# Report of the Working Group on Defining the Disease State

OARSI – FDA Initiative on
OA Trial Guidance
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# Working Group Members

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# Defining the Disease State
## *Questions Posed*

- What is OA?
  - How do we define OA for purposes of treatment or prevention?
  - Are oligoarticular, monoarticular and polyarticular OA the same disease?
  - Is hand OA different than hip OA and knee OA?
  - Where does degenerative disc disease fit in?

# Questions Posed

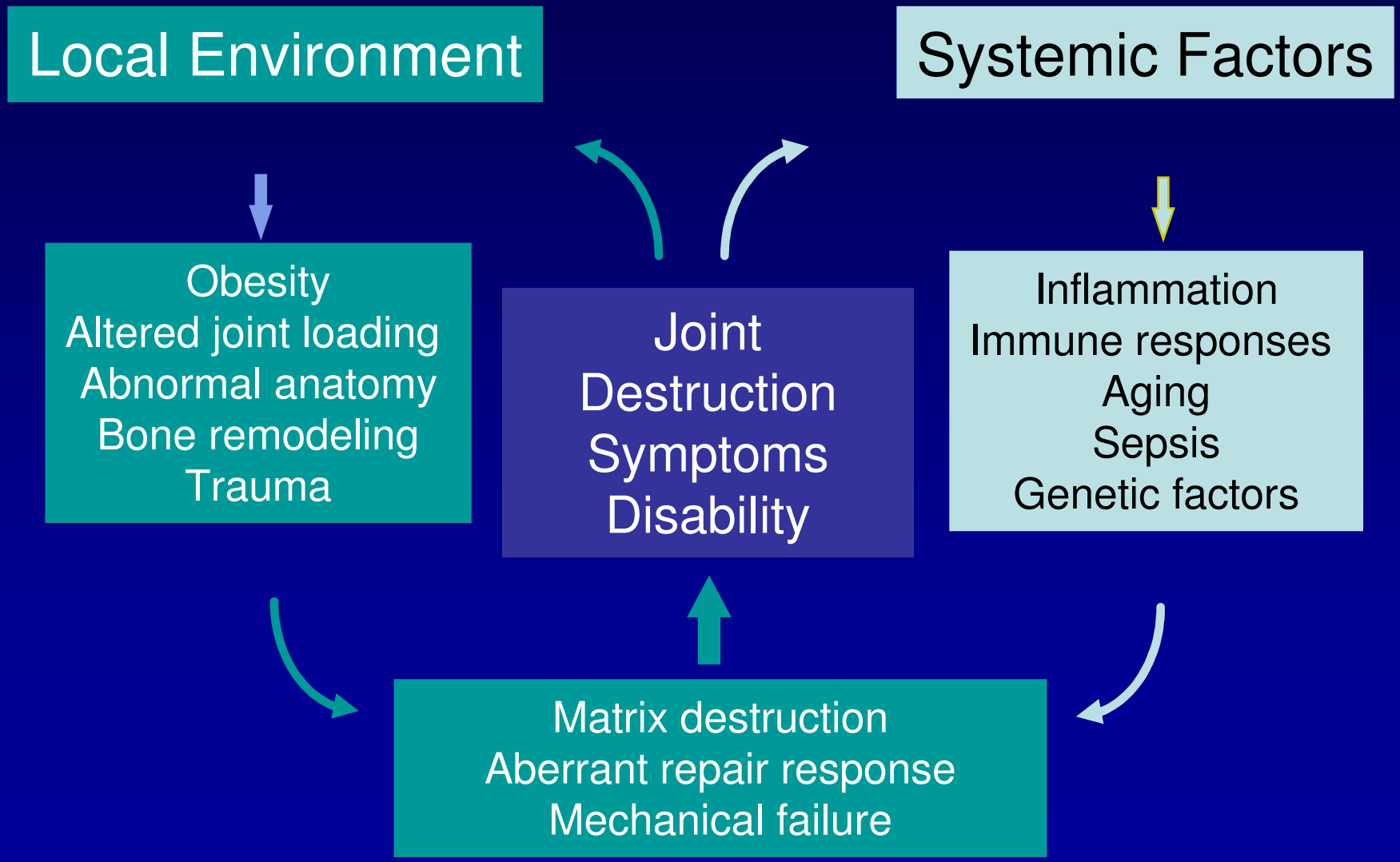
- How many sites need to be studied for approval of:
  - A systemic (oral) therapy?
  - A local therapy?
- Should there be uniform inclusion and exclusion criteria?
- What is the research agenda required to inform each of the above questions?

# Our responses…

# What is OA?

- OA is a progressive disease of synovial joints that represents 'failed repair of joint damage' resulting from *stresses* that may be initiated by an abnormality in *any* of the joint tissues (articular cartilage, subchondral bone, ligaments, menisci [when present], periarticular muscles, peripheral nerves and synovium) → breakdown of cartilage and bone

# Pathways to Osteoarthritis



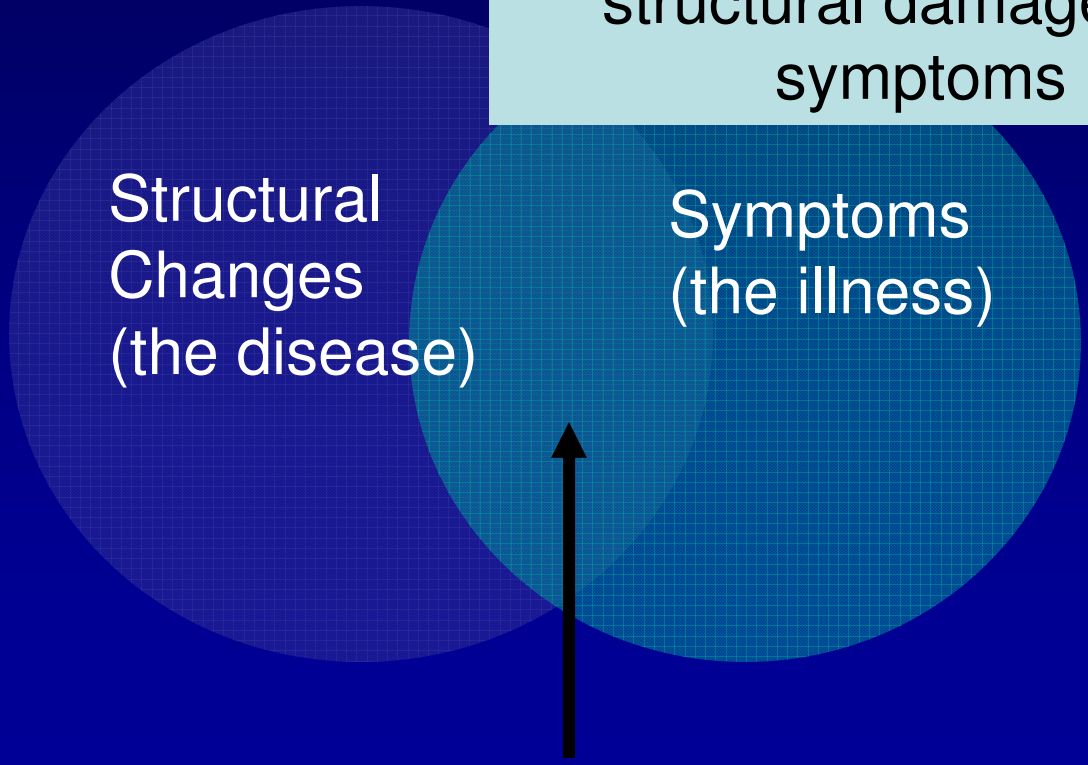
# OA is a Complex Disease

- Multiple etiologies, thus many potential treatments!

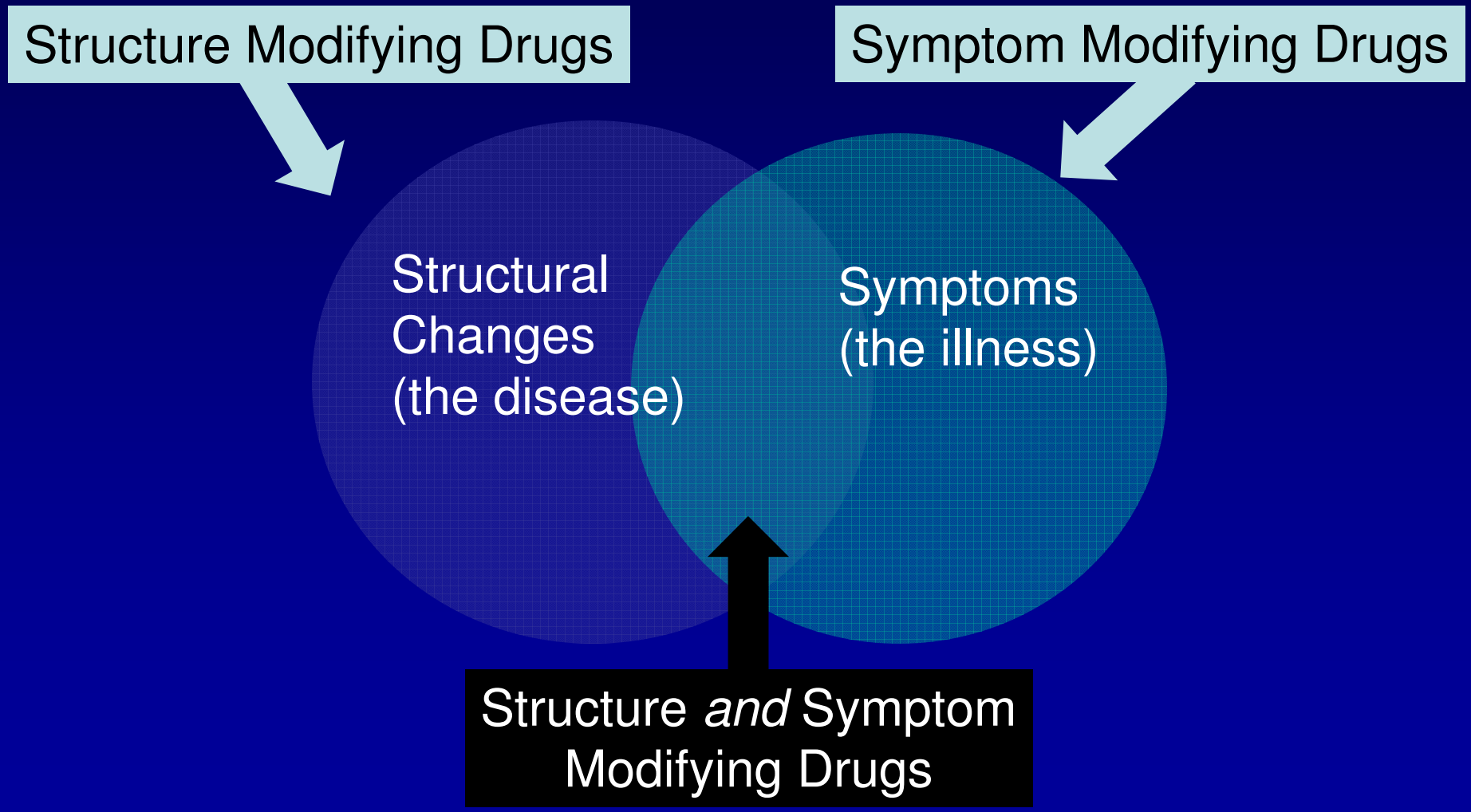
How do we define OA for the purpose of prevention or treatment?

# Osteoarthritis is…

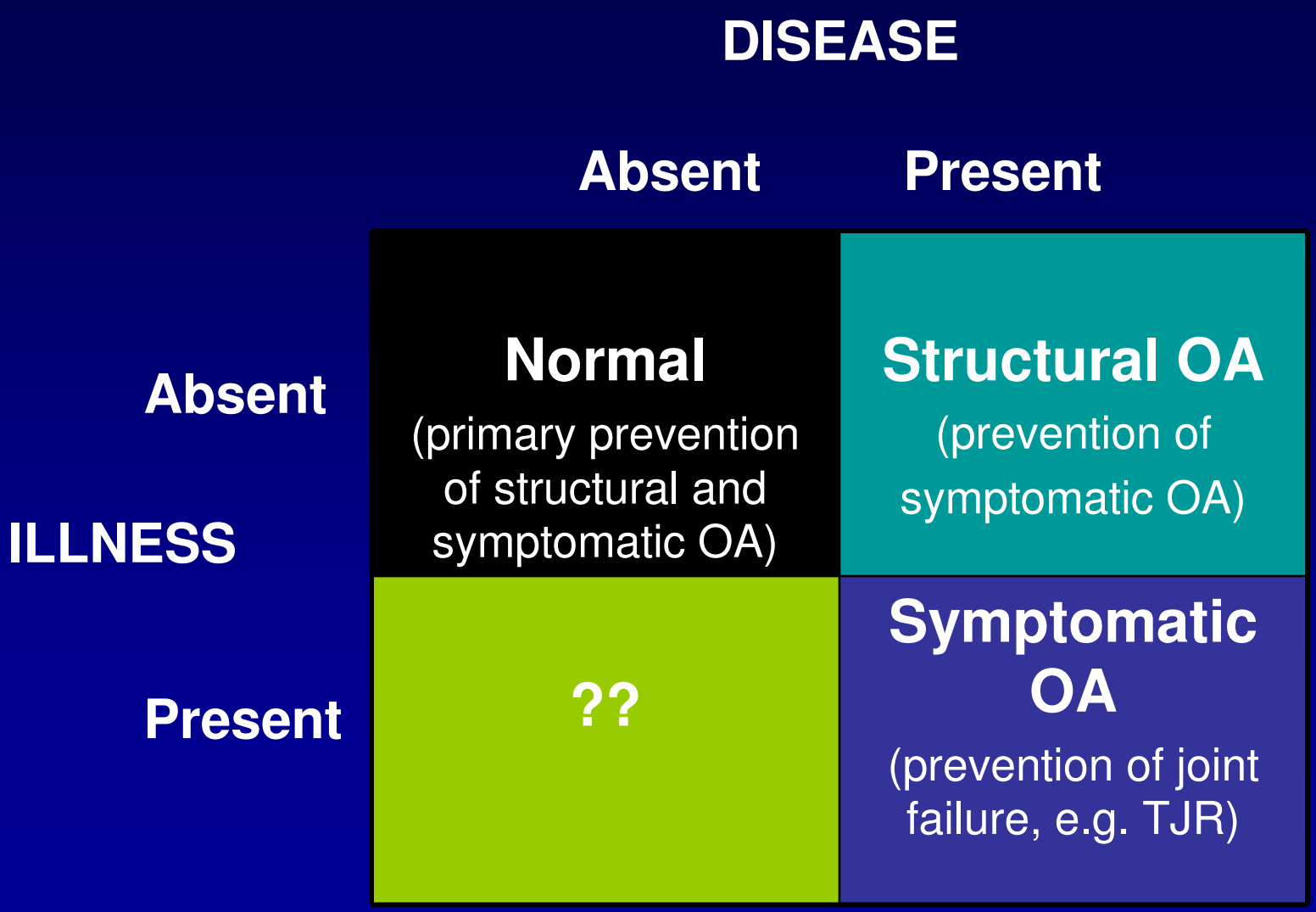
In early OA, there is often non-concordance of structural damage and symptoms



# Pharmacotherapy for OA



# Trial Design Consideration



# Considerations regarding the disease ‘OA’

# The Disease OA

- Characterized by *structural* and *compositional* changes to *all* tissues of the joint
- Thus, defining OA by plain radiographs is insufficient
  - Detects destruction / loss of cartilage by inference (JSN)
  - JSN is characteristic of late disease (like using MI to define atherosclerosis or Fx to define osteoporosis)
- Additional objective criteria are needed to characterize and define onset and early progression of OA, where preventive or restorative interventions may be more likely to succeed (biomarkers and imaging groups)

# Considerations regarding the ‘illness’ OA

# The Illness “OA”

- Should be defined separately from the structural changes of OA
  - “Symptoms”
    - Pain
    - Fatigue
    - Stiffness
    - Functional limitations
    - Reduced participation in valued activities
    - Impact on mood, sleep, overall quality of life

# The Illness “OA”

- Largely evaluated using patient self-report measures, which may be influenced by a number of factors, e.g. coping, activity level, recall, expectations, etc.

# Pain Mechanisms in OA

- Increasing evidence from animal and human studies that neuropathic-type pain exists in some people with OA (central sensitization)
  - Nociceptive pain
  - Central neuropathic pain
  - Mixed nociceptive/neuropathic

# Trial Design Consideration

- OA trials should routinely evaluate the presence/severity of features of the “illness”
  - Relative efficacy of agents for different pain types, other OA symptoms
    - Improved “targeting” of right treatment to right patient
    - Improved preference-based informed decision making about available/new treatments

# Trial Design Consideration

- OA affects older adults
  - SMOAD (structure modifying OA drug) studies should take into account confounding and/or effect modification by age-related factors (e.g. muscle weakness, sarcopenia, impaired proprioception, reduced level of physical activity / joint use)

# Trial Design Consideration

- To reduce the potential impact of confounding by age and heterogeneity of pathophysiology, studies could focus on more homogeneous groups of patients, such as younger patients with knee injury
  - Greater homogeneity → less generalizability

# Trial Design Consideration

- Complex interventional studies that mimic use of the drug in “real life” should be considered
  - Effect when used with other drug / non-drug therapies
  - Pragmatic trials / large simple trials
    - minimal exclusion criteria

Oligoarticular / monoarticular / polyarticular OA the same?

Hand / hip / knee OA the same?

# OA Phenotypes

- Not likely (more research needed)
- OA has no common pathological pathway
  - Risk factors for disease / illness may differ not only for different joints (e.g. differences in joints' protective mechanisms), but even within a single joint (e.g. TF joint – malalignment versus meniscal tear)
  - Thus, therapeutic responses may also vary

# Trial Design Consideration

- Until OA phenotypes are elucidated, trials should evaluate a *primary site*, e.g. knee, and collect data on all other joint areas that could develop incident or prevalent OA (e.g. use a homunculus to identify the number of new OA sites; number of OA sites that progress)

# Trial Design Consideration

- Biomechanical factors may serve as *risk factors for progression* AND *markers of structural damage*
- Type and degree of abnormality (e.g. valgus or varus deformity) should be included in the definition of OA and should be considered in choosing treatment (e.g. SMOADs might be coupled with strategies to correct biomechanical abnormalities)

Where does degenerative disc disease fit?
Should this be included?

# Spine OA versus DDD

- Spine OA = facet joint OA
- Degenerative Disc Disease (DDD) = deterioration of the intervertebral disc with hypertrophic spondylosis
- Advanced DDD can contribute to the onset of spine OA & the two conditions are often seen together…but, they are anatomically distinct

# Degenerative Disc Disease

- Despite the distinction between DDD and spine OA, identifying the source of back pain remains challenging
  - As for peripheral OA, there is a lack of concordance between symptoms and radiographic damage
  - Many other factors may cause low back pain (e.g. osteoporotic fracture, congenital spine deformity, muscle strains and imbalances)

DDD should be considered separately from these deliberations

# Trial Design Consideration

- However, regardless of the etiology, back pain is frequently present in patients with OA of other joints, particularly the knee
- Clinical trials of symptomatic therapy for OA should ascertain (e.g. using homunculus):
  - Presence of back pain
  - Presence of OA symptoms in other joints
  - Effect of therapeutic intervention in these secondary sites (secondary or tertiary endpoints)

How many joint sites need to be studied for approval of an oral therapy?

What about for a local therapy?

# How Many Joints?

- Systemic therapies – can treat multiple joints at one time, but may be difficulty achieving sufficient concentrations in target joints
  - Also may target a central mechanism of action (e.g. CNS)
- Local therapies – can achieve high concentrations in target joints, but may need multiple injections/applications to treat multiple joints
- Either way, efficacy may vary by joint

# How Many Joints?

- Because of the heterogeneity of causes and characteristics (e.g. impact of OA on functioning) of OA across joints, approval of local therapies should be based on *joint-specific* efficacy (e.g. hip or knee or hand)
- With systemic treatment, more than one joint could be evaluated

# Should there be uniform inclusion & exclusion criteria?

- No
- Inclusion/exclusion criteria should:
  - Reflect the intent & mode of action of the therapy
    - e.g. structure modification versus symptom modification
  - Be joint-specific
    - Factors that are known to affect incidence/progression of OA in the joint should be taken into account, e.g. inflammation, presence of malalignment
      - Confounders / effect modifiers or exclusion criteria
    - Level of symptoms, including pain and functional disability

What is the research agenda required to inform each of these questions?

# Distinguishing Risk Factors from Consequences of OA

- In absence of longitudinal observations of asymptomatic non-arthritic subjects who have recognized risk factors for OA, difficult to differentiate pathology that reflects a risk factor (e.g. bone shape abnormalities that increase intra-articular stress) from pathological consequences of OA (e.g. bony remodeling to mitigate the abnormal stress)

# Research Recommendation

- Longitudinal cohort studies that include subjects who develop symptomatic / structural OA during follow-up to identify most sensitive and specific risk factors for development and progression of OA
  - Study of homogeneous longitudinal cohorts, e.g. ACL injury, to reduce confounding by age, other diseases

# Research Recommendation

- Prospective studies of **"OA flares"**
  - What are OA flares? (trial end-point)
  - Are symptomatic flares associated with changes in structure and/or composition of joint tissues?
  - What are the risk factors for an OA flare?
  - Are flares associated with rates of progression?

# Research Recommendation

- More research needed to define OA phenotypes
  - Phenotypes should reflect pathophysiology and outcomes
    - e.g., obesity/metabolic syndrome versus joint injury
  - Information on genotypes associated with OA onset and progression may help to refine the OA phenotypes and improve study subject selection

# Research Recommendation

- Develop tools / measures to identify subjects with different OA pain types
  - Nociceptive / Neuropathic / Mixed
- Develop consensus on core set of measures to evaluate other OA symptoms, beyond pain and functional disability
  - Fatigue, sleep quality, participation in valued activities

# Summary:

- Paradigm shift away from cartilage-centric view of OA, with key etiologic role for *mechanical stress* on the joint
- Understanding of OA as structural disease + illness and need to understand and manage both
- Research needed to elucidate OA phenotypes → facilitate selection of more homogeneous subgroups to target for intervention

Thank you!

# Interrelationship of Risk Factors for OA