Use of the Forgotten Joint Score in Non-Operative Management of Knee Osteoarthritis

Request for Proposal

Purpose and Intent

Flexion Therapeutics, Inc. issues this RFP for a prospective clinical research study evaluating use of the Forgotten Joint Score (FJS-12) as a patient-reported outcome (PRO) measure pre and post triamcinolone acetonide extended release (TA-ER) treatment in patients with knee osteoarthritis (OA).

Target Audience

Healthcare professionals involved in the care of patients with knee osteoarthritis.

Timeline

The RFP application will remain open through 2021.

Background

Arthritis is a serious health crisis. CDC estimates that 1 in 4 (or 54.4 million) US adults have some form of doctor-diagnosed arthritis, a figure that is projected to reach 78 million by the year 2040.[1] While there are estimated to be more than 100 types of arthritis, osteoarthritis (OA) is the most common form of arthritis, affecting over 30 million US adults for 2008-2011.[2] Absolute estimates show that most of these adults (59% or 32.2 million) are working adults (< 65 years of age).[2] People with OA experience greater pain, fatigue, levels of disability, and activity limitations than people of their comparable age.[3] While arthritis pain is extremely individualized, severe joint pain is not uncommon. Recent estimates suggest that one-fourth of adults with arthritis experience severe joint pain, characterized by a score of 7 or greater on the 0-10 pain scale.[4]

Almost 44% of people with arthritis have "arthritis-attributable activity limitations," defined as self-reported limitations in "usual activities" because of arthritis symptoms.[1] By 2040, 11.4% of all adults will experience arthritis-attributable activity limitations.[5] Patients with OA also experience work limitations.[1]

Work Limitations[1]

- 33% of adults with arthritis find stooping, bending, or kneeling very difficult.
- 20% cannot or find it very difficult to walk 3 blocks or push/pull large objects.
- People with OA (working age) experience lower employment rates than those without OA. Research suggests that arthritis-related activity limitations might contribute to their lack of employment.

Joint arthroplasty surgery has proven to be successful in relieving pain and improving function in patients with OA.[6] Joint awareness in everyday life is a crucial criterion in the activity of daily living. The loss of awareness of a joint in everyday life is widely regarded as the ultimate goal in joint arthroplasty resulting in the greatest possible patient satisfaction.[6] The emerging concept of joint perception led to the development of the "Forgotten Joint Score" (FJS), a self-administered 12-item questionnaire assessing the ability to forget the hip or knee joint during a range of day to day and recreational activities.[6] The (FJS) was originally developed as a measurement tool in patients after arthroplasty of the hip or knee joint.[6,7] Considering a patient's evaluation of the loss of awareness of the knee joint, the FJS is a paradigm shift in patient reported outcome/PRO measurement relative to more traditional measurements of pain or activity level/function. Reflecting a patient's joint awareness, the FJS has shown high discriminative power in patients after arthroplasty of the hip and knee.[6] Therefore, the interpretation of the patient's joint awareness measured by the FJS is seen as a new dimension in PRO-measurement.[8]

The FJS questionnaire takes approximately 90 seconds to complete and comprises 12 items concerning the patient's lack of awareness of the knee joint in everyday life.[8] Higher scores represent a better result with a maximum score of 100. Developed in 2012, the FJS has shown a high internal consistency, construct validity and responsiveness in long term patient-reported outcome/PRO.[9] The FJS has been validated in patients after arthroplasty of the knee or hip, and after ACL reconstruction.[6] The FJS does not demonstrate the ceiling effect of the Western Ontario and McMaster University Osteoarthritis Score (WOMAC) or Knee Injury and Osteoarthritis Score (KOOS) pain scores so the FJS may have greater discriminatory ability.[7]

From twelve questions with five response categories, a total score is calculated from 0 to 100 (high degree of being able to forget the joint in daily life). The average total score for knees is 75.0 points and 87.5 points for hips. In the age-specific and sex-specific groups, the lowest median score for knees was 54.2 points (men aged 18-39 years) and the highest median was 97.0 (men aged above 70 years). Similarly, median scores for hips were lowest in men aged 18-39 years (60.9 points) and highest in men aged above 70 years (100 points).[10]

The FJS is now well- used in knee arthroplasty cohorts and is thought to offer improved discrimination of patients with high functional levels and little pain.[6] To date there has only been a single anchor-based estimate of minimal important difference (MID) reported for the FJS that evaluated the change between pre-operative values and 1- year outcomes.[10] Ingelsrud et al. calculated a MID of 14 points for pre-op and 1-year outcomes scores.[10]

A recent study reported on multiple patient- reported outcomes (including the Forgotten Joint Score) among 87 patients with symptomatic knee OA who had been treated with knee arthroscopy and successive intra-articular injection of concentrated adipose tissue.[11] However, Flexion is not aware of any studies in the literature describing the utilization of the FJS to assess non-operative therapeutic modalities for the treatment of knee osteoarthritis.

Knee Questionnaire (Forgotten Joint Score - 12)

Patient: _____   Date: ___.___._____

A healthy joint is not something you are aware of in everyday life. However, even the smallest problems can raise one's awareness of a joint. This means that you think of your joint or have your attention drawn to it. The following questions concern **how often you are aware of your affected knee joint in everyday life.**

Please choose the most appropriate answer for each question.

	Are you aware of your knee joint…	Never	Almost never	Seldom	Some-times	Mostly
1.	… in bed at night?	O	O	O	O	O
2.	… when you are sitting on a chair for more than one hour?	O	O	O	O	O
3.	… when you are walking for more than 15 minutes?	O	O	O	O	O
4.	… when you are taking a bath/shower?	O	O	O	O	O
5.	… when you are traveling in a car?	O	O	O	O	O
6.	… when you are climbing stairs?	O	O	O	O	O
7.	… when you are walking on uneven ground?	O	O	O	O	O
8.	… when you are standing up from a low-sitting position?	O	O	O	O	O
9.	… when you are standing for long periods of time?	O	O	O	O	O
10.	… when you are doing housework or gardening?	O	O	O	O	O
11.	… when you are taking a walk/hiking?	O	O	O	O	O
12.	… when you are doing your favorite sport?	O	O	O	O	O

Forgotten Joint Score – 12

Scoring algorithm

Every question is scored 1 (never) to 5 (mostly) according to the selected response categories. Thus, the raw score ranges from 12 to 60. The raw score is linearly transformed to a 0-100 scale and then reversed to obtain the final score.

Final score = 100 - ((sum(item01 to item12) - 12)/48*100)

For the final ‚Forgotten Joint Score -12' a high score indicates good outcome.

Missing items: In case of missing answers, the mean of the answered items is used instead of the sum of all items and multiplied by 12 (i.e. the missing values are replaced with the mean of the completed items).

If more than four of the answers are missing also the total score should be treated as missing.

Scope of Work

The successful applicant will prepare a research proposal that explores the Forgotten Joint Score (FJS) and its utility as a potential new patient reported outcome within the non-operative, osteoarthritis therapeutic landscape. Completion of the FJS should be completed both pre and post TA-ER injection.

The study proposal should include a focus on patients ($\geq$ 40 yoa) with primary knee osteoarthritis.

Flexion does not require a psychometric study, but such study designs supportive of validation work will be considered. Assessment of construct validity of the FJS to assess pain, functional impairment, and health-related quality of life in US patients with a history of primary knee osteoarthritis will be considered. Proposals should clearly define the osteoarthritis patient population to be included (i.e. radiographic Kellgren-Lawrence grade of osteoarthritis, history of synovitis and/or effusion, etc.).

Applicants are encouraged to contact Dagmara Kuliś d.kulis@forgotten-joint-score.pro to inquire about costs associated with the use of the FJS for the proposed study and then include these costs in the budget of the submitted proposal.

Flexion's IIR review committee will consider funding awards inclusive of indirect costs for the conduct of the study based on a budget within fair market value.

Your concept proposal will be considered by Flexion's cross-functional research committee that meets routinely to review IIR proposals. Flexion may make suggestions to improve the scientific merit of the proposal and enhance consistency with Flexion's support approval criteria. The principal investigator will have full and final discretion and responsibility for all aspects of the study design, implementation, data analysis, and data dissemination, including compliance with all laws and regulations applicable to research sponsors. The terms under which Flexion will provide support must be contained in a written agreement. Flexion provides no guarantees that research committee will provide support for your proposal.

TA-ER is marketed under the tradename ZILRETTA. Please see full Prescribing Information at ZILRETTALabel.com

The information within this RFP is not intended to promote any use of the product that is inconsistent with its approved labeling, nor does this RFP provide comprehensive information regarding TA-ER.

References

1. Barbour KE, Helmick CG, Boring M, Brady TJ. Vital Signs: Prevalence of Doctor-Diagnosed Arthritis and Arthritis-Attributable Activity Limitation – United States, 2013-2015. *MMWR Morb Mortal Wkly Rep.* 2017;66(9):246-253.

2. United States Bone and Joint Initiative. The Burden of Musculoskeletal Diseases in the United States (BMUS). In: Fourth ed. Rosemont, IL. 2018: Available at https://www.boneandjointburden.org/fourth-edition/iiia10/prevalence-aorc   Accessed November 21, 2020.

3. Osteoarthritis Research Society International. Osteoarthritis: A Serious Disease, submitted to the U.S. Food and Drug Administration. 2016. https://oarsi.org/sites/default/files/library/2018/pdf/oarsi_white_paper_oa_serious_disease121416_1.pdf   Accessed November 21, 2020.

4. Barbour KE, Boring M, Helmick CG, Murphy LB, Qin J. Prevalence of Severe Joint Pain Among Adults with Doctor-Diagnosed Arthritis – United States, 2002-2014. *MMWR Morb Mortal Wkly Rep.* 2016;65(39):1052-1056.

5. Hootman JM, Helmick CG, Barbour KE, Theis KA, Boring MA. Updated Projected Prevalence of Self-Reported Doctor-Diagnosed Arthritis and Arthritis-Attributable Activity Limitation Among US Adults, 2015-2040. *Arthritis Rheumatol.* 2016;68(7):1582-1587.

6. Behrend H, Giesinger K, Giesinger JM, Kuster MS. The "forgotten joint' as the ultimate goal in joint arthroplasty: validation of a new patient-reported outcome. *J Arthroplasty.* 2012 Mar;27(30: 430-436.e.1.

7. Thompson SM, Salmon LJ, Webb JM, PInczewski LA, Roe JP. Construct Validity and Test Re-Test Reliability of the Forgotten Joint Score *J Arthroplasty.* 2015 Nov;30 (11):1902-5.

8. Holtz N, Hamilton F, Giesinger JM, Jost B, Giesinger K. Minimal important differences for the WOMAC osteoarthritis index and the Forgotten Joint Score-12 in total knee arthroplasty patients. *BMC Musculoskeletal Disorders* (2020) 21:401.

9. Adriani M, Malahias MA, Gu A, Kahlenberg CA, Ast MP, Sculco PK. Determining the Validity, Reliability, and Utility of the Forgotten Joint Score: A Systematic Review. *J Arthroplasty.* 2020 Apr;35(4):1137-1144.

10. Ingelsrud LH, Roos EM, Terluin B, Gromov K, Husted H, and Troelsen A. Minimal important change values for the Oxford Knee Score and the Forgotten Joint Score at 1 year after total knee replacement. *Acta Orthop.* 2018 Oct;89(5):541-547.

11. Bistolfi A, Roato I, Fornelli G, Sabatini l, Alessandro Massè A, Ferracini R. Treatment of knee osteoarthritis by intra-articular injection of concentrated autologous adipose tissue: a twenty four month follow-up study. *International Orthopaedics* (2021) 45:627–633.