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CRITERIA TO DEFINE RESPONSE TO THERAPY IN THE PEDIATRIC RHEUMATIC DISEASES

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ABSTRACT

Purpose. In this review we describe the general methodology and the results of the international projects, conducted by the Paediatric Rheumatology International Trials Organisation (PRINTO), in collaboration with the Pediatric Rheumatology Collaborative Study Group (PRCSG) that were aimed to identify, and validate and criteria for the evaluation of response to therapy in clinical trials and in daily clinical practice in patients with the 3 major paediatric rheumatic diseases (PRD): juvenile idiopathic arthritis (JIA), juvenile dermatomyositis (JDM) and juvenile systemic lupus erythematosus (JSLE).

Methods. The methodological approach to identify and validate outcome measures can be divided into 3 main phases: 1) the development of a preliminary core set of measure to evaluate the outcome (e.g. response to therapy, remission criteria, disease activity or damage etc) through literature review and consensus techniques; 2) a large scale data collection for a prospectively evidence-based validation of the preliminary findings; 3) the final development of a validated criteria for the evaluation of the outcome.

Results. The core sets for 3 diseases included domains that are common to all diseases (physician's global assessment of disease activity; parent's global assessment of the overall patient's well-being; disability and/or health-related quality of life) plus additional domains that are specific for each disease. In order to be classified as responder to a given treatment, a patient should demonstrate different minimum level of improvement ($\geq 30\%$ in JIA, $\geq 20\%$ in JDM and $\geq 50\%$ in JSLE) with no more than 1 of the remaining worsening by more than 30%.

Conclusions. The proposed core sets and definitions of improvement incorporate clinically meaningful change in a composite endpoint for the evaluation of global response to therapy in the major PRD. The definitions are proposed for use in PRD clinical trials, and may help physicians to decide if a child has responded adequately to therapy.

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Key Indexing Terms: juvenile idiopathic arthritis, juvenile dermatomyositis, and juvenile systemic lupus erythematosus, response to therapy, clinical trials

Short running title: Response to therapy in paediatric rheumatology

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INTRODUCTION

Performing clinical trials in paediatric rheumatic diseases (PRD) is made difficult by the small number of eligible patients, the heterogeneity of disease manifestations, and the lack of standardized criteria to assess clinical response. These situation has improved over the last 10 years thanks to several factors: the implementation of adequate US and Europe pediatric legislation [1-4], the existence of two large not-for-profit networks which facilitated successful trial completion, named Pediatric Rheumatology Trials Organsition (PRINTO at www.printo.it or www.pediatric-rheumatology.printo.it) [5] and the Pediatric Rheumatology Collaborative Study Group (PRCSG at www.prcsg.org), the availability of standardized and validated criteria for the evaluation of response to therapy in for the PRD.

Indeed the availability of standardized criteria would provide a common basis for comparing different treatment options, permit study and statistical comparison of patients with different disease manifestations, and facilitate comparisons of different clinical trials with meta-analysis.

The purpose of this paper is to review the general methodology and present the criteria used to define response to therapy in the 3 major PRD: juvenile idiopathic arthritis (JIA), juvenile systemic lupus erythematosus (JSLE) and juvenile dermatomyositis (JDM).

Methodological aspects

One of the specific problem for the PRD is the lack of objective measures that can be reliably used to evaluate response to therapy. Hence the need to use some surrogate clinical and laboratory markers to assess the disease activity level.

In general the methodological approach to solve such problem can be divided into 3 main phases: 1) the development of a preliminary core set of measure to evaluate the outcome under consideration (e.g. response to therapy, remission criteria, disease activity or damage etc) through literature review and consensus techniques; 2) a large scale data collection for a prospectively evidence-based

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3 validation of the preliminary findings; 3) the final development of a validated criteria for the
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5 evaluation of the outcome under consideration.
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9 10 **Consensus methodologies**

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12 The use of well recognized consensus formation methodologies specifically designed to combine
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14 judgments from a group of experts in a particular field is considered necessary whenever there are
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16 no objective measure to properly assess the outcome. The 2 major recognised techniques are the
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18 Delphi Technique and Nominal Group Technique [6-8]. In brief, the Delphi Technique utilizes a
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20 series of well defined questionnaire based-surveys while Nominal Group Technique is a structured
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22 face-to-face meeting designed to facilitate reaching consensus on the topic of study. Consensus
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24 formation techniques require that each step is based on the results of the previous steps. These
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26 techniques have been used to develop the outcome measures of several chronic rheumatic diseases,
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28 including JIA [9, 10], adult rheumatoid arthritis [11], adult-onset SLE [12, 13], and idiopathic
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30 inflammatory myopathies [14-16] as well as JSLE [17-19] and JDM [20].
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38 **What is a core set of measures and why it is needed (e.g. in pediatric rheumatology)**

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40 The core set has to be intended as a minimum list of domains/variables to cover all (or most)
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42 aspects of the disease and also as a minimum list to be always reported in future studies. Since in
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44 pediatric rheumatology we lack true outcome measures (e.g. death, pneumonitis, glucose etc), there
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46 is a need of surrogate markers for the evaluation of the outcome under consideration (in the
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48 following paragraph briefly referred as outcome) from different perspectives.
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54 **Phase 1. The preliminary core set selection**

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56 In this initial phase, after a carefully literature review, it is essential to prepare a mailing of people
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58 potentially interested to participate to sequential questionnaire-based e-mail surveys using the
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60 Delphi Technique. The mailing list can contains up to several hundreds of people [17] and

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3 constitutes the proper denominator against which evaluate the success of the survey that usually
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5 require a response rate equal to 70-80%. The first questionnaire is generic and is used to evaluate, in
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7 broad term, which are the variables used in routine clinical practice to assess the outcome. The data
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9 from the first survey are then analysed and collated to prepare the second one in which the content
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11 is more specific. In this second survey responders can be asked to concentrate only on the variables
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13 selected by a minimum threshold of people in the first survey, to select the most important variable
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15 (e.g. usually no more than 10) and rank them in order of importance. Other surveys if necessary can
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17 be added.
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21 Usually the results of the mailing survey are not sufficient to select the final list of variables to be
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23 used. In this case the results of the survey, along with a proper literature search can be used to
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25 convene a nominal group technique consensus conference, among a restricted number of people
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27 whose goal is indeed to reach the consensus (80% required) on the measures to be included in the
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29 preliminary core set. Usually the number of person per table (max 2-3 tables) should not be greater
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31 than 10.
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38 **Phase 2. The prospective validation of the preliminary core set(s)**

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40 The second phase is aimed to formally validate the preliminary consensus based core sets through a
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42 prospective, large-scale data collection among the members. The objective of this phase is to further
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44 define and validate the preliminary core set variables to document the outcome. A detailed protocol,
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46 listing the proper inclusion/exclusion criteria, needs to be set up in order to collect data ideally in a
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48 prospective fashion. Data collection should try to mimic what is usually done in a clinical trial, with
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50 a baseline assessment at the time of the starting treatment, and a final assessment after a certain
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52 follow-up period. Data collection should include all variables in the preliminary consensus based
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54 core set, plus all additional variables that are deemed necessary in the analysis phase such as
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56 demographic, clinical and laboratory data, treatment options etc. Following the OMERACT filter
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58 for outcome measures in rheumatology [21, 22] the main purposes of the validation phase are to
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3 evaluate the following properties [17]: feasibility (brevity, simplicity, easy scoring etc); face and
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5 content validity (variables easiest to use and most credible); responsiveness (ability of each variable
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7 to detect clinically important change between baseline and 6 months) measured through the
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9 standardized response mean (SRM) [23]; discriminative ability (ability to discriminate patients who
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11 improved from those who did not); convergent construct validity to examine whether the construct
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13 in question is related to other measures in a manner consistent with a priori prediction; collinearity
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15 (or redundancy); internal consistency by Cronbach's coefficient alpha [24]; finally, the association
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17 between the core measures and response to therapy as judged by the attending physician can be
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19 evaluated through a multivariate logistic regression analysis.
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26 **Phase 3. The definition of improvement**

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28 At the end of the data collection process the related analysis should be presented to a panel of expert
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30 (or experienced clinicians) knowledgeable about the outcome, in another nominal group technique
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32 consensus based meeting. The purposes of the meeting is to discuss the statistical properties of the
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34 measures and confirm/refine the final core set of measures. Another important goal is to establish
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36 the amount of change over time, for the variables included in the core set, in order to properly
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38 quantify the outcome under consideration (e.g. criteria for response to therapy). The meeting should
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40 therefore properly define the final core set of endpoints, using a combination of statistical criteria
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42 and consensus formation techniques.
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49 **THE EXAMPLES IN PAEDIATRIC RHEUMATOLOGY.**

51 52 53 54 **The core sets of measure for JIA, JSLE and JDM.**

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56 In table 1 are reported the domains and the suggested variable to measures each domain for JIA [9,
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58 10], JSLE [17-19] and JDM [20]. Variables suggested include the measures which at the present
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time have the better statistical properties; however in the future other measures appearing in the literature might replace the existing ones if they will demonstrate better statistical properties.

The domains are divided in the common domains (to be used for all 3 diseases) and specific domains.

The common domains for JIA, JSLE and JDM include 2 global assessment, by the physician and by the parents/patients, usually measured with a 10 cm visual analogue scale (VAS) or a 21 circle VAS [25]. Additionally a measure of functional ability (disability) through the Childhood Health Assessment Questionnaire (CHAQ) [26-28] or the Juvenile Arthritis Functionality Scale (JAFS) [29] and/or a quality of life measures is also considered usually through the Physical Summary score (PhS) of the Child Health Questionnaire (CHQ) [28, 30] or the Pediatric Rheumatology Quality of Life Scale (PRQL) [31].

Disease specific domains for JIA includes 2 measures of joint involvement (the number of joints with active arthritis and the number of joints with limited range of motion) [32-35] and an index of inflammation. For systemic JIA children, absence of spiking fever (< 2 days of maximal body temperature $\leq 38^{\circ}\text{C}$ during the week preceding the evaluation) is an additional requirement.

The JSLE specific domains include a global disease activity assessment, either by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) [36] or the Systemic Lupus Activity Measures (SLAM) [37] or the European Consensus Lupus Activity Measurement (ECLAM) [38, 39] and a measure of kidney involvement (24-hour proteinuria).

Disease specific domains for JDM include a measure of muscle strength as assessed by the Childhood Myositis Assessment Scale (CMAS) [40-42] or the Manual Muscle Testing (MMT) [43]; a global disease activity assessment through the Disease Activity Score (DAS) [44] or alternatively the Myositis Disease Activity Assessment (MDAA, an instrument [45] that combines two partially overlapping tools named the Myositis Disease Activity Assessment Visual Analogue Scale (MYOACT) and the Myositis Intention to Treat Activity Index A-E version (MITAX) [45].

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Overall the measures include in the 3 core sets were found to be feasible and not redundant, to have good construct validity, discriminative ability, internal consistency, were responsiveness to clinically important change in disease activity, and were associated strongly with treatment outcome [9, 10, 17-20].

The definition of improvement for JIA, JSLE and JDM.

In table 2 are reported the definitions of improvement to be used as main outcome in trials JIA [9, 10], JSLE [17-19] and JDM [20]. The definitions require a minimum level of improvement (30% in JIA, 50% in JSLE and 20% in JDM) in x number of the variables included in the core sets (Table 1) with no more than one of the remaining variables worsened by more than 30%. For example the JIA definition of improvement for JIA is: at least 30% improvement from baseline in 3 of any 6 variables in the core set with no more than one of the remaining variables worsening by more than 30%. For trials in systemic JIA absence of spiking fever (< 2 days of maximal body temperature \leq 38°C during the week preceding the evaluation) is also required. The minimum level of improvement has to be reported in all trials as primary outcome but researchers should also report more stringent definition of improvement (50, 70, 90 or 100%) as secondary outcome in the trial results.

The definition of flare for JIA

An innovative trial design in JIA is the use of the so-called randomized, double-blind controlled, withdrawal design. This study design was proposed by Giannini and Lovell for use in pediatric rheumatology studies [46] with the rationale to avoid the placebo arm for children with chronic conditions when alternative effective treatments are available. Eligible children are treated in an open label fashion with the experimental therapy to be tested in the trial for a few months after which responders (typically those demonstrating an ACR pediatric 30 response) are randomized in a double-blind fashion either to continue the experimental therapy or to switch to placebo. In this

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segment of the study, called the double- blind withdrawal phase, patients who demonstrate a pre-defined definition of disease worsening (e.g. “flare”) are withdrawn from the double-blind withdrawal phase of the trial and re-treated with the experimental therapy in an open label fashion. A peculiarity of this trial design is therefore the need to have a proper definition of flare to be used in the double- blind withdrawal phase. The flare definition currently used in JIA is essentially the inverse of the ACR Pediatric 30 criteria for response [47]. This definition requires that there be at least a 30% worsening in three of the six JIA core set parameters, with no more than one improving by more than 30%. In addition, there are some contingencies requiring that, if either the number of active joints or the number of joints with limitation of motion are used in the flare definition, there must be at least a two joint increase in the number of active joints or those with limited range of motion, respectively. Also, if the physical or parent global scales are used in the flare definition, worsening ≥ 2 cm (on a 0-10 cm scale) is required. Additionally, for systemic JIA patients only, reappearance of spiking fever ($> 38^{\circ}\text{C}$, lasting for at least 2 days in the week preceding the evaluation) not due to infections would signify that a flare have occurred. These flares criteria have been validated and shown to be sensitive, in terms of limiting the degree of the worsening patient symptoms to avoid potential damage in subjects randomized to placebo and those children losing response to the experimental agent.

The definition of remission for JIA

An additional definition available for JIA is the CARRA/PRINTO/PRCSG criteria for inactive disease [48] that requires the absence of active arthritis, fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to JIA, active uveitis; normal ESR or CRP; and a physician’s global assessment of disease activity rated at the best score possible for the instrument used. The presence 6 continuous months of inactive disease defines clinical remission on medication, while 12 months of inactive disease off all anti-arthritis medications defines clinical remission off medication.

Final remarks and future perspective

The criteria for the evaluation of response to therapy in PRD were designed to ensure that certain minimum criteria/standards are applied to observational and randomized controlled trials and to facilitate comparison with future meta-analysis. Furthermore, they can assist in standardizing outcome measurements in daily clinical practice. The core set includes the indication of instruments that can be used to assess each domain. However the specific instrument can be modified or integrated whenever new valid tools or better laboratory indicators will be developed to measure a particular domain or more suitable for use in the paediatric age. The proposed core sets also combine aspects of the disease that can be measured easily in clinical practice and indeed only measures that can be assessed reliably world-wide were included.

In conclusion the proposed core sets and definitions of improvement incorporate clinically meaningful change in a composite endpoint for the evaluation of global response to therapy in the major PRD. The definitions are proposed for use in PRD clinical trials, and may help physicians to decide if a child has responded adequately to therapy.

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Table 1: Core sets of measure to evaluate response to therapy in JIA, JSLE and JDM. In the first column are reported the overall domain. In the following columns the suggested variables to measure each specific domain in the 3 diseases.

DOMAINS*	Juvenile idiopathic arthritis (JIA)	Juvenile systemic lupus erythematosus (JSLE)	Juvenile dermatomyositis (JDM)
COMMON DOMAINS			
Global assessment by physicians	1) Physician's global assessment of disease activity on a 10-cm Visual analogue scale (VAS) or a 21 circle VAS	1) Physician's global assessment of disease activity on a 10-cm VAS or a 21 circle VAS	1) Physician's global assessment of disease activity on a 10-cm VAS or a 21 circle VAS
Global assessment by parents/patients	2) Patient/parent's assessment of overall well-being or a 10-cm VAS or a 21 circle VAS	2) Patient/parent's assessment of overall well-being or a 10-cm VAS or a 21 circle VAS	2) Patient/parent's assessment of overall well-being or a 10-cm VAS or a 21 circle VAS
Disability or Health Related Quality of Life	3) Childhood Health Assessment Questionnaire (CHAQ) or the Juvenile Arthritis Functionality Scale (JAFS)	3) Physical Summary score (PhS) of the Child Health Questionnaire (CHQ) or the Pediatric Rheumatology Quality of Life Scale (PRQL)	3) CHAQ or JAFS 4) CHQ-PhS or PRQL
DISEASE SPECIFIC DOMAINS			
Disease specific measures	4) Number of active joints 5) Number of joints with limited range of motion		5) Childhood Myositis Assessment Scale (CMAS) or Manual Muscle Testing (MMT)
Global disease activity		4) European Consensus Lupus Activity Measurement (ECLAM) or the Systemic Lupus Activity Measures (SLAM) or the SLEDAI	6) Disease Activity Score (DAS) or Myositis Disease Activity Assessment (MDAA)
Laboratory assessment	6) Erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)	5) 24-hour proteinuria	
Additional	7) Spiking fever (to be used just for systemic JIA)		

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Table 2: Definitions to evaluate response to therapy in JIA, JSLE and JDM.

Juvenile idiopathic arthritis (JIA)	Juvenile systemic lupus erythematosus (JSLE)	Juvenile dermatomyositis (JDM)
Definition of improvement		
At least 30% (*) improvement from baseline in 3 of any 6 variables in the core set	At least 50% (*) improvement from baseline in any 2 among the 5 core set measures	At least 20% (*) improvement from baseline in 3 of any 6 core set domains
with no more than one of the remaining variables worsening by more than 30%.	with no more than 1 of the remaining worsening by more than 30%.	with no more than 1 of the remaining worsening by more than 30%, which cannot be muscle strength
For systemic JIA absence of spiking fever (< 2 days of maximal body temperature \leq 38°C during the week preceding the evaluation) is also required		
Definition of flare		
at least a 30% worsening in 3 of the 6 JIA core set parameters, with no more than one improving by more than 30%. (**)		

(*) report as secondary outcome also 50%-70%-90%-100% improvement

(**) Contingencies for JIA flare definition: if either the number of active joints or the number of joints with limitation of motion are used in the flare definition, there must be at least a two joint increase, respectively. Also, if the physical or parent global scales are used in the flare definition, worsening \geq 2 cm (on a 0-10 cm scale) is required. Additionally, for systemic JIA patients only, reappearance of spiking fever (> 38°C, lasting for at least 2 days in the week preceding the evaluation) not due to infections would signify that a flare have occurred.

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