or other aspects of osteoarthritis which are not included in this report.

The input from the meeting underscores the burden and debilitating effect OA disease has on patients' lives as well as the diversity in patients' experiences with OA, whilst providing insight on shared experiences from the patients' perspective trying to manage the endless challenges caused by OA. It further highlights the immense emotional, physical and social impact the disease exerts on patients' lives. Several key themes emerged from this meeting: difficulty with diagnosis, daily impact of OA symptoms, urgent need for additional treatment options, developing management options with meaningful benefits for patients and most importantly, developing drugs which prevent OA disease or at minimum halt disease progression.

The patient input generated through this meeting strengthens the drug development community's understanding of the burden of osteoarthritis on patients and the treatments currently used to treat osteoarthritis and its symptoms. For example, Appendix 4 shows how this input may directly support FDA's benefit-risk assessments for medical products under review. This input may also be of value to the drug development process more broadly. For example, it may be useful for drug developers to explore integrated -omics analysis and/or pathway analysis for familial or post-traumatic osteoarthritis indications or as they define clinical endpoints related to fatigue, functional limitations, impaired mobility, pain and other symptoms. Most notably, as aforementioned- this report emphasizes the need for drug developers to shift the paradigm to focusing on disease prevention and stopping progression instead of merely treating and/or masking symptoms. Patients emphasized the dire need to explore options which limit disease progression or prevent it altogether. It further highlighted the unmet need for development and qualification of early diagnostic and prognostic measures in the various phenotypes across the disease spectrum as well as joint specific locations.

Topic 1: Disease Symptoms and Daily Impacts That Matter Most to Patients

The first discussion topic focused on patients' experiences with their osteoarthritis symptoms and how these symptoms affect their daily lives. The discussion questions for this topic can be found in Appendix 1.

Five patient panelists (Appendix 2) provided comments to begin the dialogue. They included:

- Kathy was a certified group fitness instructor and personal trainer for 25 years. She managed Arthritis Foundation exercise programs for seven years until she was unable to continue this position due to her increasing challenges with osteoarthritis. She was diagnosed approximately 20 years ago with early onset OA in her 40s and has endured 10 surgeries since. She shared, *"my life with osteoarthritis is all about starts and stops... I live every day worrying about which joint will be affected next... Osteoarthritis is not an acute, life-threatening disease, but it is insidious. It slowly chips away at your cartilage and your spirit... I have finally accepted that I am living with a chronic, progressive, degenerative disease for which there is no cure and not even a way to halt its progression."* She sees her orthopedist regularly, yet her OA is not well controlled with her current treatment.
- Ed is a 69-year-old man retired in Florida. What was subsequently diagnosed as Heberden's nodes started to appear on his fingers in his early 30s. In his early 60s, he received a delayed diagnosis of osteoarthritis during an MRI examination of his knee just prior to learning he would need to undergo surgery for a total joint replacement. Many of the activities he enjoys are now much more difficult or have been discontinued because of his unremitting osteoarthritis pain symptoms. *"Vegetable gardening used to be a special pleasure. I stopped having one about six years ago. Getting up from the ground is a challenge. Pruning, no way. It was close to 30 years between the development of nodes on my finger and I got a diagnosis."* OA has impacted Ed's life considerably and he is willing to accept some level of pain in favor of improved function, yet insists on earlier diagnosis in order to intervene earlier in the disease process and prompts patient-provider concordance in the perception of OA disease.
- Donna is 72 years of age and resides in California. She realized OA was having an impact on her daily life when she had to give up her car for one with a higher seat, *"I realized that was the first big thing I gave up as my OA pain became more and more of an issue in my life. My current challenge is spinal stenosis, as the neck vertebrae begin a slow deterioration. When I reach the point where I have trouble glancing over my shoulder to change lanes, I guess I'll have to give up driving.* She considers her hip OA controlled by joint replacement surgery, yet worries she will outlive the life of her replacement and her spine osteoarthritis *"marches on"* for which she does not have an option to control the pain or stop the deterioration.
- Bruce was a pastor for forty years, recently retired. He has osteoarthritis and presently does some part-time preaching while taking care of his wife full-time. *"I am the primary caregiver for my wife. That means I'm the one has to get up and move her around, because she's a total invalid. For me, because it's in my back, it's gotten to the point I can no longer lift her. I now had to incorporate lifts in the house, so I have a track system in the bedroom and the bathroom and the living room, which of course the government and Medicare does not pay for. For my wife, it's a life-threatening issue, not only because she has it and endures the pain, but I have it and am unable to take care of her as I should."* The lack of options to control OA pain symptoms for Bruce and his wife has a profound impact not solely on his life, but also that of his wife's.

- Kay is a U.S. Army veteran. After 10 years, she ended her time in service and received an honorable discharge. Kay noticed her own struggles with pain as a result of osteoarthritis, but wasn't actively diagnosed until after her time in service. *"I'm now a part of the statistic of numerous veterans with doctor-diagnosed arthritis. Now I emphasize the word "now" because during my time on active duty, I was not able to acknowledge a pain. My pain continued to persist, and it was causing me to retreat to my bed while my other soldiers were enjoying extracurricular activities, sightseeing, and just being normal young soldiers. But that was the military culture. You suck it up and drive on. Arthritis is a silent enemy to those of us in the military.* Kay remains an active advocate for those living with OA, whilst trying to stay positive through the many aspects in which OA symptoms impact her life.

The panelists' statements provided an explicit description of the burden of daily symptoms and prolonged living with osteoarthritis. They described the day-to-day limitations of living with osteoarthritis, and in particular, the challenges they and their loved ones' face in living with the constant pain, fatigue, functional limitations, impaired mobility and stiffness. Their descriptive recounting provided additional insight into the complex multi-factorial emotional, psychological and social impacts of the condition.

Web participants similarly reported the aforementioned symptoms as most significant. The large-group facilitated discussion provided further insight into how these and other osteoarthritis symptoms were first realized and continued unrelenting to date without a viable option to halt progression, reduce pain and improve function. A delayed diagnosis was common amongst all participants, further emphasized when participants repeatedly shared a discordant patient-provider perception of OA disease. The range of symptoms discussed with in-person and web participants are described further below.

Perspectives on most significant symptoms

Pain/tenderness

Both pain and tenderness were identified as having the most significant impact on participants' daily lives. The significant impact of these symptoms was realized immediately as participants repeatedly described the many modifications they have to make on a daily basis to avoid OA pain. One participant stated, *"I began the saga of giving up and cutting down in an effort to cut down on the pain."* Several participants admitted that they *"endure the pain," "suck it up"* and *"it's life"* after listing the treatments they have tried and failed for OA pain, or were unable to try due to comorbidities. Many participants agreed that the pain is worse when sitting for prolonged periods of time and the embarrassing social implications they experience; for instance, *"I have to stand up during a conversation ... people think I want to leave... even if I explain some people with osteoarthritis are uncomfortable sitting for very long."* Participants echoed that the pain is constant and impacts their planning and decision-making daily, noting that days they are forced to endure pain require modifying plans accordingly thereafter so they may recover. One participant explained that, *"I've tried to save my good days for those moments that I wish would last forever but I know I'll never have again."*

Stiffness

After pain, stiffness was identified as a significant symptom of their OA disease. Participants described the interrelatedness of stiffness and other symptoms, describing pain and stiffness when sitting for prolonged periods, yet more pain with walking and standing as well, yet they want to stand and walk to prevent stiffness, but they are in pain doing so. One participant noticed her stiffness is worse with cold weather, which many participants echoed. Participants

commented that their stiffness is especially prevalent when going to the movies and they must choose where they sit wisely. Several participants described the pain associated with this symptom. One participant shared that it hurts to sit and it hurts to stand. Another younger participant added the social implications with her friends not understanding that she cannot sit comfortably on bar stools and that they must choose restaurants accordingly.

Functional limitations/impaired mobility/walking/standing limitations

Functional/walking/standing limitations were noted as being nearly equally as impactful on daily lives. The emotional, physical and social impact of walking/standing limitations with OA was reiterated by all panel participants. One participant noted, *"it robs you of quality life experiences and your overall well-being,"* when she explained that she sometimes couldn't go to the airport to welcome her husband home or her son's basketball games because *"it inhibits mobility."* Another said, *"it's simply unimaginable"* referring to hobbies such as hiking which he used to enjoy when noting the numerous impacts walking and standing limitations have on his social interactions. Several participants indicated that their knee or foot *"doesn't want to cooperate"* if they have to walk too far or stand too long and sometimes they experience numbness preventing them from standing or walking. One participant noted, *"I'd been using a cane, I had a handicapped parking sticker, I couldn't walk around a store without using a grocery cart to lean on, and I couldn't even go to the mall, where walking from one end of the mall to the other became impossible."* Participants emphasized that even when they are able to walk longer periods required of family events, that the increased activity forces them to take time to recover. They further shared emotional frustrations when trying to help family members understand, *"I can't,* or *"I no longer can"* when asked to join in a hobby or physical activity they used to enjoy which requires walking and standing for periods longer than their limitations allow.

Other symptoms

In addition to the aforementioned symptoms, participants also shared a range of additional symptoms, including:

- *Loss of flexibility*
- *Sleep disturbance*
- *Fatigue*
- *Grating (bone on bone) sensation*
- *Joint swelling*
- *Disfigurement*
- *Other- numbness, instability*

Overall impact of osteoarthritis on daily life

Both in-person and web participants described the impact that OA disease has on daily life.

- **Difficulty with diagnosis.** Participants noted the lack of awareness and acknowledgement as well as the hidden prevalence of OA disease. They reiterated poignantly how osteoarthritis is much more than "aging," "getting old," "bad knees" and "wear and tear." It was apparent that patient-provider communication, education regarding the countless OA phenotypes and comprehension and understanding of progression along the disease spectrum must be improved, eliciting concordance in perceptions of OA disease severity, preventing delayed diagnosis and prompting timely interventions with the most appropriate options available or foreseen. Many patients noted not being diagnosed with OA until their provider explained that they were in need of a total joint replacement.
- **Daily impact of OA symptoms.** Participants described the daily struggle of living with their OA symptoms and the emotional, physical and social impact it has on their lives, including:

anxiety, disfigurement, embarrassment, fatigue, functional limitations, grating sensation, impaired mobility, instability, invisibility, joint swelling, loss of independence, pain, shame, sleep disturbance, social isolation and stiffness. Participants shared the emotional toll and significant lifestyle changes at home and work due to OA symptoms isolating them from activities and quality time with friends and family and ostracizing them with co-workers for required adjustments to manage their symptoms at work. Participants highlighted the devastating toll OA has not solely on themselves and their families, but also on multiple generations of their families.

- **The inability to perform activities.** Adult participants shared that their symptoms, particularly pain and tenderness, stiffness, loss of flexibility, limitations standing and walking and fatigue have significant impacts on their ability to manage their work, households, and personal care. Participants explained they cannot even go to the grocery store and when they do an activity, *"it spends your energy. You don't have the energy to do regular things like go to work or cook dinner."* One participant commented that she had lumbar disc surgery, *"so basically every day, I don't do any housework, mopping, sweeping, vacuuming, any of that. Picking up, I'm careful about picking up anything that's heavier than 5 pounds. It impacts my entire spine up to my head and can give me headaches. Reading on the computer too long, anything like that. So I have a wonderful husband who is a great caretaker for me."* Many participants noted their trouble opening doorknobs which requires gripping and turning as opposed to levers. Another participant agreed, *"It's not a matter of strength. Mostly it's about my grip. Since I cannot firmly grasp things like I used to, I'm afraid of dropping things."* Participants shared the impact on their careers and ability to perform activities at work and home. One participant described her C-spine OA symptoms, *"by the end of the work day, I have spent everything I could, so when I get home I can't turn my head, I can't lift my arms above my head, I can barely move my elbows. I can't pick up coffee cups. So it's very limiting to get through the day at work so you come home and you don't do anything else."* Several participants commented on the specific impacts resulting from the inconsistency and unpredictability of their condition. One participant explained, *"so mine affects me whether or not I can sit up in bed in the morning. I didn't think I was going to get my socks on this morning."*
- **Decreased social interaction and impact on relationships.** Many participants commented that the pain, fatigue, disfigurement and limitations standing and walking has led to social isolation, also impacting their relationships with friends, family and co-workers. One participant commented, *"I took an early retirement and I joined two friends who walked three miles around a reservoir, which I thought would be very good. I soon found out I couldn't really keep up with them, because they kept up quite a pace, and I needed to stop to rest while they didn't. These friends are my age. Ultimately, I have to find other people to hang out with during the day. I sought out a group of women in their 80's, because with their assortment of canes and walkers, they moved at a pace that I could keep up with. I was 59."* A younger participant with OA shared, *"I can't even toss a frisbee with my son."* One participant simply stated, *"no social life."* Another participant stated that when his wife asks where are we going for a walk today his reply is, *"No, it isn't going to happen."* Another participant concurred the same, *"I just tell my wife I can't do it. I'm sorry when she wants to go out and walk around in Bryce Canyon for God's sake, I'll be glad to look at it from the window in the car, take my long-distance camera lens and shoot a picture because there's no way in hell I'm walking up that canyon. Get real. We have limitations."* One patient explained, *"we'll go to the store and I have to say I'll just sit in the car."* Another participant noted the strain on her husband when dealing with her pain commenting, *"the pain is excruciating, and I feel sorry for my husband because he's also living with this."*

- Embarrassment and self-consciousness.** Participants shared stories of embarrassment and shame that they or their loved ones have experienced because of their OA symptoms, especially staggering upon standing and not being able to keep up the walking pace of friends their age. One participant shared, *"If I sit here for an hour and I get up, I will stagger as if I'm drunk."* Another participant echoed the same, *"I look like I'm drunk and I'm afraid somebody's going to arrest me someday because I'm drunk- it's changed my whole life."* A father with 3 active kids explained, *"we're always sitting on the bleachers at a ball game and there are sometimes I have to leave and go home because I just can't sit here any longer."* One participant shared her embarrassing experience with hand OA, *"they're numb. Everything falls, you know."* Participants also discussed the embarrassment, *"constantly moving and shifting and standing and sitting and adjusting."* A participant from the military admitted, *"My pain became a source of shame as I tried to ignore it, but it wouldn't stop."* Other participants commented on co-workers assuming they are getting special treatment with modifications made at work, when they'd rather not be ostracized for requiring modifications to complete work and extra time to walk from their car and punch in.
- Severe emotional impact.** The majority of participants echoed that the *"invisibility"* of OA elicits an emotional toll as those not living without the burden of OA disease do not understand the limitations caused by OA. A participant explained, *"even my spouse and children seem not to be sensitive to the changes OA causes. A common refrain is, that's something you like to do. Of course it is something I used to like to do, and would still like to do..."* One participant added that he asks his wife, *"don't you remember I have arthritis"* when asked to perform tasks he can no longer perform due to the impact of pain from OA. A younger female participant noted, *"it's hard for us to even just say it at the spur of the moment because we have all had to adjust so much... every aspect of our life has been changed."* Another participant added, *"it's hard to accept"* and many repeatedly commented, *"it's frustrating."* A female participant commented, *"It's just gone so downhill I feel like I'm an old woman and I'm not."*
- Constant worrying about the future.** Participants expressed significant worry, anxiety, and fear for the unknown future facing the challenges of osteoarthritis. Participants reiterated the need for access to information and communication between doctors, *"you want to know what's out there and what the options are."* One participant expressed this anxiety and fear after being informed he had OA in his other knee as well by stating, *"now do I have it in the hips or the shoulders and so forth?"* Another participant added his concern regarding the unknown future asking, *"what is the natural progression of what we need to do to solve the problem. You're always looking at the long range. What am I going to do? Do I want to get a bigger home? Do I want to get a bigger yard?"* Participants also commented on the destructive impact of osteoarthritis on multiple generations of their families. For example, one participant shared, *"I had to make the decision not to have children and I had to work that out with my spouse."* Many participants worry about losing their future independence, *"I don't want to ever end up in a nursing home."*
- Other daily impacts.** Participants mentioned the significant amount of time and energy it requires to continually manage their symptoms daily and the inconvenience of advance planning required not only for treatments, but also for daily activities as well as vacations-ensuring medications are refilled accordingly prior to vacation when prescriptions are limited to 30 days, *"you start planning your lifestyle to meet your criteria."* Some participants commented on the inability to plan in advance, *"it's hard for us sometimes to make plans in advance because it will just be, you know, my eyes don't know until that day."* Most

importantly, all participants noted not only the impact on daily life, but the prolonged impact on life and decision making which goes on and on and on.

Topic 2: Patient Perspectives on Treatments for Osteoarthritis

The second discussion topic focused on patients' experiences with therapies used to treat their osteoarthritis. Five panelists (Appendix 2) provided comments to start the dialogue. They included:

- David is 67 years old living with neck, lumbar, cervical spine, wrists and knee osteoarthritis. He takes an NSAID twice a day, has tried Synvisc injections until switching to Medicare as they wouldn't cover such. He also uses massage therapy which he admitted may be more for his mental health and relaxation rather than physical well-being. He works with a personal trainer three times a week on strength, endurance and balance training. David told of his many accomplishments and his next adventure in Florida for a double century bike ride with his costly modified bike. He jokingly shared, "*what I haven't done yet and I've been offered both is surgery and opioids*" as there is a history of addiction in his family which frightens him and during his prior work experience in medical devices he handled many of the class action lawsuits with metal on metal claims.
- Angela is a 19-year-old college student who had to turn down the opportunity to play collegiate soccer due to two anterior cruciate ligament surgeries and several meniscus tears occurring within the timespan of a year, all on her right leg. She candidly admits, "*I am terrified for the future.*" She thought all through rehab that she would be free of knee pain after 24 months of post-op physical therapy only to learn the high risk of developing post-traumatic osteoarthritis in the near future. She shared, "*osteoarthritis is not something that can be fixed with advil or Tylenol twice a day. This disease can change someone's life.*" Angela doesn't believe there are enough treatment options today to prevent disease and she asks drug developers, "*to take interest in my quality of life*" and "*prevent the progression of OA.*"
- Fletcher is a 58-year-old software engineer in the San Francisco area whose life has been impacted primarily by osteoarthritis in his knees. He told the audience that every time he sees his orthopedist he is asked, "*when do I get to replace your knees.*" He explains he should be in pain, but he is not which he explains, "*is good because I can't take most pain medications, aspirin, Tylenol, ibuprofen.*" Fletcher explained, "*what I do for treatment is this*" and showed a photo of a 130-mile bike ride with fifteen thousand feet of climbing in the California Sierra Mountains. His doctor told him it's the only reason he is walking into his office, "*the constant work.*" "*My bike riding has helped me stay away from pain.*" Fletcher doesn't want to have a knee replacement only to find out soon after that a technology he read about previously is now available when it's no longer an option for him. He noted not having a choice today, "*I have to go to my doctor and hope that they are up to date*" with new treatments. Fletcher wants a nuanced discussion with his doctor ensuring that both are aware of all the current treatment options as well as those in the clinical trial pipeline which may be an option for him in the near future- he is willing to delay treatment for a better future option, but he is not willing to change his current treatment if it will obfuscate his opportunity in the future to receive a better option at halting disease progression.
- Janet was diagnosed 14 years ago with osteoarthritis and rheumatoid arthritis. She explains OA is part of her family. She had a, "*great left knee replacement*" but explains it's, "*not a cure in any way shape or form.*" She feels OA pain mostly in her back now. Her OA treatment has included physical therapy, dry needling, heat, electrostimulation, lots of NSAIDs, anti-

inflammatory drugs, exercise and stretching. She also includes back supports wherever she goes, massage, thermacare, and high-top sneakers. Janet feels there are limited treatment options to manage OA pain and her preference would be for a joint score, *“a score of one for a joint injury, maybe you get another score if you’re overweight and then that adds up to help predict how your future might be or help outline things that you might begin to focus on in terms of treatment. We need much more than measures of pain and function.”*

- Cindy is 60 years old, yet has been living with neck pain since she was in a car accident at age 15 which fractured her cervical vertebra. She tried everything to alleviate her OA pain and headaches, *“aquatic exercise, low impact aerobics, essence foils, tiger balm, a brace, Epsom salt baths, acupuncture, etc.”* She has also tried meloxicam, but it upsets her stomach. She also has knee pain for which she had a cortisone injection which allowed her to go dancing one weekend. She also takes Vitamin D and Calcium, Excedrin for Migraine, massage therapy and cupping. *“I had a topical cream that my legs broke out into a rash and another anti-inflammatory upset my stomach.”* She also noted trying Aleve and Tylenol, *“those things have not really helped.”* Cindy wants treatments that are, *“user-friendly”* and massage considered for OA treatment research.

In the large-group facilitated discussion that followed, patients and patient representatives discussed their experiences with behavioral interventions, prescription and non-prescription treatments via various routes of administration, including topical, oral and intravenous and surgical treatments. Participants' perspectives on the benefits and downsides of these treatments and on considerations regarding treatment decisions are summarized below. This section ends with participants' perspectives on what they would look for in an ideal treatment.

Perspectives on current treatments

Participants encouraged enhancing the available treatment options. They acknowledged the importance of their treatments, yet conveyed the burden of trial and error with therapies, complexity managing lifestyle changes adhering to treatment protocols, difficulty discerning the benefits and risks selecting the best available treatment option or delaying treatment for a prospective “better” therapy, as well as the challenges obtaining access to chosen therapy. Participants highlighted the range of variability in effectiveness and lack thereof in managing their symptoms with one or more of these therapies. While some participants were satisfied with their current treatments, others shared challenges with debilitating side effects and adjustments in their treatment plan, or a drug holiday due to new symptoms or worsening of their current condition. Participants also shared the burden of frequent monitoring, testing, clinic and physical therapy visits. Many patients noted awareness of the placebo effect and felt perhaps treatments worked initially as they had faith simply in trying something new. Younger OA patients noted being very anxious when current multi-modal treatments aren't effective and the last resort option is surgery at such a young age. Other participants worried about current oral medications being ineffective and requiring something stronger with fear of side effects, *“some of the stronger stuff have after effects.”* Many participants echoed worries regarding healthcare coverage in the future, *“now you can't retire without knowing what is my healthcare going to be.”* Nearly all participants highlighted the benefits of including non-drug therapies, such as exercise and diet modifications, with OA treatment plans for most optimal symptom management.

Participants' experiences with the various types of treatments are summarized below.

Patient perspectives on behavioral interventions

Participants broadly acknowledge the benefits and effectiveness of exercise for optimal OA symptom management. Many participants credited and expressed gratitude to the Arthritis Foundation for promoting exercise programs, including Tai Chi within their local community to reduce OA symptoms and improve overall health. While recognizing the benefits of exercise, patients also identified significant challenges when working with bars and weights which functional limitations due to OA often prevented when a patient's gripping, or grasping is impaired. Participants repeated the benefits of water therapy. One participant explained, *"I think the solution is to create some atmosphere where people will be willing, eager to move and do the exercise like stuff we do in Tai Chi. At first I thought that's Mickey Mouse and I started and realized it's not, it's just that little bit really helps."* Many participants also noted trying physical therapy with mixed outcomes. One participant noted going to physical therapy to improve her balance and not being able to perform the exercises because the pain in her knees was so bad. Most stated the benefits of weight-loss. Slightly more than one-fourth of participants indicated the importance of complementary or alternative therapy, including exercise and meditation, to manage their osteoarthritis symptoms. Participants also noted that they incorporated diet modifications as part of their treatment regimen; including, eliminating alcohol, sugar, processed foods, drugs, gluten, and tobacco.

Patient perspectives on oral prescription treatments

One participant made the comment that in addition to his prior physical therapy he was now receiving injections concomitantly with oral prescription treatments, Tylenol with codeine, gabapentin and meloxicam noting, *"those are pretty much once you start them you don't get off of them."* He started the injections as all 3 prescriptions taken together are still insufficient in controlling his OA pain. Another participant noted severe side effects prevented her from continuing with steroid dose packs. Most participants repeated that everything only works for a short period of time with pain symptoms, but nothing stops the progression.

Patient perspectives on oral non-prescription treatments

Most participants indicated using one or more non-drug therapies to manage their OA symptoms. Nearly all participants said that they value the benefits they see in non-drug therapies as adjuncts. About one third of the participants indicated having used over-the-counter products, such as acetaminophen and NSAIDs. Other non-drug therapies included a variety of dietary supplements (such as turmeric, glucosamine chondroitin, Vitamin D).

Patient perspectives on injections

Participants acknowledged the important immediate benefits steroid injections provide; however, participants noted they're only temporarily effective. One participant felt they were, *"pretty intense."* Another participant noted *"immediate relief"* with his concomitant medication and the first set of injections, walking for 2 hours upon receiving them, but four to five weeks later, *"started getting twinges as it wore off."* Participants who had tried injections noted immediate benefit, but only temporary pain relief. Many participants had also tried hyaluronic acid injections. A few participants noted a reaction to the *"rooster shot."* One participant noted, *"got one course of shot and it did absolutely nothing so I quit right there but they say every three months you should get those."* One participant did experience a benefit, *"within three days I could walk."*

Patient perspectives on surgical interventions

Almost all participants agreed that surgery was their last resort, “*don’t cut me,*” treatment option and reiterated that it depended on the location of OA, severity/stage of OA in addition to what point they were at in their life. One participant tried arthroscopy, “*didn’t do anything.*” One caregiver shared her father’s experience and her husband’s hesitation to proceed with total joint replacement surgery at his stage in life with severe OA disease, “*my dad was almost 60 when he needed more new knees or he was going to be sedentary forever, my husband is not even 40 yet.*” One participant experienced two dislocations after her total hip replacement, “*the doctor said we’re going to redo your hip, so the hip still hurts, he took x-rays recently and said your hip is fine.*” A couple patients reported benefits of having both knees replaced, “*they replaced both knees at once and now it’s amazing.*” No participant articulated specific benefits of their treatments, in terms of a percentage improvement, an amount of time without constant pain, or a reduction in specific symptoms. Several participants commented that while their treatments are effective in removing the pain in the specific joint which was surgically replaced, the surgery does not manage their walking and standing limitations due to instability, pain in other joints and stiffness. For example, “*I have both of my knees replaced but I still have trouble with the stairs because of my ankles and feet.*”

Patient perspectives regarding significant downsides of treatments

Despite treatment benefits, participants noted the treatments can be burdensome, as described below. Participants noted frustration not just trying to help others understand their symptoms, but also with medication coverage, “*we have just within the last week battled two different pharmacies for medication.*” Participants also voiced frustration at the thought of, “*having to take medication all the time. I don’t want to be dependent on the medication.*” Participants also described the emotional impact fear has with their overall distrust of drug companies and side effects from drugs years later, “*and that’s why we are so afraid.*” One participant simply stated, “*I’m at the point right now when I go to bed at night, I think well, I made it another day.*”

- **Intolerability:** Participants described **significant side effects**, including fatigue, drowsiness, nausea, fluctuations in weight, headaches, stomach swelling and not being able to breath. Participants described having to modify activities including work or learn to live with these side effects. Others commented on the intolerability of the side effects which precluded them from using particular medications. Several participants also expressed concern regarding the long-term effects of drugs and how side effects might change due to prolonged use. Many participants stated they would not try drugs due to unknown effects on the liver and within the bloodstream.
- **Obfuscating future treatment options:** Some participants expressed concern about “*compromising future treatment options.*” One participant explained, “*if I get a joint replacement, will I need another one if you get them sooner? You know, how long will this last?*” Participants do not want their chosen treatment to be their ultimate last option, nor do patients want their current treatment to prevent them from trying potential newer treatment options in the clinical trial pipeline which may be more effective. Patients described a preference for a nuanced discussion with their provider and what we’d like to call “mindful monitoring” when a good treatment option is unavailable, or their decision would obfuscate future treatment options.
- **Worsening of current condition and/or new conditions:** Some participants expressed concern that while their treatments might address specific symptoms, they can also lead to **worsening of other OA symptoms or development of new conditions.** For

example, a participant agreed to try a new prescription medication and she started having UTIs which she never had previously. Many participants reported new gastrointestinal conditions upon starting certain OA treatments.

- **Impacticality:** Several participants commented on the **burden of treatment and required blood work**. For example, one participant explained, *"it's just an inconvenience to go and do this physical therapy."* Another participant commented, *"every medication I get there's a side effect I got to go have a test done to make sure it hasn't affected my kidneys and that's just absolutely thrilling."*
- **Inaccessibility: Fair access to medications**, especially those which help with symptoms of fatigue, but are considered off-label, was also identified as an issue. Participants shared that medications indicated for work-shift disorder help with fatigue, but patients cannot get prescription coverage unless they are diagnosed with a work-shift disorder. Patients mentioned injections athletes have access to in other countries because they can afford to pay for them and also because they are available in other countries, but not the US.
- **Unaffordability:** Participants commented on the **significant out-of-pocket costs** for treatments not covered by insurance, including those with *"gold coverage"* who are concerned about treatment options for those with lower coverage. Participants echoed, *"you think about insurance, you think about costs."* One participant added, *"you can't retire without knowing what is my healthcare going to be."* Another added, *"do I eat today or do I take medication today."*

Patient perspectives on ideal treatments for osteoarthritis

In response to solicitation for their ideal treatment perspective, participants repeatedly emphasized treatments for disease prevention and to halt progression. Participants also identified reduced pain and regained function, mobility, walking and standing as benefits they would consider to be the most meaningful when considering OA symptoms. Participants also identified a reduction in fatigue, stiffness and disfigurement as meaningful benefits as well as reducing bone loss and improving bone density.

Participants also stressed the need to enhance the treatment options available, given current challenges with variability in effectiveness, tolerability, access to available treatments, and uncertainty regarding prolonged use of available treatments. One participant reiterated providing treatment options which may be individualized as, *"it affects everyone so differently. Everybody has different joints that are affected in different ways and at different levels."* Several participants commented on the need to advance treatments that help with early diagnosis in an effort to intervene earlier and prevent the years of OA progression they live with. A participant commented, *"I would like to see something come along that would just get to the root of it and get us going."* Another echoed the same sentiment, *"I'm really hoping there'll be a drug or a procedure that could stop or slow down the process that the OA does. It's nice to stop the pain, although I never found a pill that really did that. And replacement surgery is amazing, although I always have to worry that I will live longer than my joints. And the vertebrae aren't, at this point, replaceable. But if the OA could have been stopped or slowed down when I had mild hip pain, that would have been wonderful and a true miracle."* Other aspects of ideal therapy included: developing drugs with fewer side effects, medication that is effective for longer periods of time, and a treatment that could prevent osteoarthritis from being inherited.

In addition to their perspectives on ideal therapies, participants throughout the meeting commented on other issues that they believed are important to any discussion on osteoarthritis healthcare, including early and more accurate diagnosis and fast tracking the approval of effective osteoarthritis treatments. Patients repeatedly voiced concern with delayed diagnosis as well as discordant patient-provider perceptions and employer perceptions of OA disease severity, suggesting, *"maybe it's not a surgery or medication- maybe it's education."* Transparent access to comprehensive, relevant information on new treatment options in language patients understand to make informed decisions. One participant commented, *"the abundance of studies, I really don't know in my heart which ones are true and which ones aren't, what you believe."*

Outcomes that are most meaningful to osteoarthritis patients

Participants emphasized a priority be placed on treatment options which prevent disease and delay or stop worsening of symptoms and disease progression. Patients requested improving the availability of treatment options, given current challenges delineating effectiveness in the various OA phenotypes, variability in tolerability and common side effects, burdensome treatment administration, rare yet serious and life-threatening side effects, variability in effectiveness, lack of meaningful effectiveness, fair access to treatment, uncertainty of current therapies obfuscating future treatment options and long-term effects of current treatments. Patients emphasized the need for earlier detection and diagnosis, suggesting biomarker research and accelerated clinical trials. Patients further suggested research determining predictive biomarkers to provide an OA score and personalized OA roadmap as biomarkers and symptoms change, directing treatment plan modifications in the management of OA disease. Patients want a nuanced discussion with their providers so both may "mindfully monitor" their condition together and select the best treatment option(s) available for their present state as the disease progresses along the OA spectrum being mindful of what options may or may not be available in the future. The discussion also highlighted the unmet medical need for treatments in younger OA patients who will require a prolonged management plan, juvenile/pediatric, post-traumatic, iatrogenic, etc. populations living with osteoarthritis.

Why osteoarthritis patients choose the treatments they select

Throughout the day, participants described a complex process of trial and error to find an effective multi-modal approach (including behavior, pharmacological, and non-pharmacological therapies) to fit their specific needs. Participants were also asked how they approach decision making with respect to starting, continuing, or stopping a medication. One participant shared, *"well my son took me to a neurologist. I left that day without anything. I'm not going to be a guinea pig."* One participant commented, *"Every change in therapy has been due to a lack of response to the therapy."* Many total joint replacement participants echoed trying all options prior to surgery, *"I have used medication, physical therapy, occupational therapy, hot and cold packs, acupuncture, massage, injections of all kinds, and surgery."* While some participants stated that they could determine whether a medication is or is not effective immediately, others shared that they try a medication for a few months before making changes. For example, one participant shared, *"I'm not opposed to trying [a treatment] on a short-term basis to see how my body responds to it. If my osteoarthritis responds favorably to the treatment... then I need to re-evaluate at that time the benefits and the risks of a long-term regimen."*

In order to gain additional insight, participants were asked for their perspective of a new osteoarthritis treatment. Participants were asked what thoughts first came to mind and what questions they would pose to their healthcare provider. A few participants indicated their interest ("sign me up") explaining that any new medication that might reduce their symptoms was worth a

try. Other participants raised questions: whether the treatment was an immunosuppressive; how this new medication might affect their co-morbid conditions; and how might this treatment work in comparison to their current treatment. Several participants wanted more information regarding the side effects, including the frequency of the side effects and any long-term effects. Several participants also expressed concern regarding the administration, availability, or cost of the medication.

Conclusion

This Patient-Focused Drug Development meeting on osteoarthritis provided the FDA the opportunity to hear first-hand from patients and caregivers the significant and debilitating impact that osteoarthritis has on their lives. As Dr. Peng, Clinical Reviewer, CDER, FDA voiced during her closing remarks, patients and caregivers each presented unique burdens of disease and individual impacts, yet a shared commonality was an urging for earlier diagnosis with better biomarkers to intervene earlier and halt disease progression with treatment options addressing symptoms which are most meaningful to patients living with OA disease.

Patients identified key impacts and elements of disease experience. Implications for drug development consideration: Patients want access to all relevant data for the various treatment options, including personalized data about how it will impact them along the spectrum of OA disease. They are potentially willing to accept minor side effects, but not serious side effects and again, they want clear, comprehensive information to empower their decision-making. Most importantly, patients want therapies which stop progression whilst alleviating pain and improving function, yet stopping disease progression is their utmost concern and desire for new therapies.

We are grateful to the OA patients and caregivers, expert advisers and partners, who so thoughtfully, generously, and indeed courageously shared their personal experiences living with osteoarthritis. This meeting emphasized what matters most regarding symptoms, impacts, and most meaningful aspects of osteoarthritis treatments to be factored into clinical trials. The participants' sense of community and their desire to advocate for current and future generations at risk for osteoarthritis were strikingly clear.

Again, we thank people living with OA disease for their voice and continued engagement in activities across the research healthcare continuum, sharing their lived experience to prompt better OA treatments and shape the system that serves them!

Appendix 1: Meeting Agenda and Discussion Questions

Public Meeting on Patient-Focused Drug Development for Osteoarthritis March 8, 2017

12:00 – 1:00 pm	Registration
1:00 – 1:05 pm	Welcome Ann M. Palmer <i>CEO & President, Arthritis Foundation</i>
1:05 – 1:10 pm	Opening Remarks Janet Woodcock, MD <i>Director, Center for Drug Evaluation and Research, CDER, FDA</i>
1:10 – 1:20 pm	Overview of FDA’s Patient-Focused Drug Development Initiative Suzette Peng, MD <i>Clinical Reviewer, CDER, FDA</i>
1:20 – 1:30 pm	The Voice of the Osteoarthritis Patient Amanda Niskar, DrPH, MPH, BSN <i>National Scientific Director, Arthritis Foundation</i>
1:30 – 2:15 am	Patient Panel #1 Discussion on Topic 1 Topic 1: Disease symptoms and daily impacts that matter most to patient. <i>A panel of patients will provide comments to start the discussion.</i>
2:15 – 3:00 pm	Large-Group Facilitated Discussion: Topic 1 Patients and patient representatives in the audience will be invited to add to the dialogue.
3:00 – 3:20 pm	Break
3:20 – 4:05 pm	Patient Panel #2 Discussion on Topic 2 Topic 2: Patient perspectives on current approaches to treating osteoarthritis. <i>A panel of patients will provide comments to start the discussion</i>
4:05 – 4:50 pm	Large-Group Facilitated Discussion: Topic 2 Patients and patient representatives in the audience will be invited to add to the dialogue.
4:50 – 4:55 pm	Open Public Comment
4:55 – 5:00 pm	Closing Remarks Amanda Niskar, DrPH, MPH, BSN <i>National Scientific Director, Arthritis Foundation</i>

Discussion Questions

There will be opportunities for open-ended responses to discussion questions. In addition, an expert panel of clinicians, scientists, patients, and caregivers will recommend polling question response options for the discussion question topics.

Topic 1: Osteoarthritis Symptoms and Daily Impacts That Matter Most to Patients

1. What are the most significant symptoms that you experience resulting from osteoarthritis? (Examples may include exhaustion, pain, depression, etc.)
2. What are the most negative impacts on your daily life that result from your experience with osteoarthritis and its symptoms? (Examples may include difficulty with specific activities, sleeping through the night, etc.)
 - a. How does osteoarthritis affect your daily life on the best days and worst days?
 - b. What changes have you had to make in your life because of osteoarthritis? (Examples may include career changes, hobby changes, family activity changes, etc.)

Topic 2: Patients' Perspectives on Current Approaches to Treating Osteoarthritis

1. What treatments are you currently using to help treat your condition or its symptoms? (Examples may include FDA-approved medicines, over-the-counter products, and other therapies, including non-drug therapies such as activity limitations, physical therapy, surgery, yoga, chiropractor, and acupuncture, etc.)
 - a. What specific symptoms do your treatments address?
 - b. How has your treatment regimen changed over time and why?
2. How well does your current treatment regimen treat the most significant symptoms of your experience with osteoarthritis?
 - a. Have these treatments improved your daily life (for example, improving your ability to do specific activities)? Please explain.
 - b. How well have these treatments worked for you as your osteoarthritis experience has changed over time?
 - c. What are the most significant downsides of these treatments (for example, specific side effects, time, expense, etc.)?

Appendix 2: Patient Panel Participants

Patient Panel, Topic 1

- Kathy Geller
- Ed McGrath
- Donna Dernier
- Bruce Hanson
- Kay Harvey

Patient Panel, Topic 2

- David Shuey
- Angela Tucci
- Fletcher Johnson
- Janet Stearns Wyatt
- Cindy Copenhaver

Appendix 3: Meeting Polling

The following questions were posed to in-person and web meeting participants at various points throughout the March 8, 2017, Patient-Focused Drug Development for Osteoarthritis public meeting. Participation in the polling questions was voluntary. The results were used as a discussion aid only and should not be considered scientific data.

Demographic Questions

1. Where do you live?
 - a. Within Washington, D.C. metropolitan area (including the Virginia and Maryland suburbs)
 - b. Outside of the Washington, D.C. metropolitan area
2. Have you ever been diagnosed as having osteoarthritis?
 - a. Yes
 - b. No
3. Have you ever been diagnosed with osteoarthritis?
 - a. Yes
 - b. No
4. What is your age?
 - a. Younger than 18
 - b. 18 – 29
 - c. 30 – 39
 - d. 40 – 49
 - e. 50 – 59
 - f. 60 or greater
5. Do you identify as:
 - a. Male
 - b. Female
6. What is the length of time since your osteoarthritis diagnosis?
 - a. Less than 5 years ago
 - b. 5 years ago to 10 years ago
 - c. 10 years ago to 20 years ago
 - d. More than 20 years ago
 - e. I'm not sure

Appendix 4: Incorporating Patient Input into a Benefit-Risk Assessment Framework for Osteoarthritis

Introduction

Over the past several years, FDA has developed an enhanced structured approach to benefit risk assessment in regulatory decision-making for human drugs and biologics.² The Benefit-Risk Assessment Framework involves assessing five key decision factors: *Analysis of Condition*, *Current Treatment Options*, *Benefit*, *Risk*, and *Risk Management*. When completed for a particular product, the Framework provides a succinct summary of each decision factor and explains FDA's rationale for its regulatory decision.

In the Framework, the *Analysis of Condition* and *Current Treatment Options* rows summarize and assess the severity of the condition and therapies available to treat the condition. The assessment provides an important context for drug regulatory decision-making, including valuable information for weighing the specific benefits and risks of a particular medical product under review.

The input provided by patients and patient representatives through the Arthritis Foundation's externally-led Patient-Focused Drug Development Public Meeting for Osteoarthritis will inform FDA's understanding of the *Analysis of Condition* and *Current Treatment Options* for this disease.

The information in the top two rows of the sample framework for osteoarthritis below draws from various sources, including what was discussed at the Patient-Focused Drug Development Public Meeting for Osteoarthritis held on March 8, 2017 as well as the Arthritis Foundation sponsored white paper published by OARSI on the Serious Burden of OA Disease. This sample framework contains the kind of information that the Arthritis Foundation anticipates could be included in a framework completed for a drug under review for osteoarthritis. This information is likely to evolve over time based on a further understanding of the condition or changes in the treatment options.

² Commitments in the fifth authorization of the Prescription Drug User Fee Act (PDUFA V) include further development and implementation of the Framework into FDA's review process. Section 905 of the FDA Safety and Innovation Act also requires FDA to implement a structured benefit-risk framework in the new drug approval process. For more information on FDA's benefit-risk efforts, refer to <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm>.

Dimensions	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> - Prevalence of doctor-diagnosed osteoarthritis, OA, is estimated at 30 million patients, approximately 13% of the United States population. - OA is a whole joint disease with tissue changes underlying clinical symptoms; including, peri-articular muscle, ligament, cartilage, bone and synovium. - Symptoms include fatigue, functional limitations, impaired mobility and pain. Other symptoms include stiffness, instability, standing and walking limitations. - One third of adults aged \geq 45 years report anxiety or depression. - Adults with arthritis are more than twice as likely to report an injury related to a fall. - Physical activity can reduce pain and improve physical function by approximately 40%; however, one in three adults with arthritis report no leisure time physical activity. - OA is a leading cause of morbidity and disability with high socioeconomic costs; a massive rise in morbidity and costs attributed to OA is expected. - <i>See the Voice of the Patient report for a more detailed narrative.</i> 	<ul style="list-style-type: none"> - OA is a serious burden as a debilitating chronic disease that has a significant impact on daily life and how patients feel and function; it imposes a tremendous individual and societal burden. - OA is a highly prevalent, heterogenous disease of joint tissues with symptoms having considerable detrimental effects on a patient's quality of life both personally and professionally, ability to function in daily activities, overall social and societal engagement in addition to limiting patients' ability to self-manage comorbid conditions. - Lack of insight into underlying pathophysiology as well as tools to stratify and monitor the various patient phenotypes has contributed considerably to this slow advancement. - There is no measure for early stage disease to allow immediate, pre-emptive treatment prior to irreversible organ failure. - The reasons for lack of FDA-approved treatment options are multi-factorial; including, poor relationship between traditional radiographic measures assessing joint structural pathology and symptoms, limitations of current biomarkers to adequately assess efficacy and multiple OA phenotypes which may each require a different treatment approach. - Based on traditional OA risk factors, clinical trials have the disadvantage of enrolling less than 30% of patients with progressive knee OA; moreover, approximately 50% of phase III clinical trials fail without selection biomarkers. - More robust quantitative measures are needed to enrich OA clinical trials for relevant progressor subjects, enhancing trial efficiency. - <i>See the Voice of the Patient report for a more detailed narrative.</i>

Dimensions	Evidence and Uncertainties	Conclusions and Reasons
<p>Current Treatment Options</p>	<ul style="list-style-type: none"> - Current treatment options used alone and in combination, include: behavioral therapies, oral non-pharmacological and pharmacological therapies, injections and surgical interventions. - Two factors influence how OA is managed- the presence of comorbidities and involvement of other joints. - A set of non-pharmacological core treatments is recommended as appropriate for all individuals: land-based exercise, weight management, strength training, water-based exercise, self-management and education. - Comorbidities such as diabetes, hypertension, cardiovascular disease, renal failure, GI bleeding, depression, physical impairment, obesity, etc. limit additional treatment options for OA patients. - Little progress has been made in the development of effective therapies. - <i>See the Voice of the Patient report for a more detailed narrative.</i> 	<ul style="list-style-type: none"> - Presently there are no pharmacological, non-pharmacological, or surgical therapies approved which can prevent, stop, or even lessen progression of OA. - Non-pharmacological and pharmacological treatments which control or manage the symptoms of osteoarthritis are available for patients; however, efficacy varies from patient to patient, and significant side effects can limit benefits or preclude the use of these therapies in patients with comorbid conditions. - NSAIDs have been associated with a clinically relevant 50-100% increase in the risk of myocardial infarction or death compared to placebo. - Importantly, frequency of dosing and route of administration can often be burdensome on patients. - Surgery replacing the joint may require further revision surgery as well, depending on the life of the implant and age of the patient at time of surgery. - There is an urgent need for additional tolerable treatment options with a meaningful effect for patients to improve their quality of life and ability to self-manage, which concomitantly intervene in the pathophysiology and progression of OA. - <i>See the Voice of the Patient report for a more detailed narrative.</i>

Appendix 5: Supplementary Patient Engagement Strategy Findings

Pre-meeting patient engagement strategies overview

In January 2017, the Arthritis Foundation initiated a series of patient engagement strategies aimed at gathering preliminary data from OA patients on symptoms and impacts on daily life as well as soliciting the patients' perspective on ideal current and emerging treatment approaches, culminating with the externally led PFDD public hearing on March 8th, 2017. Patient engagement strategy data is provided in text following discussion questions as well as graphic representation following summary text of findings.

Focus Group and Panel Discussion Questions

OA symptoms and daily impacts

- Right now, what would you say are the most significant symptoms that you experience from your OA?
- Thinking about those symptoms and how they impact your daily life;
 - Are there specific activities that you can't do because of your OA, or activities that you've had to modify, or you now need assistance with?
 - What are they?
 - How much does this change from good days to bad days? What is your OA like on bad days? What is it like on good days?
- Do you take your OA into consideration when you make decisions?
 - Current—daily--decisions?
 - What about decisions for the future?

Current approaches to treatment

- What treatments or therapies have you used for your OA?
 - Did it/they help? Which symptoms did it/they help with? Are there symptoms it/they didn't address?
- What about right now? Is what you are using helping with the most troublesome symptoms? Do your treatments or therapies help to improve your daily life?
- During the time that you've had OA, have you changed the treatment or therapy that you use?
- Have you had to deal with any side effects or other negative issues because of a treatment?

New approaches to treatment

- If there was an "ideal" treatment or therapy, what would that look like for you?
 - Would you want it to help with your symptoms (refer back to what they've mentioned already—pain, stiffness, etc.)? Or would you want it to help prevent the disease from progressing (i.e., damaging your joints)?
- What risks would you be willing to take for a treatment or therapy that worked for you (whether that's to control symptoms or prevent progression)? Would you be willing to try the treatment if it required you to get an injection? More than one injection?
- If there was a new treatment available that could control symptoms or prevent progression would you try it? Why/why not?

Nationwide poll

A nationwide poll conducted online with patients participating from 45 states and the District of Columbia launched the series. The PFDD poll respondents demonstrated broad geographic representativeness. Ninety-six percent of poll participants responded "yes" to the question, "have you been told by a doctor or other health professional that you have osteoarthritis?" Gender was represented predominantly by females as 90% of the participants and males representing 10%. Poll respondents were representative of the general OA population with 88% between 51-80 years of age. Most notably, 96% of patients responded "yes" when asked, "have you ever been told by a doctor or other health professional that your osteoarthritis is associated with a previous injury or trauma," suggestive of post-traumatic OA, PtOA. Sixty-five percent of poll respondents answered "yes" when asked, "do you have a family history of osteoarthritis." Participants were asked to identify osteoarthritis symptoms which have had the most significant impact on daily life. Pain and tenderness, stiffness and walking and standing limitations comprised the top three reported symptoms, followed by loss of flexibility, sleep disturbance, fatigue, joint swelling, grating (bone on bone) sensation and disfigurement.

Focus groups

Five focus groups were conducted in five local markets during the last two weeks of January with 20 patients in total participating: 1 Indianapolis, IN; 2 West Palm Beach, FL; 3 New York City, NY; 4 Phoenix, AZ; and 5 San Leandro, CA.

OA symptoms and daily impacts

Across all five focus groups pain was the most significant symptom followed by loss of independence and reduced level of activity.

When asked about limitations and difficulty with specific activities, loss or limitation with major physical activities such as walking and going up and down stairs was often mentioned. Inability to complete certain ADLs and frustration about this inability were also frequently cited (fastening bra, grasping and turning doorknobs, gripping, picking things up, fastening seatbelt, cooking, grooming).

Participants discussed how their OA symptoms varied between a good day and a bad day. One participant commented that on her best day, "I can go for a bike ride with my spouse" and on worst days, "My husband has to bring me coffee in bed before I can move out of bed." When asked to describe good days versus bad days, participants almost always mentioned that the weather was a significant determining factor, with moderate temperatures preferred over extreme hot or cold days. Good days were described as days with greater levels of activity and participation; instead, bad days were described as days experiencing increased pain and immobility.

When asked to comment on the impact of OA on thinking and decision-making, responses were overwhelmingly, yes OA impacted thinking and decision-making daily as they constantly had to stop and think about "whether or not they can do..." an activity given their current pain and limitation. Several participants discussed that they'd have to allow for recovery time after a particularly busy day or period of activity. Furthermore, they reported OA impacting long-term decision making and planning for the future, citing examples of decisions to quit working and reducing travel.

Current approaches to treatment

Patients reported trying the following types of current treatments; NSAIDs (Celebrex, Arthrotec, Naprosyn), Tylenol, Corticosteroid injections, creams, salves, oils (Emu oil, aspercreme, icy-hot, etc.), physical therapy, occupational therapy, splinting/wrapping, heat and cold, acupuncture, soaking in hot water and/or Epsom salts, surgery and exercise.

When asked how well do the current treatments/therapies address significant problems there was considerable variability with a portion of the oldest respondents indicating that exercise was the only option which kept them moving and many noted having a general distrust or dislike of pharmacotherapy options. Those exercising or

using PT and OT had positive comments, but did not express that it was resolving their OA challenges. Those who took oral medications were either uncertain if there was benefit or indicated that they helped “some” or “seemed to help”. Those who had undergone cortisone shots almost all described benefit from the shots but explained that the relief was too short-lived. Those who had undergone joint replacement surgery had positive things to say about the surgically-repaired joints.

When asked about changing treatments/therapies over time (corresponding to changes in disease over time) there was little discussion and detail with most participants simply mentioning that they had tried different approaches here or there.

The overall negative impacts from OA included an inability to do the things “I used to do,” loss of independence, needing assistance or help, and the frustration related to that loss. Several participants discussed the difficulty in helping others to understand what they were going through and that they had limitations, they described the “invisibility” of the disease. A significant concern over iatrogenic side effects was repeatedly shared, with one patient noting an increased risk of cancer with biologic treatments which modify the natural immune response. Some participants shared that they couldn't take an OA drug because of comorbidities like hypertension. Each focus group also raised the concern of possible side effects from anesthesia use during surgical procedures and several individuals stated that they were leery or completely resistant to the idea of surgery because of possible side effects from anesthesia.

There was a concern from one person about embarking upon knee replacement surgery “too soon” only to learn that a better option was coming down the pike (like regenerating cartilage in the knee).

Cost came up in each focus group.

New approaches to treatment

Participants were asked what an ideal treatment would look like. Older individuals encouraged exercise as the ideal treatment. Remaining participants collectively expressed interest in something—a pill, shot, or something similar that stopped pain and restored function. When asked if they would prefer a treatment which stopped disease progression or alleviated symptoms, the majority answered that their preference is to stop disease progression. Importantly, participants further indicated that their preference is to stop disease progression whilst restoring lost function and alignment (reverse enlargement of joints, Bouchard's and Heberden's nodes, etc.) so that their joints looked normal again.

Patients struggled answering, “what downsides/risks or side effects are you willing to tolerate?” They struggled to identify specific issues which would be impermissible or permissible, yet answered generally that they do not want anything “serious”—blindness, cancer or heart problems for example—from an OA therapy. One group discussed not wanting to be required to live in a “bubble” because the therapy made you susceptible to things. In each of the groups at least one participant made reference to direct-to-consumer advertising of therapies and the lengthy list of side effects which come at the end of the commercials. Some respondents were willing to deal with side effects if the treatment guaranteed that their pain would be reduced and function restored.

Patients were also asked if they were willing to undergo injection(s) into the joint. Many had already tried treatment with injections and did not find it problematic as long as it worked; a small number (again, the oldest of participants) did not want any part of injections as a treatment option.

When considering surgery as an option, several were fearful that something could “go wrong” and they felt that the OA would have to be severe in order for them to be willing to undergo surgery. Those who had already undergone surgery as well as the younger participants were more likely to consider surgical treatment as an option; the older participants and those who had not undergone surgery as a prior treatment option were less likely to consider surgical treatment and more skeptical.

Graphic Representation of Combined Focus Group and Poll Respondent Data

Figure 1. Respondents' length of time since OA diagnosis. N=320

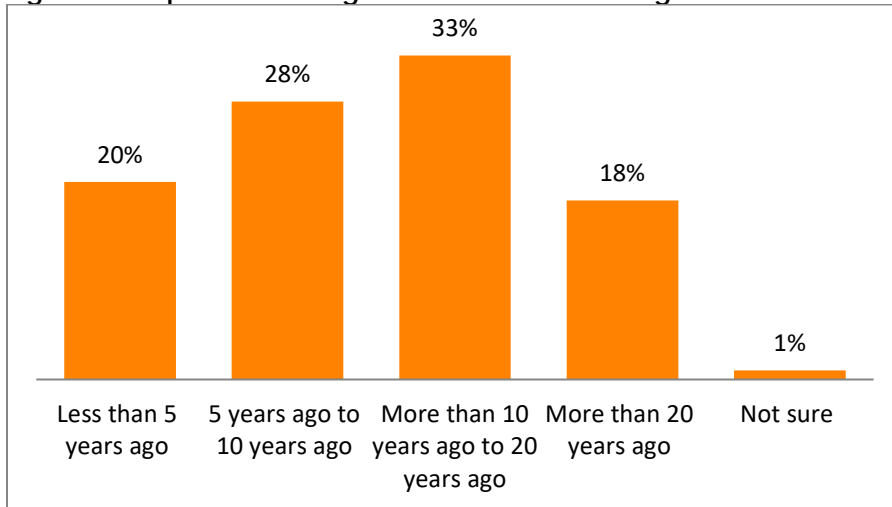


Figure 2. Respondents with a family history of OA. N=320

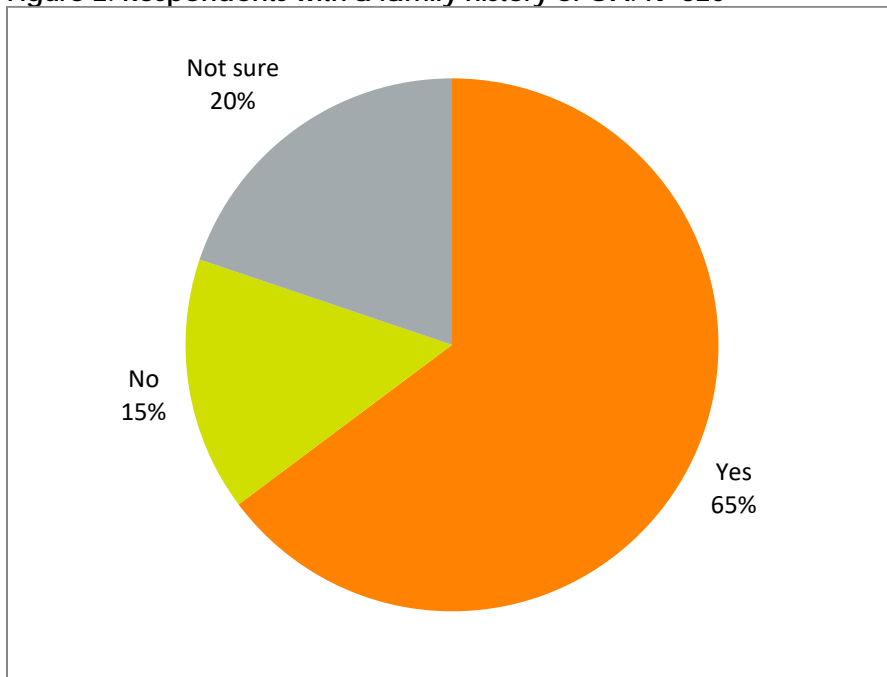


Figure 3. Respondents whose OA is associated with a prior injury or accident. N=320

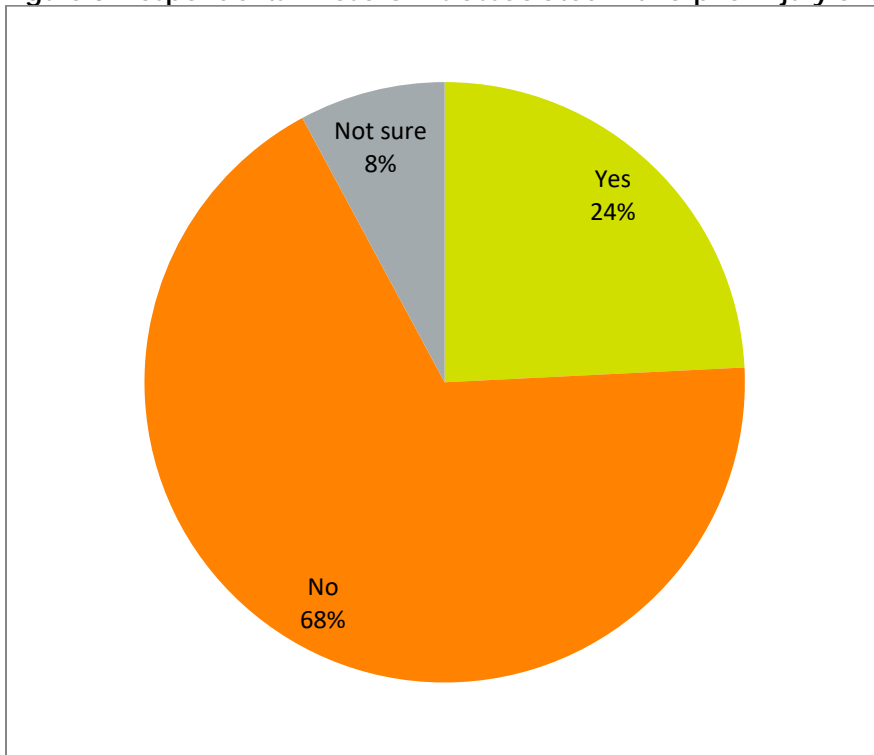


Figure 4. Respondents' most significant symptoms experienced from OA. N=315

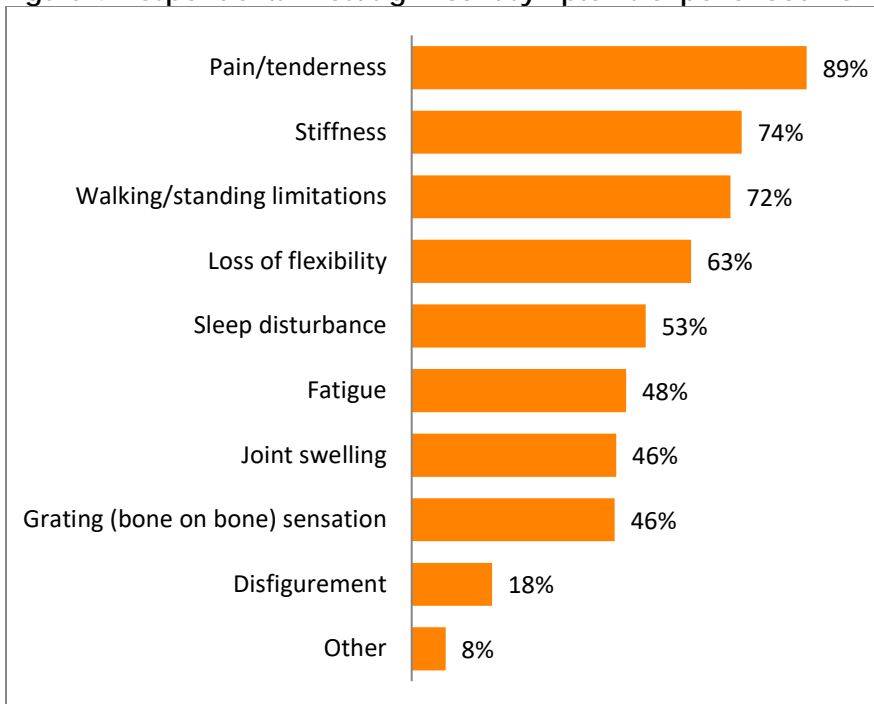


Table 1. Respondents' complex array of treatment options used alone and in combination:

- alternative therapies (acupuncture, cupping, massage, spinal manipulation),
- assistive devices (bracing, cane, compression, splinting, wrapping),
- behavioral therapies (exercise, counseling, diet, meditation, occupational therapy, physical therapy),
- electrical stimulation (TENS),
- herbal supplements (arnica, ginger, turmeric),
- homeopathy,
- hyaluronic acid injections (Hyalgan, Orthovisc, Supartz, Synvisc),
- ice or cold application,
- lifestyle modifications (diet and weight loss),
- massage,
- nutraceuticals (chondroitin, glucosamine, vitamin D)
- opioids (codeine, oxycontin, oxycodone),
- oral or injected non-prescription medications (acetaminophen, OTC NSAIDs- ibuprofen, diclofenac sodium, naproxen),
- oral or injected prescription NSAIDs (Celebrex, Arthrotec, Voltaren, cortisone),
- prescription pain killers (Tramadol, Duloxetine),
- service animals,
- soaking in hot water and/or Epsom salts,
- spinal manipulation/adjustment,
- surgery (arthroscopic, total joint replacement),
- thermal modalities (ultrasound and heat application),
- topical non-prescription pain relief creams, salves, or essential oils (Emu oil, orthoease, aspercreme, bengay, icy-hot, arnica),
- topical prescription pain relief creams, or salves (Pennsaid, Voltaren).

Figure 5. Respondents' non-drug therapies used to manage their OA symptoms. N=315

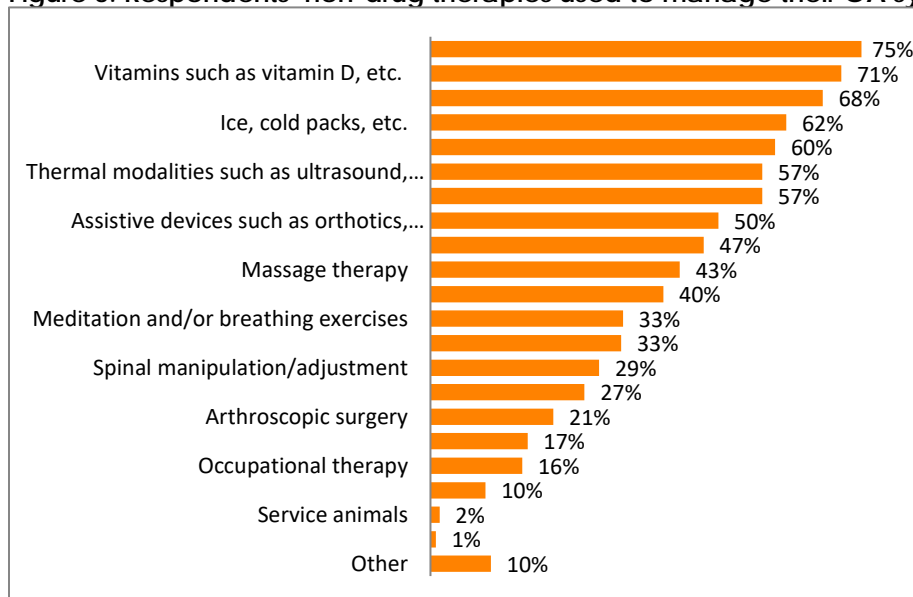


Figure 6. Respondents' drug therapies used to manage their OA symptoms. N=315

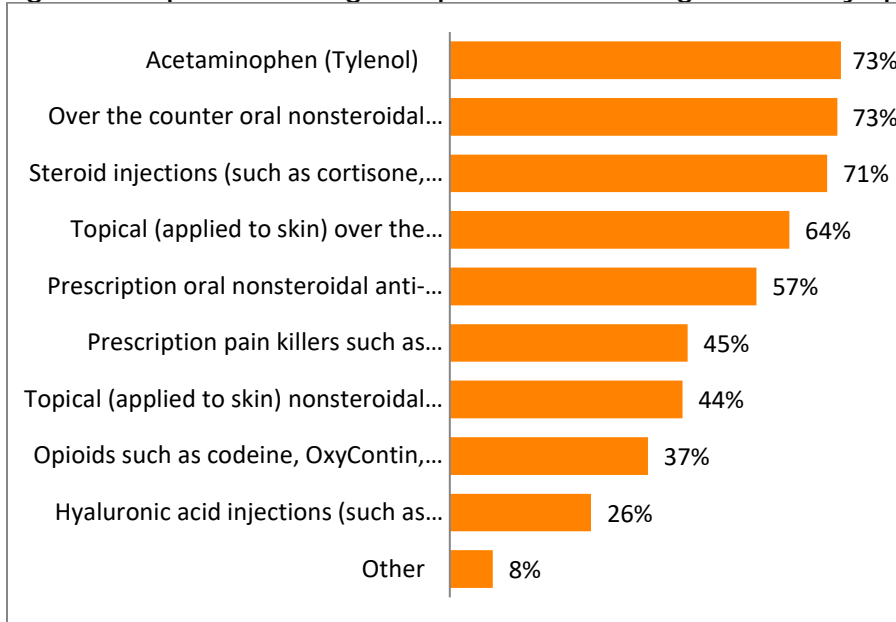


Figure 7. Respondents' most meaningful outcomes of a drug therapy on quality of life. N=304

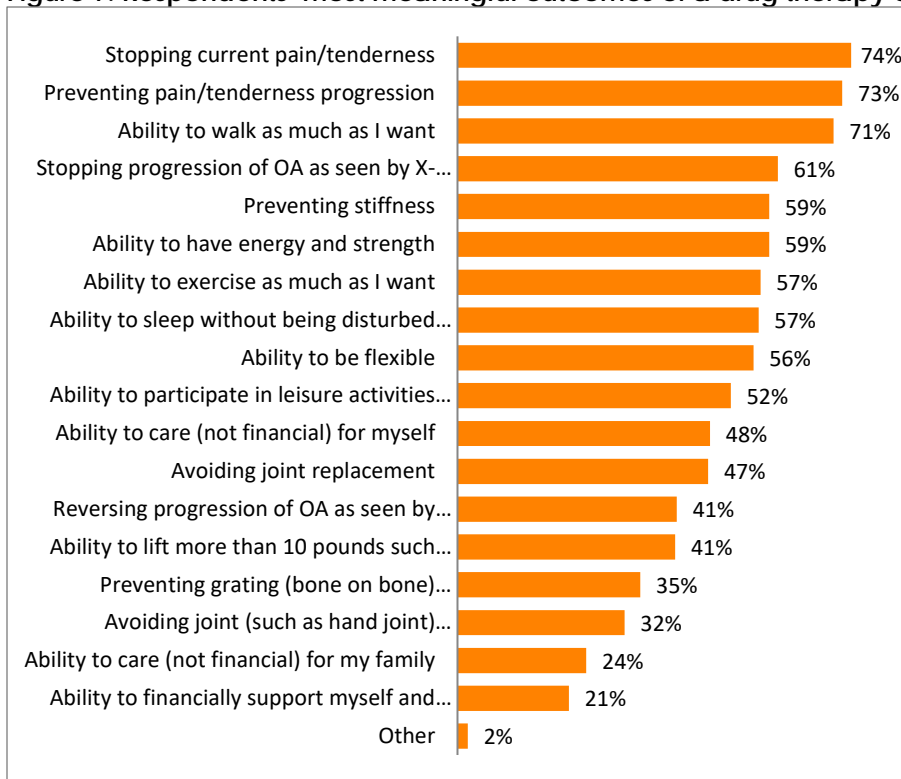
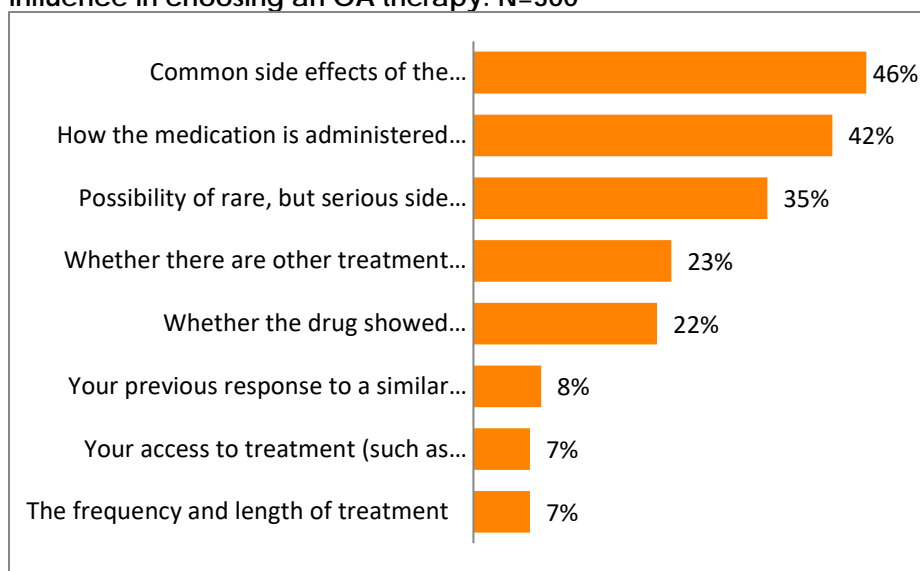


Figure 8. Respondents' meaningful outcomes/benefits and access to treatment which carry the most influence in choosing an OA therapy. N=300



Additional notes/findings:

Notably, they felt that the FDA had a role in ensuring that there is accessible information available to patients explaining the array of options. The issue of cost and “fair” access to coverage and drugs came up across all five groups as well—including those who are well covered expressing their concern for those who are not.

Interest in and willingness to try a new therapy was correlated to increased disease severity and younger age. The oldest of the participants had a more relegated (yet hopeful) perspective that all they can do now is continue exercising/moving, whereas younger individuals, especially those with multiple joints involved, were interested in finding better treatment options. There was a similar divide concerning trust of the pharmaceutical companies and the government, with a highly skeptical sentiment coming from older participants and less or no skepticism coming from younger participants.

Exercise and remaining active and mobile was a shared common theme (and likely a selection bias as these are the volunteers who chose to participate and attend in person) as they were all aware that movement is crucial for joint health.

Implications for drug development consideration: overall those who are interested in accessing new therapies (including surgical interventions) want access to all relevant data for the various treatment options, including personalized data about how it will impact them. They are potentially willing to accept minor side effects but not serious side effects and again, they want clear, comprehensive information to empower their decision-making. They want therapies which stop progression whilst alleviating pain and potentially reverse damage.

Appendix 6: Proposed Content for Osteoarthritis Draft Guidance

The purpose of this Appendix is to provide proposed patient experience content for consideration by the U.S. Food and Drug Administration (FDA) as draft guidance for industry on the clinical development of medical products seeking approval for osteoarthritis (OA) treatment indications. This content summarizes considerations for drug development stakeholders based on patients' lived experience and preferences for ideal treatment options as described during the Arthritis Foundation's externally-led Patient Focused Drug Development meeting (see *The Voice of the Patient: Osteoarthritis* report to which this is appended). It is intended to guide future clinical trial design by including the voice of the OA patient community so that future medical product development is patient-focused.

Specific Efficacy Trial Considerations for Disease-Modifying Drugs

The consensus among individuals with OA is that they are not served by the current standards of care for the treatment of their condition. Physicians routinely treat the symptoms of OA (e.g., pain) through various products that seek to improve how a patient feels, but these therapies do not correct the underlying pathophysiology of OA. In addition, symptomatic relief provided by such therapies is currently, and can be expected to continue to be, only temporary in nature and not fully effective. OA patients continue to seek treatment for these symptoms that burden them in day-to-day life, yet they have also expressed a desire for products that will stop their disease progression and restore joint homeostasis. Such disease-modifying drugs have the potential to ameliorate symptoms (e.g., reduce pain), improve physical function, and/or extend the time to or reduce the need for costly and burdensome procedures related to the consequences of OA (e.g., joint replacement).

Efficacy Endpoints for Disease-Modifying Drugs

While efficacy endpoints for symptomatic relief (i.e., pain measured on a Likert or 10cm VAS scale) and function (i.e., Lequesne and the Western Ontario and McMaster Universities OA indices) in OA are well-established, there is no set of required or recommended clinical outcome measures for studies on structural improvement in OA. Given that biochemical and structural changes may not be detected with standard methods for assessing joint abnormalities and treatment efficacy of disease-modifying OA therapies, FDA will consider proposals using new outcome measures that assess such changes (e.g., to support Accelerated Approval), as well as clinical outcome measures that address one or more of the anticipated benefits to patients as aforementioned. To address this unmet medical need and priority for the OA patient community, sponsors are encouraged to propose, and, if necessary, develop clinical endpoints that better assess changes in the joint environment and structure.

Biochemical and imaging biomarkers that are pending validation as surrogate efficacy endpoints may be the basis for Accelerated Approval given the absence of validated clinical outcome assessments. Specifically, joint injury and structure abnormalities appear to be the proximate cause of the symptomatic and functional consequences of OA, justifying particular interest in biochemical and imaging endpoints. Traditionally, X-ray measures of anatomic features of OA (e.g., joint space narrowing) have been used to assess structural changes. However, technological advances in biochemical and imaging technology now allow for more precise measurement of changes within the joint environment (e.g., CTXII, bone trabecular integrity, cartilage volume) that are relevant to OA. Although the clinical benefit of non-traditional imaging endpoints has not been confirmed, if supported by sufficient scientific evidence and acceptable analytical methods, these endpoints can be the basis for Accelerated Approval. Drug development stakeholders considering a program for Accelerated Approval should enter into discussion with the FDA early in drug development.

Ultimately a disease-modifying therapy for OA should improve how the patient feels and functions to support approval or to be confirmed post-approval as a condition of Accelerated Approval. As previously discussed, there are three general approaches to how patients could benefit from structural improvement: (1) symptomatic relief, (2) improvement in physical function, or (3) extend the time to or reduce the need for medical procedures related to the consequences of OA. Traditional measures of symptomatic relief, especially

pain, can be subject to a significant placebo effect, which is exacerbated by active- or vehicle-controls, making it difficult for controlled trials to identify a between-group difference in response without lengthy trials where this effect would be expected to diminish. Therefore, more objective clinical endpoints for the benefits of structural improvements in OA should be considered in order for clinical trials to be conducted in reasonable timeframes. Objective functional endpoints can be measured in a variety of ways, including performance-based outcome assessments that demonstrate the patient's ability to perform a specific activity or set of activities. Finally, endpoints to capture reduced burden of OA-related medical procedures can be measured as time-to-event for a clinically meaningful consequence of the structural deterioration, including joint replacement surgery. Because there is limited consensus on the criteria for deciding if and when to conduct joint replacement surgery, developing a set of objective criteria as a proxy for or to supplement the actual events would improve the ability to see differences in a vehicle-controlled setting.

Benefit-Risk Considerations for Disease-Modifying Therapies

When making regulatory decisions regarding drugs to stop OA disease progression, FDA will consider patient tolerance for risk, given the debilitating nature and long-term healthcare consequences of this condition. Risk tolerance for a new therapy may be dependent on several factors such as disease severity, functional limitations of the affected joint, worsening symptoms, patient stage in life, management of comorbidities, and desired activity levels; FDA will consider the many factors which influence patients' decisions for treatment choice when assessing risk tolerance for OA therapeutic indications seeking regulatory decisions.

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