

OVERVIEW
JOINT ASSESSORS FOR TRIALS PERFORMED BY THE
PEDIATRIC RHEUMATOLOGY COLLABORATIVE STUDY GROUP (PRCSG) AND
THE PEDIATRIC RHEUMATOLOGY INTERNATIONAL TRIALS ORGANISATION
(PRINTO)

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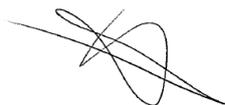
Consistency in joint assessments is of critical importance to the overall validity of clinical trials performed by the PRCSG/PRINTO. The Core Set of Outcome Measures for Juvenile Rheumatoid Arthritis/Juvenile Idiopathic Arthritis (JRA/JIA) includes six parameters. Two of the six are directly derived from the joint exam. Accordingly, the PRCSG and PRINTO developed common standardized guidelines used by both networks to certify joint assessors for JIA clinical trials in 2003. These guidelines underwent minor revision in 2006 (i.e. section 2c added) and an overview statement was added December, 2007. In all instances, changes have been reviewed and approved by leaders of the PRCSG and PRINTO networks. The current guidelines are shown in Attachment. Both PRCSG and PRINTO require extensive training in pediatric rheumatology to be eligible for membership in either network. It is expected that any person proposed as a joint assessor in a PRCSG/PRINTO trial already would have extensive training in the basics of performing a joint exam as part of this training in pediatric rheumatology. Members of PRCSG/PRINTO who participated in an investigator meeting joint assessment training and evaluation at a pre-study investigator meeting for a Phase III pharmaceutical clinical trial (method described in 2a below) prior to 2003 were certified. The Coordinating Center for each network maintains a list of certified joint assessors for that network. The mechanism, method of performing a joint exam and method of assessing a joint exam in PRCSG/PRINTO trials has remained stable and uniform. Therefore, the certification of joint assessors is not limited in duration. If however, performance of the joint exam to be performed by the joint assessors' changes in any systematic way, e.g. introduction of ultrasound into joint assessment, then all joint assessors will need to be recertified in using the new assessment approach. This Overview statement has been reviewed and agreed to by leaders of both the PRCSG and PRINTO as attested by signatures below.



Daniel Lovell, MD, MPH
PRCSG Chairman



Alberto Martini, MD
PRINTO Chairman



Hermine Brunner, MD.
PRCSG Scientific Director



Nicola Ruperto, MD, MPH
PRINTO Senior Scientist

ATTACHMENT

INSTRUCTION AND EVALUATION OF JOINT ASSESSORS FOR TRIALS PERFORMED BY THE PEDIATRIC RHEUMATOLOGY COLLABORATIVE STUDY GROUP (PRCSG) AND THE PEDIATRIC RHEUMATOLOGY INTERNATIONAL TRIALS ORGANISATION (PRINTO)

Revised 12-1-07

1. Background. The following is a description of the procedures to be utilized for increasing the standardization, reproducibility and validity of joint assessments in trials performed by members of the PRCSG and PRINTO.

Consistency in joint assessments is of critical importance to the overall validity of clinical trials. The Core Set of Outcome Measures for Juvenile Idiopathic Arthritis (JIA) includes 6 parameters. Two of the 6 are directly derived from the joint exam. These sessions are designed to increase the standardization of the study subject evaluations by joint assessors and not to provide basic instruction in how to perform a joint exam. It is expected that any person proposed as a joint assessor in a trial already would have extensive training in the basics of performing a joint exam. This document describes 3 methods of performing this evaluation: a) at the Investigators' meeting; b) at an individual site with a certified joint assessor and c) at an individual site without a certified joint assessor.

It is expected all assessors will use a standard approach to the physical exam of the joint system with the following specifics: for each joint all possible movements will be examined (e.g. measurement of hip extension), temporomandibular motion will be assessed by measurement of inter-incisor distance (normal for subjects at least 5 years old is ≥ 4 cm) and lumbar spine flexion will be measured by marks placed at the upper end of the gluteal cleft and then 10 cm superior to that while the child is standing erect. The child is then asked to forward flex as far as possible keeping the legs straight (normal for subjects at least 5 years old will be ≥ 15 cm between the 2 marks). Separate exams should be done for "joint tenderness" and "pain on motion". Although these measures may be consolidated into a single item on the case report form (CRF), each should be evaluated separately in the patient. All assessments of pain on motion or limitation of motion should be done with passive, not active, motion. *The greatest variation among examiners is seen in the assessment of joint swelling. The demonstration exams should provide in-depth (preferably hands-on) practice in assessing joint swelling.* At best, these procedures will decrease but will most certainly not eliminate differences in joint assessments between different examiners. **It is expected that, with rare exceptions, for a given subject in the trial all joint assessments will be performed by the same joint assessor.**

2. Joint Examination Procedures.

a) Investigators' Meeting Procedure. At the investigators' meeting, an introductory oral presentation will be given to discuss the importance of the joint exam in the particular trial, background of the role of joint exam in the JIA Core Set of Outcome Measures and Definition of Improvement (the ACR Pediatric 30), parameters to be assessed in the joint exam and the particular case report forms to be used in the trial. Thereafter, there will be a hands-on demonstration of the joint exam on children with active JIA by one or more pediatric rheumatologists who have participated in prior PRCSG/PRINTO studies. Following this, each candidate joint assessor will independently perform a joint exam on a minimum of 2, preferably 3, JIA patients who have arthritis of a severity to be eligible for the study in question. Each examiner will record their findings on case report forms identical to those to be used in the study. On each case report form

page both the numeric identifier for the subject (i.e. do not use subject's initials) and the name of the assessor are to be indicated.

b) On-site evaluation with a certified joint assessor. Assessment of potential joint assessors can be performed on site in one of the following circumstances: a) a previously approved joint assessor is part of the clinical staff or faculty at a particular site and can provide an onsite workshop for other potential joint assessors, b) an approved joint assessor from another site can travel to the candidate joint assessor site and provide the workshop on site, c) the potential joint assessor can travel to the site of another approved joint assessor and perform the evaluation there.

At the site the approved joint assessor and all the other potential joint assessors should each independently examine the same child with active JIA. Each examiner should record their findings on the joint exam CRF pages. After all examiners have completed their exams, the group should meet to share results of their exams and areas of variation on findings should be demonstrated by repeating that part of the physical exam on the patient to increase agreement in the joint exam. The case report forms from this training exam will not be submitted for scoring. Following this training exam, the approved joint assessor and the potential joint assessor/s should each independently evaluate at least 2 children with JIA with active arthritis and record their findings on standard case report forms. On each case report form page both an identifier for the subject and the name of the assessor should be indicated. These CRF pages from the exams on these subjects should be sent to Daniel Lovell or Nicola Ruperto as per next section.

c) On-site evaluation without a certified joint assessor. Assessment of potential joint assessors should be performed with a certified joint assessor if at all possible. However, in circumstances when a certified joint assessor is not available, then the following procedure should be followed. At least 3 individuals will be required to perform the joint exams. At the site all the potential joint assessors should each independently examine the same child with active JIA. Each examiner should record their findings on the joint exam CRF pages. After all examiners have completed their exams, the group should meet to share results of their exams and areas of variation on findings should be demonstrated by repeating that part of the physical exam on the patient to increase agreement in the joint exam. The case report forms from this training exam will not be submitted for scoring. Following this training exam, all the potential joint assessor/s should each independently evaluate 3 children with JIA with active arthritis and record their findings on standard case report forms. On each case report form page both an identifier for the subject and the name of the assessor should be indicated. These CRF pages from the exams on these subjects should be sent to Daniel Lovell or Nicola Ruperto as per next section.

3. Joint Examination Assessment. The case report forms sheets should be mailed or faxed to Dan Lovell (PRCSG) or Nicola Ruperto (PRINTO). The forms will be analyzed to determine the number of swollen joints, number of joints with limitation of motion, number of tender joints, number of joints with pain on motion and number of active joints. Assessors found to have results at substantial variance to other assessors at the investigators' meeting or to the approved assessor at on-site workshops will be instructed to undergo additional instruction in the standardized performance of the joint exam. In those instances where no certified joint assessor is participating in the exams, then any examiner demonstrating results more than 1 standard deviation above or below the group mean on the parameters of number of joints with active arthritis or number of joints with loss of motion on any of the 3 patients will need to repeat the certification process by completing independent joint exams on at least 2 additional JIA subjects with a certified examiner.

4. Joint Examination Certification. Individuals who successfully complete the joint assessor evaluation will be issued a certificate. Record of certificates granted will be kept on file at the

PRCSG and PRINTO Coordinating Centers. This information will be released to sponsors for future studies to provide an expedited way of determining those individuals who have been assessed to have demonstrated validity of performing a joint exam in subjects with JIA. This information will only be released to sponsors after sites have been identified by the sponsor for participation in the trial as a means of identifying which individuals will and will not need to be evaluated to become certified joint assessors.

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