PROACTIVE
Pre-Competitive Consortium for Osteoarthritis
Clinical Trial Outcomes Improvement

Kick-off Meeting
W Hotel Philadelphia
November 13, 2022

WELCOME
Lee Simon, MD

This is the first official meeting of PROACTIVE, a public private partnership. We thank the members of the FDA who are willing to collaborate with us on how to go about studying patients with OA; understanding the natural history of the disease; and, how to measure change that will allow drugs which may alter the natural history of OA to be approved. The dilemmas are enormous, and it is quite complicated.

The FDA published a paper regarding their thinking on these topics and highlighted specific areas of interest. It is important that the design of OA clinical trials be feasible and reasonable to answer specific questions that result in approval of therapies that will be able to improve the lives of OA patients, a disease that affects 527 million individuals globally.

<u>What is a public private partnership?</u>

There have been numerous workshops focused on OA overseen by the Arthritis Foundation as well as the Osteoarthritis Research Society International (OARSI) in which the FDA has participated. In 2008, a federal register notice was posted asking for input on 23 questions that would provide a scientific update of OA. From 2008-2012, under the auspices of OARSI, 120 individuals worked on answering these questions and an 400+ page document was subsequently submitted to Janet Woodcock, former FDA Director of the Center for Drug Evaluation and Research (CDER). Subsequently, at an Arthritis Foundation SNOW conference, Dr. Woodcock indicated that OA was not being considered as a serious disease. This led to the development of a manuscript, also under the oversight of OARSI, by an international group of experts focused on the current data supporting OA as a serious disease, based on the FDA definition for a disease to be considered serious. The paper was published and was also submitted to the FDA. The data was accepted by the FDA and OA is now acknowledged as being a serious disease. As a result of this designation, there is the possibility that a surrogate measure could be used in a clinical program, thus allowing for an accelerated approval. The surrogate measure would need to be validated as providing information that would be reasonably likely to predict a clinical outcome. The successfully measured surrogate would need to be correlated at a later date to a meaningful clinical outcome, specifically how a patient feels, function or survives. In RA, this is simple, one can assess how a patient feels and functions and one can measure structural change. In OA, it is not as easy. The OA population is

heterogenous, and we are unable to identify who will or will not progress in consequent damage to the joint structure.

Within a workshop, it is difficult to have lengthy discussions, thus the creation of PROACTIVE, a non-competitive, public-private consortium which will allow the opportunity for collaborative discussions. How the PROACTIVE consortium evolves will be the responsibility of all participants and will be enhanced by the participation of the FDA.

CHALLENGES
Philip Conaghan, MBBS, PhD

Clinical trials in OA are challenging. There are challenges in understanding the correct tools as well as identifying and including the appropriate patient populations within symptom modifying trials. Including structure modification to a trial with a measured outcome creates substantial additional challenges and cost. OA is a slowly evolving disease and, a clinical trial requires reasonable patient numbers over a long period of time to assess change.

When studying structure and consequent pain reduction, the question is what are the key structures to be targeted and subsequently measured?
There have been studies that showed a modification of structure (e.g., cartilage or bone), but no modification of symptoms.

The term DMOAD may have taken us down the wrong route as it grew out of the designation of DMARD in RA whereby if inflammation was reduced, subsequent damage could be prevented.

OA seems more similar to osteoporosis, years of slow structural asymptomatic deterioration in joints followed by the time when one begins to have symptoms. We should think of symptoms, and what structures are relevant and then think about how a patient feels, functions, and survives.

Dr. Francis Berenbaum has been considering trial designs for OA. While we are not focused on identifying a trial design in this kick-off meeting, we do need to begin thinking about potentially feasible OA trial designs.

Dr. Berenbaum's presentation shared thoughts regarding trial designs and pathways towards regulatory approval.

Companies are not able to support a 7-year trial to demonstrate clinical benefit. Using the accelerated approval regulatory pathway and receiving a conditional approval affords companies the opportunity to subsequently conduct the necessary trial(s) to demonstrate the clinical benefit of the new therapeutic. To navigate the accelerated approval pathway, the use of an in-silico trial could potentially be used. The in-silico trial design is based on the Model-Informed Drug Development Paired Meeting Program (MIDD).

The remit of PROACTIVE is not just developing an outcome measure, but also about models that could allow companies to obtain regulatory approval. The in-silico model was presented as an example.

Discussion

The FDA is only one piece of this multi stakeholder consortium. What is missing is the science that would drive FDA decisions. Accelerated approval has been implemented and used by the FDA and is a viable regulatory pathway. The approval relies on a surrogate marker, surrogate of some type of clinical outcome. Substantial evidence is needed to support the surrogate marker, but we need to understand what it is a surrogate of. Currently, this is unknown and must be addressed to advance the field.

If the standard is met for the surrogate then one could receive accelerated approval without waiting for 5 years to see the clinical benefit. At this point there are still discussions about what the surrogate should be, is it cartilage thickness, 3-D structure, synovitis, or a biochemical marker? And again, what are they surrogates of? The FDA provided an approach in the Kim, et al paper – how to assess clinical benefit when we don't have good outcomes.

A key issue when thinking about surrogacy is that it must be measurable and reasonably likely to predict a clinical outcome. Some people have a lot of OA damage and are doing well. What do we really know? What is the meaningfulness of change? We must understand what we are measuring and what the changes mean. We need to begin thinking out of the box about new ways to achieve our goal.

What are the problems we are trying to solve?
The Kim, et al paper is a first step, but PROCTIVE needs to take the next step to build upon the Kim publication and make the trials more feasible. OA is a disease of the whole joint, not just one part of the joint; and cartilage is not enough of an answer. Members of the PROACTIVE Consortium will have the opportunity to work together to look at the current issues.

In osteoporosis, there has been preliminary approval for the surrogate of fracture in osteoporosis trials. The fracture data from clinical trials has been accumulating over many years. A review of this data was undertaken resulting in a database of 150,000 patients allowing one to assess the meaningfulness of fracture as a surrogate. One might consider whether there is enough similarity in OA trials that could be gleaned which would allow for a similar review and subsequent database. Currently, X-ray is the data in common within all the OA trials.

Biochemical markers will probably not become a surrogate outcome for OA clinical trials, but panels of biochemical markers may be good for subtyping patients/groups in individual trials based on the MOA of the drug being studied. Patient groups need to help PROACTIVE with the digital biomarkers of how a patient feels and functions.

NEXT STEPS

Committees

The work of the Methodology Committee is a key issue. Data sets will need to be identified and accessed. The Methodology Committee will prepare a draft work plan that will identify and prioritize the necessary data analyses to be undertaken. The work plan will be reviewed by all sponsors of PROACTIVE prior to initiating work.

It is anticipated that a number of virtual meetings will be confirmed as we work through the initial process of identifying and obtaining data sets; and confirming an initial work plan.

Executive and Steering Committees

Sponsors participating in PROACTIVE will be contacted with a request to identify individuals from their company for membership on the Executive and Steering Committees.