

OARSI FDA OA INITIATIVE

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Prevention & Risk Reduction Working Group

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Prevention or Risk Reduction

- **Prevention**
 - curtail or delay the occurrence of a disease or its consequences

- **Risk reduction**
 - decrease the frequency or occurrence of risk factors for a disease (obesity, injury) or intermediate states (BML), with anticipation of decreasing the occurrence of disease

Prevention or Risk Reduction

- **Primary**
 - Intervening on modifiable risk factors
 - Obesity, biomechanics, diet, exercise, muscle strength

- **Secondary**
 - most attention would likely be here initially

- **Tertiary**
 - Preventing progression

Prevention: 1° and 2°

<ul style="list-style-type: none">- Symptoms- Structural Abn'l <p>→</p>		<ul style="list-style-type: none">+ Symptoms- Structural Abn'l	
	↓		↓
<ul style="list-style-type: none">- Symptoms+ Structural Abn'l		<ul style="list-style-type: none">+ Symptoms+ Structural Abn'l	
	→		

Potential Outcomes: Prevention

- Which joints?
 - Knee
 - Hip
 - Hand
 - Spine
 - Unilateral, bilateral
 - New joint sites in person with OA

Prevention or Risk Reduction

- **potential outcome measures**
 - different for prevention & risk reduction
- **desirable duration**
 - dependent upon trial outcomes
- **desirable population**
 - dependent upon trial outcomes

Prevention or Risk Reduction

- **appropriate safety database for prevention**
 - Is any risk acceptable in a therapy designed for someone with no signs or symptoms of disease?
- **meaning of prevention or risk reduction in terms of a clinical study and therapeutic intervention**
- **research agenda required to inform each of the above questions**

Potential Outcomes: Prevention

- **What are we trying to prevent?**
 - Structural OA
 - Symptomatic OA
 - Functional decline
 - Joint failure/replacement
 - OA in new joint sites

Potential Outcomes: Prevention

- **Structural OA**
 - **Radiographic**
 - KL grade
 - Osteophytes
 - JSN
 - JSW
 - **MRI and fMRI**
 - Cartilage volume
 - Cartilage thickness
 - Bone marrow lesions, focal lesions
 - Synovitis
 - Bone size/shape
 - dGEMRIC

Potential Outcomes: Prevention

- Symptomatic OA
 - Pain
 - Function
 - WOMAC, KOOS, HOOS, etc.
 - Patient global assessment

Prevention: populations

- High risk groups
 - Older
 - Obese, overweight
 - Joint injury
 - Family history
 - Nodal OA
 - Biomarker profiles
- General population

Prevention: Duration

- **Depends upon pop'n and risk factors**
 - Shorter for symptoms
 - Longer for structural, natural history
 - Obesity, injury

Safety

- **Higher tolerable risk in those at high risk of rapid progression**
- **Lower tolerable risk in those at low risk**

Prevention

- **Lipids Research Primary Prevention Trial**
 - Cholestyramine to ↓ lipids → ↓ CVD, mortality
 - Statins, anti-oxidants, diet
- **Dementia**
 - Antioxidants
 - HRT

Prevention

- **Primary prevention trials**
 - **Preceded by observational studies**
 - Identify frequency of intermediate measure in pop'n (cholesterol levels)
 - **Expensive**
 - Long duration
 - Large sample sizes
 - **Surveillance for other outcomes, effects**
 - Cancer, etc.

Characterization of risk factors

- **define and measure risk factor unambiguously**
- **know the relative contribution of risk factor to OA disease development**
- **average duration to disease among those w/ and w/o risk factor**
- **prevalence of the risk factor in the population**

RCT: Prevent Knee OA in obese

- **ambulatory, community-dwelling men & women**
- **aged 50-65 years**
- **(KL 0, 1)**
- **knee varus or valgus malalignment (angle ≥ 2 degrees and ≤ 10 degrees)**

Prevention RCT: Knee OA for obese- con't

- **BMI ≥ 30 kg/m² and ≤ 45 kg/m²**
- **absence of knee pain for a month-long time period**

Prevention RCT: Knee OA for obese- con't

- **Primary outcomes**
 - **Structural factors**
 - **Symptoms**

Prevention RCT: Knee OA for obese- con't

- **Secondary outcomes**
 - clinical function, pain and mobility
 - mechanistic measures
 - alignment, external adductor moment, compressive and shear forces
 - pro-inflammatory biomarkers
 - lower extremity strength and power
 - limb proprioception
 - abdominal and thigh fat depots on CT

Prevention RCT

- **Other factors**
 - Intervention-related processes
 - Adherence
 - Retention
- **Duration**
 - 10 years
 - Intervals: biennially, annually, biannually
 - ? shorter by drug, mechanism, pop'n

Prevention RCT

- Design
 - Randomized, controlled, placebo, active comparator
- Adherence
 - Effects of menopause, depression, comorbidities
 - Long-term incentives to participate and adhere

Prevention RCT

- Safety database
 - Pleiotropic effects
 - statins
 - Long-term
 - Reproduction
 - Immunologic
 - infection
 - cancer

Prevention RCT

- testing on
 - healthy volunteers
 - people with early disease
 - people who may not have OA
 - people who may not ever get the disease
 - people who might have a relatively benign course even with no intervention
- administered for a prolonged time, possibly beginning at an early age

Prevention RCT

- Other design issues
 - preventive misconception
 - “the overestimate in probability or level of personal protection that is afforded by being enrolled in a trial of a preventive intervention”
 - behavioral disinhibition
 - the adoption of behaviors that may pose a risk to the participant or others
 - HIV vaccine trial
 - OA diet/obesity, genetics

Research Agenda

- **Observational studies**
 - Long- and short-term follow-up
 - Predictors for incident disease/illness
 - Gender, ethnic/racial sub-populations
- **Biomarkers**
 - Genetic, immunologic, imaging, etc
 - Systemic, local
 - Dynamic, change in biomarkers

Research Agenda

- **Study of threats to validity**
 - Selection bias
 - Adherence
 - Retention
 - Preventive misconception
 - Behavioral disinhibition
 - others

Summary

- None of these potential pitfalls precludes a successful and scientifically rigorous process and outcome.

The Future

