

# Osteoarthritis and Cartilage



## Methodologic issues in clinical trials for prevention or risk reduction in osteoarthritis

J.M. Jordan †\*, M.F. Sowers ‡, S.P. Messier §, J. Bradley ||, G. Arangio ¶, J.N. Katz #††‡‡§§, E. Losina ‡‡§§|||, L. Rovati ¶¶, N. Bachtell ##, C. Cooper †††, T. Spector ‡‡‡, W. Zhang §§§, J. Gardiner ||||, M. Wahba ¶¶¶

†Thurston Arthritis Research Center, University of North Carolina, Chapel Hill, NC, USA

‡University of Michigan, School of Public Health, Department of Epidemiology, Ann Arbor, MI, USA

§Department of Health and Exercise Science, Wake Forest University, Winston-Salem, NC, USA

||Pfizer Global Research & Development, Groton, CT, USA

¶Pennsylvania State Hershey Medical College, Hershey, PA, USA

#Department of Orthopedic Surgery, Harvard Medical School, Boston, MA, USA

††Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

‡‡Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA

§§Orthopedic and Arthritis Center for Outcomes Research, Department of Orthopedic Surgery, Brigham and Women's Hospital, Boston, MA, USA

|||Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA

¶¶Division of Research & Development, Rottapharm SpA, Monza, Italy

##Genzyme Corporation, Cambridge, MA, USA

†††MRC Environmental Unit, Southampton General Hospital, Oxford, UK

‡‡‡Department of Twin Research, St Thomas' Hospital Campus, Kings College London School of Medicine, London, UK

§§§Academic Rheumatology, University of Nottingham, Clinical Sciences Building, City Hospital, Nottingham NG5 1PB, UK

||||Discovery Translational Medicine, Wyeth Research, Collegeville, PA, USA

¶¶¶US Arthritis, Novartis Pharmaceutical Corporation, East Hanover, NJ, USA

### ARTICLE INFO

#### Article history:

Received 20 June 2010

Accepted 26 October 2010

#### Keywords:

Prevention

Clinical trial

Obesity

Injury

Osteoarthritis

### SUMMARY

The design and execution of prevention trials for OA have methodological issues that are distinct from trials designed to impact prevalent disease. Disease definitions and their precise and sensitive measurement, identification of high-risk populations, the nature of the intervention (pharmaceutical, nutraceutical, behavioral) and its potential pleiotropic impacts on other organ systems are critical to consider. Because prevention trials may be prolonged, close attention to concomitant life changes and comorbidities, adherence and participant retention in the trial is of primary importance, as is recognition of the potential for "preventive misconception" and "behavioral disinhibition" to affect the ability of the trial to show an effect of the intervention under study. None of these potential pitfalls precludes a successful and scientifically rigorous process and outcome. As technology improves the means to measure and predict the OA process and its clinical consequences, it will be increasingly possible to screen individuals for high-risk phenotypes, combining clinical factors with information from imaging, genetic, metabolic and other biomarkers and to impact this high-risk condition to avoid or delay OA both structurally and symptomatically.

© 2011 Published by Elsevier Ltd on behalf of Osteoarthritis Research Society International.

Osteoarthritis (OA) is the most common specific arthritis condition, affecting 27 million people in the United States in 2005<sup>1</sup>. Knee and hip OA are generally considered to have the greatest impact due to effects on ambulation<sup>2</sup>. OA of these joints accounted for 97% of the total knee replacements and 8% of the total hip

\* Address Correspondence and reprint requests to: J.M. Jordan, Thurston Arthritis Research Center, University of North Carolina, Chapel Hill, NC 27599-7280, USA.

E-mail address: joanne\_jordan@med.unc.edu (J.M. Jordan).

replacements for arthritis in 2004<sup>3</sup>. OA, however, is frequently a generalized condition, involving multiple joint sites, including the hand, knee, hip, great toe, and spine, all of which can be associated with significant symptoms and disability<sup>4–6</sup>.

In 2007, the Osteoarthritis Research Society International (OARSI) was awarded a contract from the Federal Drug Administration (FDA) to review issues related to the design and conduct of clinical trials for OA, particularly pertaining to agents purporting to effect disease modification (See Introduction to Issue). Several categories of

inquiries, and Working Groups to examine them, were established, including Imaging, Biomarkers, Definition of Disease State, Safety, and Prevention and Risk Reduction. This paper will discuss the outcome of deliberations by the Working Group for Prevention and Risk Reduction. This Working Group was composed of individuals from academia and the pharmaceutical industry. The remit of this group was to examine potential outcome measures, the desirable duration of, and population for, an OA prevention trial, and the safety database and acceptable risk that would be required for prevention. Lastly, a research agenda to inform these issues was requested. Through a series of face-to-face meetings, telephone conferences, and electronic mail exchanges over almost 2 years, the members of the Working Group discussed these relevant questions, reviewed literature as required to inform answers, and presented the final product to a public forum attended by representatives from the FDA, the OARSI, and the National Institutes of Health (NIH), and academic and industry/private foundation communities.

Generally, clinical trials in OA have addressed three major types of outcomes: (1) symptoms of pain, function, and stiffness; (2) structural disease progression; and (3) replacement of affected joints. The clinical trials in OA to relieve symptoms of pain or stiffness and to improve function may involve pharmaceutical or nutraceutical agents<sup>7</sup>, devices (i.e., braces, shoe orthotics), or behavioral interventions, such as weight-reduction, exercise, or increased physical activity<sup>8–12</sup>. The less common disease-modifying trials aim to demonstrate slowing of the rate of structural progression, (frequently measured by change in joint space narrowing on radiographs of the knee or hip<sup>13–15</sup>) and have employed pharmaceuticals or nutraceutical with, for example, putative anti-oxidant properties, the ability to inhibit cartilage degradative enzymes, impact bone turnover, modulate inflammation, or enhance or induce cartilage repair and/or lubrication<sup>16,17</sup>. The goal of these trials is to prevent *structural progression of established disease*, or to prevent disability or the need for total joint replacement, an indicator of total joint failure, in those with established disease, ie tertiary prevention. A third major type of OA trial involves evaluation of actions intended to assure the safety, efficiency, and efficacy of joint replacement.

This report will address the *primary and secondary prevention and risk reduction* of structural and symptomatic indicators of OA. These types of trials face specific hurdles because the onset of OA can be insidious and progression slow, with consequently, the need for trials of long duration, or the use of proxy measures with imperfect sensitivity and specificity for development of OA clinical outcomes, to allow the trial to be feasible. This report will discuss definitions, eligible populations and high-risk groups to whom initial prevention efforts might be directed for proof of concept, and possible outcome/surrogate outcome measures for primary and secondary prevention and risk reduction (Fig. 1). Then, an example

of a prevention and a risk reduction trial for knee OA, directed at the high-risk group of those who are overweight or obese, and young athletes at risk of knee injury, respectively, will be proposed. These example trial designs are directed at knee OA with the understanding that OA in other joint sites (i.e., hands and hip) may have different prevalences, different risk factor profiles, different natural history of development and unique measures to define the disease state. Therefore, the approaches in these examples may not be generalizable to OA affecting joints other than the knee. In these examples, the recommended duration of a trial and appropriate database for safety will be outlined. Finally, ethical issues surrounding the conduct of clinical trials for OA prevention will be introduced.

**Definitions of prevention and risk reduction**

For the purposes of this report, *prevention* refers to those agents or actions that curtail or delay the onset or new occurrence of clinically diagnosed OA at the joint site of interest, in someone initially without evidence satisfying the clinical definition of the condition. Components of this definition may include structural evidence, e.g., on radiographs, and characteristic signs and symptoms, e.g., bony enlargement, crepitus, and/or pain. This report will **not** address tertiary prevention, or treatment, to modify the progression of established disease or achieve the maximum accommodation of living with established disease. *Risk reduction* refers to decreasing specific and modifiable risk factors associated with the development of OA, in an attempt to decrease the likelihood of developing OA or to delay its onset. For example, since obesity and overweight are strong risk factors for knee OA, a weight loss intervention could be evaluated to determine its ability to reduce the risk of developing knee OA in the obese. Similarly, since joint trauma, with its frequently resultant altered biomechanics, is a strong risk factor for the development of OA, an intervention to alter abnormal biomechanics in those with joint injury could also be considered in a preventive context for OA. Further, an intervention to prevent joint injury in the first place would be an example of risk reduction. It must also be acknowledged that an intervention may be both a preventive measure and a risk reduction measure, i.e., a weight loss intervention would fit both categories though the outcomes would differ (incident OA vs loss of weight).

Because the presentation of OA is frequently generalized, i.e., occurs in more than one joint in more than one joint group, an intervention could be applied in someone with OA in one joint site, in order to prevent the development of OA in another joint site unaffected at the start of the trial. For example, those with hand OA could be the subject of a prevention trial to prevent the development of OA in the knees or hips<sup>6</sup>. This situation blurs the distinction between incidence of new disease and progression of established disease, and may need to be considered on a case-by-case basis, with statistical methodology applied to allow for the non-independence of multiple joints within the same person. This also suggests that collection of information about joints beyond the target joint should be considered at the beginning and throughout the trial, both for the purpose of recognizing important secondary effects of the intervention and for identifying potential safety signals of the intervention.

**Study populations**

In a prevention trial, the optimal study population to demonstrate efficacy most efficiently would be at high risk for future OA, but free of full evidence satisfying an accepted and operational disease definition. However, the initial testing of an intervention on

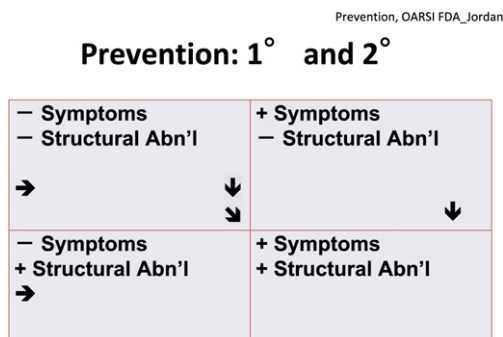


Fig. 1. Structural abn'l = structural abnormality.

a high-risk population is not without drawbacks, as this may limit generalizability, necessitating further testing on others with varying degrees of risk. Or, the efficacy of agents which might be effective in those of lower risk, but prove ineffective in the “high-risk” population, would remain undiscovered. Ultimately, the study population selection cannot be dictated and is dependent upon the definition of disease that is employed and overall goals of the trial.

A prevention trial study population can be selected to represent the three major domains of disease definition related to OA: (1) structural compromise, (2) pain and other symptoms, and (3) impaired function. Additionally, physiological/immunological/genetic locally or systemically measured biomarkers, such as synovial fluid aggrecan, serum C-reactive protein (CRP) or cartilage oligomeric matrix protein (COMP), urinary type II collagen telopeptides (uCTX-II), or combinations of biomarkers, might be incorporated to either define an at-risk population or to exclude individuals from selection into a prevention trial<sup>18</sup>. Further, population selection can be predicated on addressing each of these domains singularly or in combination<sup>19</sup>. For discussion of the current state of qualification of biomarkers for OA, the reader is referred to the article in this issue on Biomarkers.

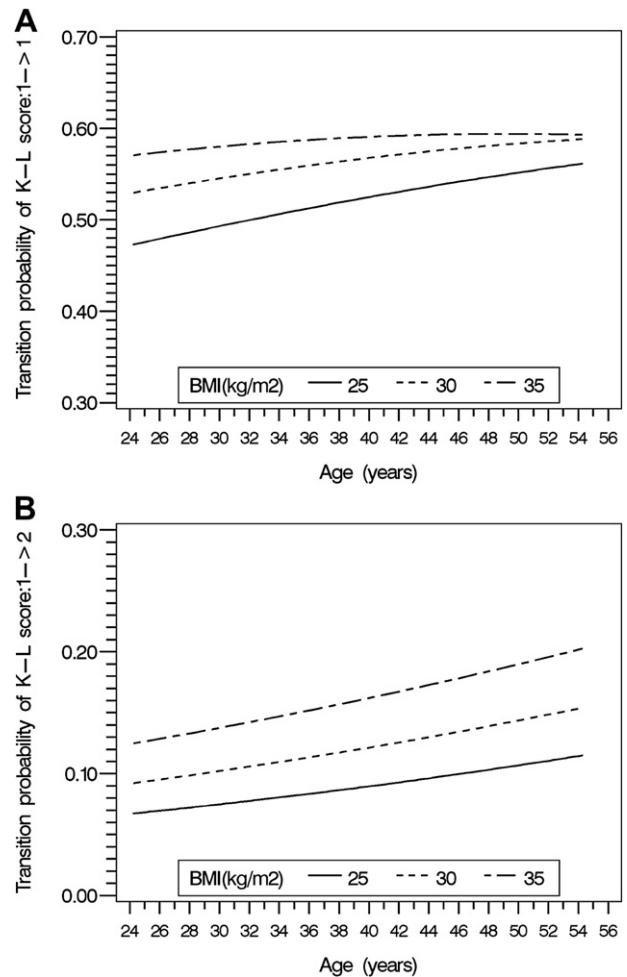
#### Eligible study populations for trials to prevent structurally-defined OA

If the eligible population for a prevention trial is to be free of structurally-defined OA, one option for defining a “disease-free” population includes enrollment of persons with Kellgren–Lawrence (K–L) radiographic grades 0 or 1. Decision-making based on the selection of a population with a K–L score of K–L=0 vs K–L=1, which is designated as “doubtful OA” must acknowledge that there is an embedded probability that individuals with a K–L=1 have early OA<sup>20</sup>, or the underlying conditions leading to OA, but have not yet been identified definitively radiographically. This probability should be factored into estimating the sample size and developing data analytic strategies. Similar concepts apply if the study population lacks knee OA, defined as the absence of a definite osteophyte. Currently, there are very limited data organized to inform these design issues; this is the rationale for this report including a call to identify and organize data to support making evidence-based design choices.

An example of the type of data needed comes from the 15-year study of the natural history of knee OA development (the Michigan Bone Health and Metabolism Study) encompassing 660 women who were aged 24–44 at the 1992 study inception. The women were recruited from a population-based sample to increase the likelihood of generalizability of the findings. Radiographs, taken every 3 years, were scored by two radiologists using K–L definitions for OA knee severity.

The probability of moving from one K–L score to the same or a different K–L score in a 3-year period was estimated using Markov transition modeling. Estimating the probabilities of transitioning from a K–L score of 1 (proposed here as an example for a prevention trial) to other K–L scores reveals the impact of age and body mass index (BMI) and provides evidence to define inclusion and exclusion criteria in the prevention trial.

At age 50, the probability that a K–L=1 score would remain at a K–L=1 score 3 years later was 54–59% when BMIs ranged from 25 kg/m<sup>2</sup> to 35 kg/m<sup>2</sup> [Fig. 2(A)]. The probability of transitioning from K–L=1 score to K–L=2 score in a 3-year period ranged from 8% in non-obese women to 15% in women with a BMI  $\geq$  35 kg/m<sup>2</sup> [Fig. 2(B)]. The probability of transitioning from a K–L=1 score to a K–L=3 score in a 3-year period is less than 2% (data not shown graphically). This evidence-based approach increases the likelihood



**Fig. 2.** Three-year transition probabilities of K–L score of 1 (doubtful OA) staying at a K–L=1 or progressing to a K–L=2 to OA as a function of age (years) and BMI (kg/m<sup>2</sup>): designing a prevention trial of knee OA. (A) Transition probability of K–L=1 score staying at K–L=1; (B) Transition probability of K–L=1 score to a K–L=2 score, indicative of OA.

of having efficiently designed trials of prevention practices to forestall the development of knee OA.

Efforts are underway to define structural changes of knee OA by techniques other than the standing knee radiograph. For instance, static magnetic resonance imaging (MRI) to define OA based on morphologic changes in cartilage, bone or other soft tissues<sup>21</sup> or functional magnetic resonance imaging (fMRI) or other types of MRI measures (such as delayed gadolinium-enhanced MRI of cartilage [dGEMRIC], T2-mapping, T1rho, sodium imaging, etc) to define OA based on compositional changes in cartilage, bone or other soft tissues<sup>22,23</sup> may become modalities of choice. Currently, there is no agreed upon definition of OA based on these technologies. However, the field is rapidly evolving, i.e., the OARSI FDA Initiative Imaging Working Group is currently developing criteria for the early diagnosis of knee OA using MRI, and these developments must be anticipated in developing future trials (See article on Imaging in this issue).

#### Eligible study populations for trials to prevent symptoms of OA

If the eligible population lacks characteristic defining symptoms, especially pain or stiffness, the limits of allowable symptoms must be carefully defined, including how pain is to be assessed, its severity and duration, and the allowable frequency for transient pain, and potentially whether or not pain in joints apart from the target joints are

considered informative. The use of usual and rescue medications, such as analgesics or non-steroidal anti-inflammatory drugs (NSAIDs), also needs to be factored into the methodologic strategy to assess symptoms of OA<sup>24</sup>. Depending upon the mode of action of the agent under study, it may be necessary to disallow some usual or rescue medications to decipher the effect of the intervention unambiguously. For example, if the mechanism of action of the agent to be used effects pain relief through disruption of bone turnover, it might be necessary to exclude the use of drugs that affect bone turnover, such as bisphosphonates. If a drug is related to narcotics, it might be necessary to exclude the use of narcotics as rescue medication. Again, these issues, critical to the design of prevention trials, cannot be dictated and must be decided in the context of the trial under consideration.

#### *Eligible study populations for trials to prevent functional decline from OA*

If the eligible study population is to be free of functional performance impediments, investigators will need to determine whether inclusion criteria are based on self-report instruments or performance-based assessments. There are numerous questionnaire-based instruments to characterize functional status (See article on Functional status measures in this issue). For the selection of a study population, it is particularly important to choose an instrument or combination of instruments that have a known specificity (the known probability of truly being free of functional compromise), and that specificity should be relevant to the population from which the prevention trial population will be recruited. The use of performance-based assessment in prevention trial recruitment is limited by the relative absence of normative data in persons younger than age 65, thereby precluding the ability to estimate the probability of any specific assessment value's actually representing the disease-free state for a prevention trial. Further, there are many determinants of function which may or may not be directly relevant to OA. Alternatively, these measures may be considered to be estimates of an "at-risk" state and therefore eligible for study in a prevention trial; it is important that the predictive capacity of these performance measures over a period of time for increased compromise be known.

#### *Use of biomarkers to define eligible study populations for prevention trials in OA*

If the eligible study population will be selected based on physiological or immunological biomarker measures, there are at least two expectations. First, there must be adequate information to discern when a specific value of the biomarker(s) truly represents a "disease-free" state and, second, information about the rapidity of the biomarker change (if treated as a continuous variable) or conversion (if treated as a discrete variable) in relation to the development of disease, must be known and available. Additionally, the biomarker must have been previously validated against a clinically relevant endpoint for its use as a surrogate measure<sup>25</sup>. Even if the biomarker is used only as a criterion for inclusion or exclusion for participation in a prevention trial, it must have sufficient evidence of predictive relevance to warrant its application. Further discussion of this topic is found in the article on Biomarkers.

#### *High-risk groups to target for prevention and risk reduction*

For primary prevention and risk reduction, careful characterization of the relevant risk factor of interest is as critical as being able to define the absence of OA. It is important to be able to (1) define and measure the risk factor unambiguously, and (2) know

the relative contribution of the risk factor to OA disease development, the average duration to disease manifestation among those with and without the risk factor, and the prevalence of the risk factor in the population. Clinical risk factors for OA may be joint-site specific, i.e., rupture of the anterior cruciate ligament (ACL) as a risk factor for the development of knee OA. Other risk factors may exert systemic effects on risk of OA in multiple joints. The latter situation includes factors such as age, female gender, overweight and obesity, endocrine disorders, and family history or genetically-defined population subgroups. Although not all of these are modifiable, they may influence participant selection criteria in certain trials.

As our measurement tools become increasingly sensitive and precise, it may be possible to classify the risk status of individuals and groups based on characteristics such as cartilage lesions on MRI, levels of biomarkers associated with OA development, or possession of a specific genotype.

#### **Sample trial design for prevention of knee OA in overweight and obese**

- The following is presented for illustrative purposes only, and should NOT be considered a prescriptive mandate for the design of a prevention trial. Further, as definitions of at risk populations change and measurements of the disease process and outcomes advance, it is expected that design features of such a trial would necessarily evolve as well. It is critical to enrich the probability of including individuals who may develop knee OA in a shorter and feasible time frame that acknowledges that clinical trials of long duration are not only costly, but are difficult to implement (i.e., to conduct an intervention without drift or maintain a study group compliant with the protocol, etc.). Including persons with an increased likelihood of developing disease will improve the ability to determine the intervention's effectiveness in preventing disease, but may limit generalizability.

#### *Proposed study population*

The study population for a primary or secondary prevention trial should be structured to the proposed intervention. A reasonable "high-risk" study population for a prevention trial could consist of ambulatory, community-dwelling men and women aged 50–65 years with: (1) no more than a "questionable" osteophyte (K–L = 1) in the medial or lateral tibiofemoral compartment (2) knee varus or valgus malalignment (angle  $\geq 2^\circ$  and  $\leq 10^\circ$ ); (3) BMI  $\geq 30$  kg/m<sup>2</sup> and  $\leq 45$  kg/m<sup>2</sup>; (4) sedentary lifestyle, i.e., no participation within the past 6 months in an exercise program that incorporated more than 30 min/week of formal exercise; and, (5) the absence of interview-determined knee pain or limited function for a month-long time period. Scores on either questionnaire-based or performance-based functional assessment will reflect values considered in the "normal" range for men and women in the 50–65 year age range. A detailed record of medication use should be collected at baseline and for each specific follow-up testing interval.

#### *Rationale for criteria*

- Use of K–L = 1 rather than K–L = 0, 1 should increase the likelihood that individuals will develop OA<sup>20</sup>.
- A  $30 < \text{BMI} < 45$  kg/m<sup>2</sup> is likely to include a population that is obese but able to participate in a designated intervention, and for which normative measures are interpretable. The range of BMI should be evaluated for population groups of shorter stature, such as first generation Asian enrollees to BMI of 25–35 kg/m<sup>2</sup>.

- Potential study participants with a BMI > 45 kg/m<sup>2</sup> should be considered for exclusion because of the difficulty in using computerized tomography and MRI equipment to characterize hard and soft tissue structures. Additionally, in this group, there is a lower exercise compliance rate associated with high BMIs<sup>26</sup>.
- Including only those with moderate malalignment (varus or valgus knee angle  $\geq 2$  and  $\leq 10^\circ$ ) will potentially allow more rapid development of disease, because medial and lateral knee OA progression is strongly associated with moderate malalignment, and this may or may not be independent of body size<sup>27</sup>. However, this is not absolute, since data supporting the role of malalignment in the development of new knee OA is controversial<sup>28,29</sup>.

#### Possible interventions

Interventions could be pharmacologic or non-pharmacologic. Importantly, an intervention in a primary or secondary prevention trial has unique elements in that (1) implementation is likely, but not definitely, to require a protracted administration period; (2) the administration cannot generate risk of accentuating other potential on-going disease processes; and (3) a careful weighing of the costs and benefits must occur. For example, bariatric surgery might be considered a candidate intervention for a primary prevention trial for OA, but its use imposes unique consideration for other health costs and risks of morbidity and mortality. One way to address this issue could be to append an ancillary study for prevention of knee OA to an on-going trial of bariatric surgery for other outcomes. An active drug (unknown at this point) could be directed toward decreasing inflammation and/or pain or improving weight management. A functional intervention might include measures to modify alignment and/or build strength. A behavioral intervention could be directed toward increasing physical activity, changing the type of physical activity, or modifying dietary practices.

It is also possible that a preventive intervention might not have to be administered over prolonged periods of time. Such a situation might obtain in the setting of acute joint injury, in which hypothetical Agent X might be injected into the injured joint weekly for 4 weeks. Assessment of such a regimen could improve the feasibility and tolerability of delivering the intervention itself, but would not eliminate the need for prolonged assessments to ascertain whether the agent inhibited the onset of OA and whether it is safe.

#### Primary outcomes

If the trial hypothesis is that an intervention in a prevention trial among obese adults with no or doubtful evidence of radiographic knee OA (K–L = 0, 1) will be associated with a delayed onset of knee OA compared to the placebo group, this delay could be reflected in two co-primary outcomes: less symptom report and minimal structural change in relation to the untreated group. Candidate measures to detect these areas include changes in: (1) K–L score or minimal joint space and (2) questionnaire-based pain assessment. Other potentially relevant outcome measures could include newer technologies once they have been validated, such as MRI with or without T2-mapping to assess morphological changes in joint structures or articular cartilage degradation and/or bone marrow lesions. As imaging and molecular techniques advance to the stage where they could be surrogates of downstream clinical outcomes, it may be that an intervention might be able to show a primary effect on structure of the OA process, regardless of its immediate effect on symptoms. While examples of prevention in other medical conditions abound, e.g., interventions directed toward lowering serum cholesterol or altering lipid profiles to prevent future

cardiovascular events<sup>30,31</sup>, or altering bone mineral density to prevent osteoporotic fractures<sup>32</sup>, it is unlikely that requirements for a proposed intervention to affect relevant clinical outcomes would be waived entirely.

#### Secondary outcomes

Secondary outcomes could include some or all of the following largely predicated on the nature of the proposed intervention: (1) clinical measures of function, pain and mobility; (2) mechanistic measures of the OA disease pathways such as knee alignment, knee external adductor moment, knee joint compressive and shear forces, and; (3) biomarker measures of pro-inflammatory molecules (e.g., interleukin-6 (IL-6), Tumor Necrosis Factor- $\alpha$ , CRP) and joint metabolism (e.g., uCTX-II, COMP); (4) lower extremity strength and power; (5) limb proprioception; and (6) abdominal and thigh fat depots measured by CT; (7) adverse effects associated with the intervention; and (8) quality of life.

In addition to OA outcome measures, investigators need to select or develop appropriate measures of intervention-related processes and adherence to the intervention.

#### Study time line

Depending upon the factors discussed above, a primary prevention trial is likely to require a 10-year follow-up with data collected from participants at 1 or 2-year intervals. The interval distance should be based on time required to detect meaningful differences in the measures of interest and motivate subjects to maintain optimal participation in the trial. For example, MRI, knee X-ray, gait, and strength might be measured biannually (years 2, 4, 6, 8, and 10), while biomarker levels might be assessed every 3–6 months. Proposed trials of shorter duration, with proper justification of clinically relevant outcomes and safety monitoring, would likely improve feasibility.

#### Sample trial design for prevention of knee OA by preventing knee injury

Many of the issues above also apply to trials of injury prevention, but the latter have a number of unique, key design features worthy of separate discussion and illustrated by a trial of an educational/exercise intervention vs an attention control to prevent knee injury in high school female basketball players. This is an example of a risk reduction trial to prevent injury that might later lead to knee OA.

#### Selecting a sample/population

Injury prevention trials must identify populations at considerable risk of the relevant injury. Low risk populations are inefficient to study because event rates are minimal, requiring very large samples or longer trial duration, which may lead to contamination across study arms and considerable attrition of study participants. Sports teams, military trainees and other such groups exposed to high levels of demanding physical activity are appropriate at-risk populations.

#### Unit of randomization

Such prevention studies often require cluster-randomized designs, in which the unit of randomization is the group, not the individual subject. These may include sports teams, schools, sports leagues, or even towns. For the trial of female basketball players, the cluster group is the high school team. The rationale for randomizing at the group level is to reduce contamination, or diffusion of the intervention to the control group. For example, if two basketball

players on the same team are randomized to separate arms, the player randomized to receive exercises may show the exercises to the player in the control group. Cluster randomization reduces this risk. Furthermore, cluster randomization permits the group to be incorporated into the intervention. When an entire school is randomized to an educational intervention arm, the investigators can display injury prevention educational posters in the school and not worry about contamination. Cluster-randomized designs are typically costly in terms of sample size because each observation is not independent. The more similar the outcomes are among members of the group, and the larger the cluster group, the greater the sample size needed to overcome the non-independence.

#### *Intervention protocol*

Interventions in injury prevention trials must be delivered in a standardized fashion at all intervention sites. This requires training, reliability assessment, site visits, and logistical work to ensure that the intervention is administered similarly across diverse settings. In this example, a basketball injury prevention program allocated at the school level needs to be delivered identically despite differences in the gyms, practice schedules and coaches' styles in different schools.

#### *Outcome assessment*

Assessments must be done in a standardized fashion at regular intervals using well-defined, reproducible outcome definitions. In many trials the outcome is injury, but investigators must clarify what constitutes an injury (a sore knee for an hour? a day? with swelling, defined by whom? had to leave practice or game? had to miss next game? radiographic or imaging findings, e.g., ligamentous injury, meniscal injury, fracture?). This assessment should ideally be made by an observer blinded to random intervention assignment.

#### *Statistical analysis*

The analysis of cluster-randomized intervention trials must use techniques (such as generalized estimating equations) that account for clustered observations<sup>33</sup> or risk artificially lowering variance estimates and over-stating the statistical significance.

### **Methodological considerations for prevention trials**

#### *Study design*

As these examples illustrate, the double blinded, randomized, *placebo* or active comparator study design is the gold standard, but its appropriateness is dependent upon the agent and the availability of known effective interventions for primary preventions. Many likely interventions may be difficult or impossible to blind completely. Further, many potential primary prevention interventions, such as the injury prevention trial, may be more effectively delivered using cluster randomization, where the community is the unit of analysis, rather than the individual<sup>33</sup>. In this case, contamination related to community behavioral or other change can influence results and must be rigorously addressed<sup>34</sup>. Therefore, selection of study design for the trial will be dependent upon intervention, the degree to which individual implementation is feasible, and the capacity to include an effective *placebo*.

#### *Adherence*

It is a particular problem for long-term interventions, particularly if participants do not readily perceive benefit from continued

participation or experience other barriers. Both the active intervention and *placebo* groups will require supplemental behavioral components to maintain adherence, and the inclusion of an adherence specialist on the study team may be wise.

There are also organic factors that may influence adherence. It may be appropriate to assess for depression symptoms and design interventions and intervention monitoring to address their impact in terms of both individual behaviors as well as interactions of depression therapy with the intervention for OA. Female enrollees are likely to be in the midst of the menopause transition and the degree of symptoms and stage of the transition are likely to influence both behaviors and potentially structural tissue responses. This suggests that adherence management needs to be prepared to deal with concomitant symptomatic conditions and potential interventions associated with those symptoms. The proposed age range is likely to reflect other competing illness processes that may affect adherence, as well as directly impact intervention effectiveness and potential for side-effects.

#### *Recruitment*

It is the life-blood of any clinical trial; however, recruiting for a primary prevention trial imposes requirements that are not always evident in treatment trials. Recruitment could be enhanced by using complementary strategies coupled with a system that provides feedback on each strategy's effectiveness and cost<sup>35</sup>. Mass mailings and media (newspaper, television, internet) may be effective in some settings. Depending upon the age of the primary prevention target population, having strong ties with local aging service networks and access to senior centers, churches, drug stores, shopping malls, and other sites where older adults gather could be important but may be ineffective for the population 50–65 years. Most health science centers maintain a large database of adults who have signed consent to be contacted about participating in future clinical trials; however, it is important to identify why these adults are associated with such registries and if their registration is associated with diseases that may impinge on the intervention or decrease the likelihood that they are going to be free of OA.

Experience has proven that *on-going monitoring of the recruitment process is necessary* to achieve study goals and to review recruitment activities, plan new activities, and monitor the number of contacts<sup>24</sup>. Close attention should be given to the gender and minority frequencies of those who qualify for, and enroll in, the study.

### **Safety database for trials of prevention of OA**

Because a prevention trial for OA could involve an intervention with active agents administered to otherwise healthy individuals, or to individuals with co-morbid conditions, for extended periods of time, the safety database must be extensive and involve information from multiple organ systems. The extent of this safety database may depend upon the intervention. For example, systemically-administered interventions may have pleiotropic effects, e.g., statins or bisphosphonates<sup>36–39</sup>, reinforcing the need to monitor multiple organ systems for toxicity. A more localized intervention, such as an unloading brace, might not require the same degree of vigilance for safety in remote organ systems. Observations must also be long in duration, particularly for agents that might impact the immune system and be associated with infections or subsequent development of cancer. Finally, when trials are of considerable duration, such as in these cases of OA prevention, careful monitoring of evolving technology that might impact the long-term assessment of outcome must also occur. See article on Safety as part of this issue.

## Ethical issues for prevention trials

As recently reviewed<sup>40</sup>, rheumatology clinical trials may involve some issues that pose specific ethical concerns. This may particularly be the case in prevention trials for OA. First, since currently no clearly effective agents exist, novel agents to be used in primary prevention must first include substantial testing on healthy volunteers or people with early disease to establish viability. Prevention trials necessarily involve people who may not have the disease in question, who may not ever get the disease, or who might experience a relatively benign course even with no intervention. Further, for a condition such as OA, which develops over years, any effective agent for prevention would likely need to be administered for a prolonged time, possibly beginning at an early age. The potential for multi-system toxicity must be monitored, especially in younger individuals who may be of reproductive age when the agent is started.

Some preventive interventions may be directed at the population level, rather than provide benefit to a specific individual. An example of this would be a vaccine study. In this instance, studying a treatment in a person with disease can be profoundly different than studying an intervention in healthy people. Studies in other diseases have shown that study participants may have misconceptions about the potential effectiveness of a preventive intervention and/or may have inflated estimates of the likelihood that they will be randomized to get the active agent, and may have exaggerated impressions of the likelihood that the intervention will be personally effective for them. Simon and colleagues have called this the “preventive misconception,” defined as “the overestimate in probability or level of personal protection that is afforded by being enrolled in a trial of a preventive intervention”<sup>41</sup>. This can be particularly problematic when accompanied by “behavioral disinhibition” or the adoption of behaviors that may pose a risk to the participant or others. This has been observed in persons participating in a HIV vaccine trial, in which individuals had an increase in risky behaviors<sup>41</sup>. In the case of OA, various scenarios could be imagined, in which behavioral disinhibition could occur. One could imagine that someone with a strong family history of OA, or even someone who possessed a very high-risk genotype, might be less vigilant about maintaining a normal weight because of a false expectation that the preventive agent he/she received in a trial will be effective and protect him/her from his/her increased risk of OA. These issues emphasize the critical importance of the informed consent process in OA trials, particularly those for prevention.

## Recommendations for future research

First and foremost is the requirement that research continue to work to refine definitions of OA, utilizing genetic, biochemical, and imaging biomarkers and psychometrically valid questionnaires and performance measures, with the goal of diminishing ambiguity in the currently used metrics and increasing their clinical relevance. Collection of extensive biological specimens, e.g., serum, plasma, DNA, RNA, urine, should be a part of all of these on-going and future studies.

Observational studies with both short and long-term follow-up can be particularly helpful in this regard, to define molecular, structural and symptomatic correlates of disease and to identify risk factors predictive of the development of disease and its clinical impact. Attention to gender and minority inclusion, with the requisite consideration of distinct issues regarding their propensity to participate in prevention trials, should be a part of this research agenda. Observational studies can be particularly helpful in the following activities:

- Evaluation of existing datasets with particularly long follow-up times (10, 20 or more years) in order to identify risk factors that may be exposed long in advance of disease onset.
- Extended follow-up as adults of cohorts established during childhood, adolescence, and early adulthood, for the development of OA.
- Extended, detailed follow-up of inception cohorts of those with acute joint injury, with detailed information regarding the events and treatment modalities applied in the acute setting, as well as other potential risk factors.
- Evaluation of existing datasets with detailed genetic, biomarker, and imaging data to expand our information about various OA phenotypes along the continuum from molecular to pre-radiographic OA, to radiographic to symptomatic OA.
- Addition of short follow-up times (i.e., months), to studies of existing cohorts to obtain sensitive, dynamic imaging and other biomarker data to aid prediction of the development of structural and clinical disease.
- Evaluation of distinct ethnic/racial sub-populations to ascertain accurate assessment of the burden of disease in these groups, differences in risk factor profiles, and genetic, imaging, and biomarker sub-types in order to tailor trials to relevant groups, (i.e., differences in BMI that might be used to screen Asians or African Americans into prevention trials for the overweight/obese).
- Methodological studies of distinct threats to validity of prevention trials and their execution, related to cultural differences in attitudes toward trial participation and risk factor reduction; techniques to maximize adherence and retention; and ways to measure and overcome biases such as preventive misconception and behavioral disinhibition. As one example, the use of technology, such as hand-held devices and the Internet, for participant recruitment, retention and data collection, is becoming more widespread and will continue to evolve. The study of the impact of such methods upon prevention trials in general will likely inform future prevention trials for OA.

An additional future direction may be a multi-center clinical trial of a non-pharmacologic intervention, alone and in combination with a pharmacologic co-therapy, that can alter mechanisms in the pathological pathway (e.g., decrease knee joint loading and reduce inflammation) to OA and thus lower its incidence. The 2009 NIAMS Roundtable presented a roadmap for how prevention trials should be organized. For large multi-center trials, NIAMS will identify the most qualified investigators who will be required to first establish the need for a larger trial with results from a planning grant or similar study. This will allow applicants to demonstrate their abilities to design and manage clinical trials before launching a full-scale project. The large-scale project should be comprehensive, incorporating clinical (e.g., pain, function), mechanistic (e.g., inflammation and knee joint loading), and structural (e.g., quantitative cartilage morphology with qMRI, semi-quantitative whole joint scoring) outcomes. Demonstrating the ability to identify and target people who are at high-risk of OA will be crucial as this will lay the foundation for primary prevention efforts.

Secondary prevention is equally important. Knee trauma, such as ACL or meniscus injury, is a strong predictor of subsequent knee OA. Considering the young age at which many of these injuries occur, knee joint replacement at a relatively young age is a distinct possibility, possibly followed by a second replacement after 10–15 years. A secondary prevention trial with outcomes related to the risk of knee replacement would have important public health implications. Knee and hip strengthening in young adults with knee trauma to reduce the risk of knee replacement would be an example of a secondary

prevention trial. A synopsis of the NIAMS roundtable can be found at the location listed below.

- ([http://www.niams.nih.gov/news\\_and\\_events/Meetings\\_and\\_Events/Roundtables/2009/ortho\\_OA.asp](http://www.niams.nih.gov/news_and_events/Meetings_and_Events/Roundtables/2009/ortho_OA.asp)).

#### Declaration of funding and role of funding source

The OARSI FDA OA Initiative received financial support from the following professional organization:

American College of Rheumatology.

Additionally the OARSI FDA OA Initiative received financial support from the following companies: Amgen; ArthroLab; Astra-Zeneca; Bayer Healthcare; Chondrometrics; CombinatoRx; Cypress BioScience; DePuy Mitek; Expanscience; 4QImaging; Genevriar/IBSA; Genzyme; King (Alpharma); Merck; Merck Serono; NicOx; Pfizer; Rottapharm; Smith & Nephew; Wyeth.

While individuals from pharmaceutical, biotechnology and device companies actively participated in on-going working group discussions, due to the conflict of interest policy enacted by OARSI, these individuals were not allowed to vote on the final recommendations made by OARSI to the Food and Drug Administration.

#### Author contributions

JM Jordan: Chair, Prevention and Risk Reduction Working Group; conception and design; drafting of the article; critical revision of the article for important intellectual content; final approval of the article.

MF Sowers: conception and design; drafting of the article; critical revision of the article for important intellectual content; final approval of the article.

SP Messier: conception and design; drafting of the article; critical revision of the article for important intellectual content; final approval of the article.

J Bradley: conception and design; critical revision of the article for important intellectual content; final approval of the article.

G Arangio: conception and design; drafting of the article; critical revision of the article for important intellectual content; final approval of the article.

JN Katz: drafting of the article; critical revision of the article for important intellectual content; final approval of the article.

E Losina: drafting of the article; critical revision of the article for important intellectual content; final approval of the article.

L Rovati: conception and design; critical revision of the article for important intellectual content; final approval of the article.

N Bachtell: conception and design; critical revision of the article for important intellectual content; final approval of the article.

C Cooper: critical revision of the article for important intellectual content; final approval of the article.

T Spector: critical revision of the article for important intellectual content; final approval of the article.

W Zhang: critical revision of the article for important intellectual content; final approval of the article.

J Gardiner: critical revision of the article for important intellectual content; final approval of the article.

M Wahba: critical revision of the article for important intellectual content; final approval of the article.

#### Conflict of interest

MFS, TS, GA, JNK, EL, and WZ: Authors have nothing to disclose.

JJ: received research support or compensation from Cerimon Pharmaceuticals, Endo Pharmaceuticals, GlaxoSmithKline, Novartis, Eli Lilly, Interleukin Genetics, Wyeth.

SPM: received research support or compensation from General Nutrition Company.

CC: received research support or compensation from Alliance for Better Bone Health, MSD, Eli Lilly, Servier Laboratories, Roche Pharmaceuticals, GSK, Amgen, Novartis.

JG: previous employee of Wyeth.

LR: employee of Rottapharm SpA.

NB: employee of Genzyme Corp.

#### Acknowledgment

Valorie J. Thompson of Innovations Consulting Group, LLC for administrative and logistic support.

#### References

1. Lawrence RC, Helmick CG, Arnett FC, Deyo RA, Felson DT, Giannini EH, *et al.* Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. *Arthritis Rheum* 1998;41(5):778–99.
2. Dillon CF, Rasch EK, Gu Q, Hirsch R. Prevalence of knee osteoarthritis in the United States: arthritis data from the Third National Health and Nutrition Examination Survey 1991–94. *J Rheumatol* 2006;33(11):2271–9.
3. The Burden of Musculoskeletal Diseases in the United States: Prevalence, Societal and Economic Cost. Rosemont, IL: Bone and Joint Decade; 2008. p. 79.
4. Kraus VB, Jordan JM, Doherty M, Wilson AG, Moskowitz RW, Hochberg MC, *et al.* The Genetics of Generalized Osteoarthritis (GOGO) study: study design and evaluation of osteoarthritis phenotypes. *Osteoarthritis & Cartilage* 2007;15(2):120–7.
5. Cimmino MA, Sarzi-Puttini P, Scarpa R, Caporali R, Parazzini F, Zaninelli A, *et al.* Clinical presentation of osteoarthritis in general practice: determinants of pain in Italian patients in the AMICA study. *Semin Arthritis Rheum* 2005;35(Suppl 1):17–23.
6. Englund M, Paradowski PT, Lohmander LS. Association of radiographic hand osteoarthritis with radiographic knee osteoarthritis after meniscectomy. *Arthritis Rheum* 2004;50(2):469–75.
7. Sawitzke AD, Shi H, Finco MF, Dunlop DD, Bingham III CO, Harris CL, *et al.* The effect of glucosamine and/or chondroitin sulfate on the progression of knee osteoarthritis: a report from the glucosamine/chondroitin arthritis intervention trial. *Arthritis Rheum* 2008;58(10):3183–91.
8. Messier SP, Loeser RF, Miller GD, Morgan TM, Rejeski WJ, Sevick MA, *et al.* Exercise and dietary weight loss in overweight and obese older adults with knee osteoarthritis: the arthritis, diet, and activity promotion trial. *Arthritis Rheum* 2004;50(5):1501–10.
9. Messier SP, Legault C, Mihalko S, Miller GD, Loeser RF, DeVita P, *et al.* The Intensive Diet and Exercise for Arthritis (IDEA) trial: design and rationale. *BMC Musculoskelet Disord* 2009;10:93. PMID: PMC2729726.
10. Vitiello MV, Rybarczyk B, Von KM, Stepanski EJ. Cognitive behavioral therapy for insomnia improves sleep and decreases pain in older adults with co-morbid insomnia and osteoarthritis. *J Clin Sleep Med* 2009;5(4):355–62. PMID: PMC2725255.
11. Rannou F, Poiraudou S, Beaudreuil J. Role of bracing in the management of knee osteoarthritis. *Curr Opin Rheumatol* 2010;22(2):218–22.

12. Wang C, Schmid CH, Hibberd PL, Kalish R, Roubenoff R, Roness R, et al. Tai Chi is effective in treating knee osteoarthritis: a randomized controlled trial. *Arthritis Rheum* 2009;61(11):1545–53.
13. Reginster JY, Deroisy R, Rovati LC, Lee RL, Lejeune E, Bruyere O, et al. Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomised, placebo-controlled clinical trial. *Lancet* 2001;357(9252):251–6.
14. Pavelka K, Gatterova J, Olejarova M, Machacek S, Giacovelli G, Rovati LC. Glucosamine sulfate use and delay of progression of knee osteoarthritis: a 3-year, randomized, placebo-controlled, double-blind study. *Arch Intern Med* 2002;162(18):2113–23.
15. Brandt KD, Mazzuca SA, Conrozier T, Dacre JE, Peterfy CG, Provvedini D, et al. Which is the best radiographic protocol for a clinical trial of a structure modifying drug in patients with knee osteoarthritis? *J Rheumatol* 2002;29(6):1308–20.
16. Brandt KD, Mazzuca SA, Katz BP, Lane KA, Buckwalter KA, Yocum DE, et al. Effects of doxycycline on progression of osteoarthritis: results of a randomized, placebo-controlled, double-blind trial. *Arthritis Rheum* 2005;52(7):2015–25.
17. Bingham III CO, Buckland-Wright JC, Garnero P, Cohen SB, Dougados M, Adami S, et al. Risedronate decreases biochemical markers of cartilage degradation but does not decrease symptoms or slow radiographic progression in patients with medial compartment osteoarthritis of the knee: results of the two-year multinational knee osteoarthritis structural arthritis study. *Arthritis Rheum* 2006;54(11):3494–507.
18. Garnero P, Aronstein WS, Cohen SB, Conaghan PG, Cline GA, Christiansen C, et al. Relationships between biochemical markers of bone and cartilage degradation with radiological progression in patients with knee osteoarthritis receiving risedronate: the Knee Osteoarthritis Structural Arthritis randomized clinical trial. *Osteoarthritis Cartilage* 2008;16(6):660–6.
19. Dam EB, Loog M, Christiansen C, Byrjalsen I, Folkesson J, Nielsen M, et al. Identification of progressors in osteoarthritis by combining biochemical and MRI-based markers. *Arthritis Res Ther* 2009;11(4): R115.
20. Hart DJ, Spector TD. Kellgren & Lawrence grade 1 osteophytes in the knee – doubtful or definite? *Osteoarthritis Cartilage* 2003;11(2):149–50.
21. Davies-Tuck M, Wluka AE, Forbes A, Wang Y, English DR, Giles GG, et al. Development of bone marrow lesions is associated with adverse effects on knee cartilage while resolution is associated with improvement – a potential target for prevention of knee osteoarthritis: a longitudinal study. *Arthritis Res Ther* 2010;12(1): R10.
22. Yao W, Qu N, Lu Z, Yang S. The application of T1 and T2 relaxation time and magnetization transfer ratios to the early diagnosis of patellar cartilage osteoarthritis. *Skeletal Radiol* 2009;38(11):1055–62.
23. Taylor C, Carballido-Gamio J, Majumdar S, Li X. Comparison of quantitative imaging of cartilage for osteoarthritis: T2, T1rho, dGEMRIC and contrast-enhanced computed tomography. *Magn Reson Imaging* 2009;27(6):779–84. PMID: PMC2722506.
24. Brandt KD, Mazzuca SA. Lessons learned from nine clinical trials of disease-modifying osteoarthritis drugs. *Arthritis Rheum* 2005;52(11):3349–59.
25. Bauer DC, Hunter DJ, Abramson SB, Attur M, Corr M, Felson D, et al. Classification of osteoarthritis biomarkers: a proposed approach. *Osteoarthritis Cartilage* 2006;14(8):723–7.
26. van Gool CH, Penninx BW, Kempen GI, Rejeski WJ, Miller GD, Van Eijk JT, et al. Effects of exercise adherence on physical function among overweight older adults with knee osteoarthritis. *Arthritis Rheum* 2005;53(1):24–32.
27. Felson DT, Nevitt MC, Yang M, Clancy M, Niu J, Torner JC, et al. A new approach yields high rates of radiographic progression in knee osteoarthritis. *J Rheumatol* 2008;35(10):2047–54. PMID: PMC2758234.
28. Hunter DJ, Niu J, Felson DT, Harvey WF, Gross KD, McCree P, et al. Knee alignment does not predict incident osteoarthritis: the Framingham osteoarthritis study. *Arthritis Rheum* 2007;56(4):1212–8.
29. Tanamas S, Hanna FS, Cicuttini FM, Wluka AE, Berry P, Urquhart DM. Does knee malalignment increase the risk of development and progression of knee osteoarthritis? A systematic review. *Arthritis Rheum* 2009;61(4):459–67.
30. Amarenco P, Labreuche J. Lipid management in the prevention of stroke: review and updated meta-analysis of statins for stroke prevention. *Lancet Neurol* 2009;8(5):453–63.
31. Narla V, Blaha MJ, Blumenthal RS, Michos ED. The JUPITER and AURORA clinical trials for rosuvastatin in special primary prevention populations: perspectives, outcomes, and consequences. *Vasc Health Risk Manag* 2009;5:1033–42. PMID: PMC2801627.
32. Ensrud KE, Lui LY, Taylor BC, Schousboe JT, Donaldson MG, Fink HA, et al. A comparison of prediction models for fractures in older women: is more better? *Arch Intern Med* 2009;169(22):2087–94.
33. Green SB. The advantages of community-randomized trials for evaluating lifestyle modification. *Control Clin Trials* 1997;18(6):506–13.
34. Kouyate B, Some F, Jahn A, Coulibaly B, Eriksen J, Sauerborn R, et al. Process and effects of a community intervention on malaria in rural Burkina Faso: randomized controlled trial. *Malar J* 2008;7:50. PMID: PMC2287184.
35. Brandt KD, Mazzuca SA. Experience with a placebo-controlled randomized clinical trial of a disease-modifying drug for osteoarthritis: the doxycycline trial. *Rheum Dis Clin North Am* 2006;32(1):217. xii.
36. Athyros VG, Kakafika AI, Tziomalos K, Karagiannis A, Mikhailidis DP. Pleiotropic effects of statins—clinical evidence. *Curr Pharm Des* 2009;15(5):479–89.
37. McGuinness B, Craig D, Bullock R, Passmore P. Statins for the prevention of dementia. *Cochrane Database Syst Rev* 2009 Apr 15;(2). CD003160.
38. Garrett IR, Gutierrez G, Mundy GR. Statins and bone formation. *Curr Pharm Des* 2001;7(8):715–36.
39. Saag KG. Bisphosphonates for osteoarthritis prevention: “Holy Grail” or not? *Ann Rheum Dis* 2008;67(10):1358–9.
40. Sugarman J, Bingham III CO. Ethical issues in rheumatology clinical trials. *Nat Clin Pract Rheumatol* 2008;4(7):356–63.
41. Simon AE, Wu AW, Lavori PW, Sugarman J. Preventive misconception: its nature, presence, and ethical implications for research. *Am J Prev Med* 2007;32(5):370–4.