

OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL **OMERACT**
Outcome Measures in Rheumatology

Virtual joint replacement as an outcome for OA trials
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Outcome Measures in Rheumatology

Introduction

- Process
- Pain
- Function
- Structure
- Combination of the 3 domains

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Outcome Measures in Rheumatology

Outcome measures for OA trials

- a) Symptoms
- b) Structure
- c) Biomarkers
- d) Total joint replacement?

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Outcome Measures in Rheumatology

Surgery versus indication of surgery

```

    graph TD
      S([Symptoms]) --> TJR([Total joint replacement])
      St([Structure]) --> TJR
      B([Biomarkers]) --> TJR
    
```

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Outcome Measures in Rheumatology

Surgery versus indication of surgery

```

    graph TD
      S([Symptoms]) --> TJR([Total joint replacement])
      St([Structure]) --> TJR
      B([Biomarkers]) --> TJR
      HCS([Health care system]) --> TJR
      PSF([Psychosociologic factors]) --> TJR
      Surgeon([Surgeon]) --> TJR
    
```

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Outcome Measures in Rheumatology

Background

Usefulness of a « hard » endpoint in OA
 Context: hip/knee OA

Theoretical indication for total joint replacement
 (« virtual joint replacement »)

Mallefort JF et al. J Rheumatol, 2005

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Criteria for theoretical indication for total joint replacement

- To evaluate the burden of the disease
- « Hard endpoint » in longitudinal epidemiological studies evaluating potential predisposing factors of OA progression
- « Hard endpoint » in clinical trials evaluating potential disease modifying agents
- External criterion to evaluate orthopaedics departments
- To help the surgeon in daily practice by facilitating his/her decision
- To help the non-surgeon (G.P., rheumatologist, ...) by facilitating referral
- To help the health service system to facilitate the prioritization process
- ...

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Criteria for theoretical indication for total joint replacement

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Objectives

To propose a set of criteria defining theoretical need for total joint replacement for use in clinical trials evaluating potential DMOADs.

Gossec L. et al. J Rheumatol, 2007

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Introduction

Process

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Combination of the 3 domains

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- **Facilitator:** Maxime DOUGADOS
- **Chair-persons:** Gillian HAWKER, Jean-Francis MAILLEFERT, Stefan LOHMANDER
- **Scientific committee members:** Roy ALTMAN, Jolanda CIBERE, Paul DIEPPE, Maxime DOUGADOS, Karsten DREINHÖFER, Laure GOSSEC, Klaus-Peter GÜNTHER, Gillian HAWKER, Marc HOCHBERG, Joan JORDAN, Jeff KATZ, Stefan LOHMANDER, Jean-Francis MAILLEFERT, Lyn MARCH, Nizar MAHOMED, Karel PAVELKA, Maria SUAREZ ALMAZOR, Gustavo ZANOLI
- **Health Agencies representatives:** James WITTER (FDA), Pekka KUKKI (EMA)
- **Drug Companies representatives:** Janice CANVIN (AstraZeneca), Philippe COSTE (Pharmascience), Marie-Pierre HELLIO Le GRAVERAND (Pfizer), Dominique LARZABAL (Negma-Lerads), Lucio ROVATI (Rotta Research), Simon Blake (Centocor), Thasia WOODWORTH (Novartis)

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Choice of domains

Expert meeting in 2004

Set of criteria for severity of OA, defining requirement for total joint replacement, combining

- **Pain**
- **Function**
- **Structure**

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Combination of 3 domains

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Background - Pain in OA

G. Hawker

- Qualitative studies (Canada + UK)
 - Pain experience in OA is not adequately assessed using existing pain measures, including WOMAC
- WOMAC pain scale – responses confounded by function

Need for a new pain measure

Hawker G, OARSI 2006

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Pain sub- task force

G. Hawker, P. Dieppe

- Focus groups to obtain detailed descriptions of hip / knee pain
- Standardized questionnaire: Patient Generated Index – to determine which aspects of the OA pain people consider most distressing (i.e. most important to target for further interventions)

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OARSI-OMERACT - Pain – Knee/Hip

- **Constant pain**
 1. In the past week, how intense has your constant knee/hip pain been?
 2. In the past week, how much has your constant knee/hip pain affected your sleep?
 3. In the past week, how much has your constant knee/hip pain affected your overall quality of life?
 4. In the past week, how frustrated or annoyed have you been by your constant knee/hip pain?
 5. In the past week, how upset or worried have you been by your constant knee/hip pain?

Hawker G et al. Osteoarthritis Cartilage, 2008

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OARSI-OMERACT - Pain – Knee/Hip

- **Pain that comes and goes**
 1. In the past week, how intense has your knee/hip pain that comes and goes been?
 2. In the past week, how frequently this knee/hip pain that comes and goes occurred?
 3. In the past week, how much has your knee/hip pain that comes and goes affected your sleep?
 4. In the past week, how much has your knee/hip pain that comes and goes affected your quality of life ?
 5. In the past week, how frustrated or annoyed have you been by your knee/hip pain that comes and goes?
 6. In the past week, how upset or worried have you been by your knee/hip pain that comes and goes?

Hawker G et al. Osteoarthritis Cartilage, 2008

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Function sub- task force
A. Davis, S. Lohmander

- **Objective:** using existing KOOS/HOOS/WOMAC data from people with knee or hip OA, determine a short measure of physical function
- **Method:** RASCH modeling

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OARSI-OMERACT - Function - Knee

1. Rising from sitting
2. Standing
3. Walking on flat
4. Rising from bed
5. Taking off socks/stockings
6. Getting on/off toilet
7. Squatting
8. Running
9. Jumping
10. Twisting/pivoting on your injured knee
11. Kneeling

Perruccio AV, et al. Osteoarthritis Cartilage, 2008

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OARSI-OMERACT - Function - Hip

1. Descending stairs
2. Getting in/out of bath
3. Sitting
4. Running
5. Twisting/pivoting on your loaded leg

Davis A, et al. Osteoarthritis Cartilage, 2008

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Structure sub-task force
J-F. Maillefert – L. Gossec

- **Range of motion?**
- **Method:**
 - Systematic literature research
- **Conclusion:** Not well correlated to structure

Use standard X Rays

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Structure sub-task force
J-F. Maillefert – L. Gossec

- Comparison of Kellgren-Lawrence, OARSI JSN And joint space width in millimeters

Methods:

- Evaluation of sets of X-rays
- Psychometric properties

Conclusion:
Joint space width in millimeters more reproducible and more sensitive to change

* Gossec L et al. Osteoarthritis and Cartilage, 2008

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Combination of the 3 domains

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Planned format of the criteria

Structure

AND

Symptoms

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Combination of domains

- Structure = radiological progression
- Symptoms = Non Acceptable State

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Rationale

The final set of OARSI-OMERACT criteria requires for each domain a DICHOTOMOUS variable
e.g. for the structure/JSW, a radiological non acceptable condition.

Absolute value
e.g. JSW < 0.5 mm

Relative
e.g. JSW change ≥ 0.5 mm

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~~e.g. JSW < 0.5 mm~~

Relative
e.g. JSW change ≥ 0.5 mm

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Objectives

To propose a radiological progression defined by a relevant change in Joint Space Width, evaluated in millimeters on plain X-rays in hip/knee OA.

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OARSI-OMERACT definition of radiological progression

Methods

Systematic literature research	Experts
<ul style="list-style-type: none"> Fellow: Paul ORNETTI Librarian: Guillemette UTARD Supervisor: Maxime DOUGADOS 	<ul style="list-style-type: none"> Maxime DOUGADOS Marie-Pierre HELIO-LE GRAVERAND Marc HOCHBERG Margreet KLOPPENBURG Nancy LANE Jean-Francois MAILLEFERT Steven MAZZUCCA Tim SPECTOR Eric VIGNON

Ometti P et al. Submitted to Osteoarthritis Cartilage

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OARSI-OMERACT definition of radiological progression

- The definition of radiological progression should take into account the measurement error of the technique.
- The measurement error should be calculated on the reliability of the technique (Bland & Altman).
- The radiological progression is defined by a change above the Smallest Detectable Difference calculated in a reliability study (Bland & Altman).
- The reliability study should evaluate the whole process (e.g. patient positioning, JSW measurement technique).
- The reliability study should enroll at least 30 patients / centers representative of the study/centers population enrolled in the clinical study.

Ometti P et al. Submitted to Osteoarthritis Cartilage

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Combination of domains

- Structure = radiological progression
- Symptoms = Non Acceptable State

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Objectives

To define a non acceptable symptom state for pain and function, based on the indication of total joint replacement.

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Planned format of the criteria

- Format of the combination of the 2 symptomatic domains

Pain > Z (high) with Function > W (low)
 OR
 Function > V (high) with Pain > N (low)
- Technique to define the thresholds/cut-offs
 - ROC analysis
 - 75th percentile
- Inclusion of the « duration » of the condition « during at least X weeks »

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« Definition of a non acceptable symptom state »

Synopsis

- **Study design:** cross-sectional, multicenter, international
- **Patients:** hip/knee OA
- **Gold standard:** decision of total articular replacement
- **Outcome variables:** pain, function
- **Co-variates:** orthopaedist's characteristics, patient's characteristics, disease characteristics

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Study size

- ❑ 11 countries
- ❑ 100 knee / 100 hip
- ❑ Per center
- ❑ 2,600 planned total

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Eligibility criteria

- **Inclusion criteria:**
 - All the consecutive knee/hip OA patients
- **Exclusion criteria:**
 - Prior joint replacement
 - Prior osteotomy of the targeted joint
 - Concomitant inflammatory disease
 - Unability to understand/to fill the questionnaire

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Orthopaedist Case Report Form

- Does the patient have hip/knee OA? yes no
- Does the patient have radiographic signs of hip/knee OA? yes no
- Is the patient recommended for total joint replacement? yes no

If no, surgery is not recommended because of : *(one single answer)*

- symptoms not severe enough
- symptoms are severe enough BUT
 - patient declined surgery
 - because of co-morbidity
 - the main problem is not hip/knee OA
 - further investigations are required before I am prepared to make a decision, for other MS conditions (e.g. concomitant back pain)
 - another treatment should be tried first
 - other, if yes, please specify:

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Methods: Scientific aspects – Outcome variables

- Mandatory**
 - OARSI – OMERACT Pain
 - OARSI – OMERACT Function
- Optimal... but welcome**
 - WOMAC
 - KOOS - HOOS - QoL

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Current status

- 11 countries
- > 500 patients
- End of inclusions 2009
- Presentation of results OARSI 2009

Country	Principal investigators
Australia	Lyn March Keith Lim
Canada	Gillian Hawker
Czech Republic	Karel Pavelka
France	Jean-Francis Maillefer
Germany	Klaus-Peter Gunther
Italy	Leonardo Punzi
Netherlands	Margreet Kloppenburg
Spain	Emilio Martin-Mola
Sweden	Stefan Lohmander
UK	Phil Conaghan
USA	Maria Suarez-Almazor Jasvinder Singh

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Conclusion

- Need for a hard outcome for clinical trials
- 3 items: pain, function, structure
- New questionnaires for pain and function
- Structural degradation on X Rays above measurement error
- Association to define theoretical indication of total articular replacement
- Ongoing international combination study

