EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Core outcome sets – regulatory view

European Medicines Agency
Working to protect public health in the European Union since 1995

COMET VI
Amsterdam, 11 November 2016

Presented by Richard Veselý, MD
Head of the Rheumatology, Respiratory, Gastroenterology and Immunology Office
Scientific and Regulatory Management Department

Declaration of conflict of interest

No interest to declare.

The views and opinions expressed in the following PowerPoint slides are those of the individual presenter and should not be attributed to the European Medicines Agency.

Update on EMA

Office address

European Medicines Agency
30 Churchill Place
Canary Wharf
London E14 5EU
United Kingdom

www.ema.europa.eu
Tel. +44 (0)20 3660 6000
Fax: +44 (0)20 3660 5555

EMA in the EU

Who do we work for?

tervist salud
zdravie saúde saħħa gezondheid
veselība
sundhed υγεία
zdrowie
Gesundheit
terveys здраве
egészségügyi
santé zdravlje zdravie
sveikata
health
hälsa
zdravje
sláinte sănătate

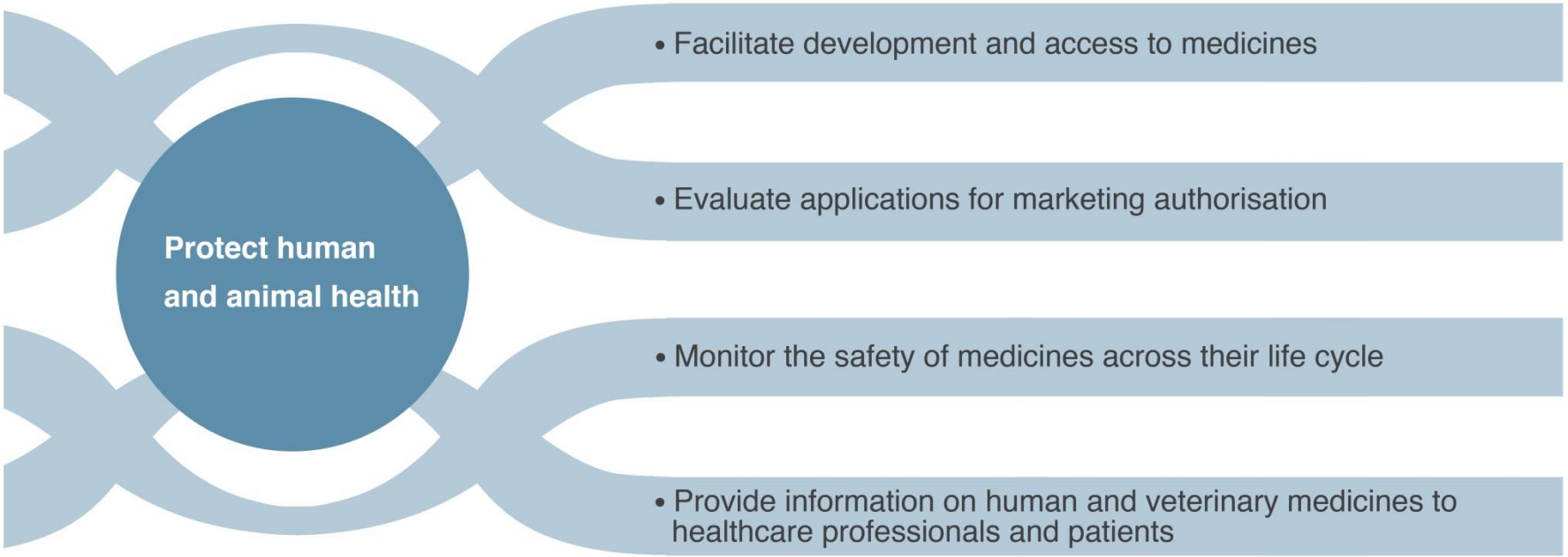
over **500** million people living in the European Union

28 member states

27% of global sales of medicines

24 official languages

What do we do?

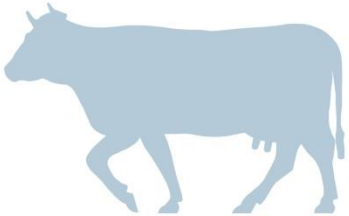

Protect human and animal health
• Facilitate development and access to medicines
• Evaluate applications for marketing authorisation
• Monitor the safety of medicines across their life cycle
• Provide information on human and veterinary medicines to healthcare professionals and patients

Who we are

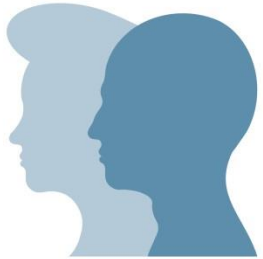
~4000 Scientific experts from right across Europe

7 Scientific committees

over 1000 marketing authorisations recommended



CHMP
CVMP
COMP
HMPC
PDCO
CAT
PRAC

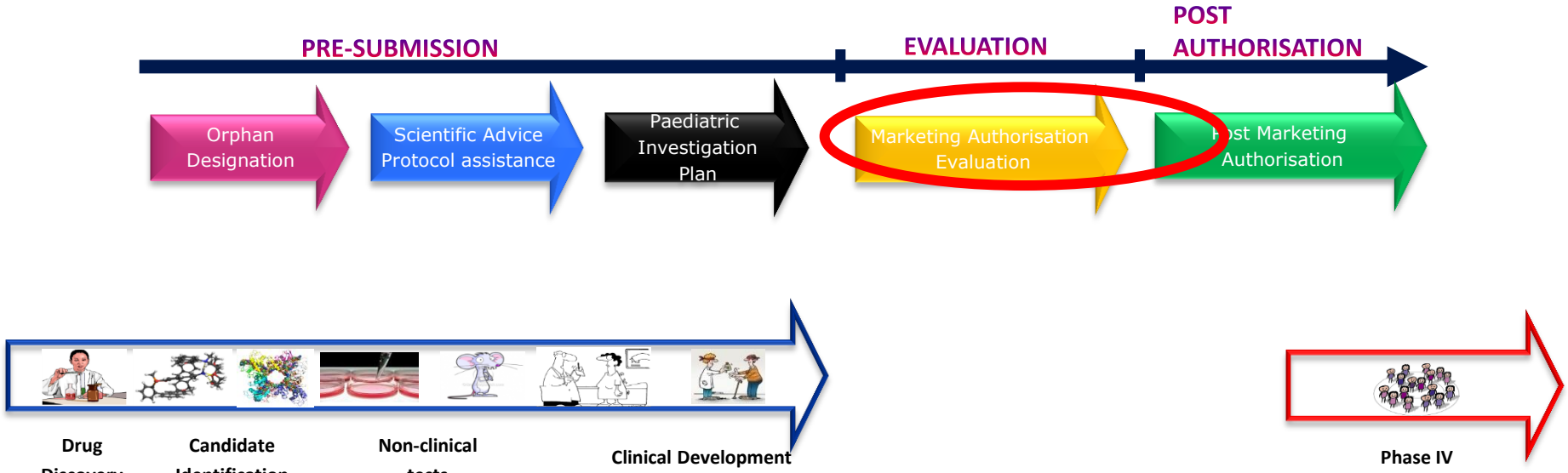


1995 EMA established to evaluate medicines for use in the EU

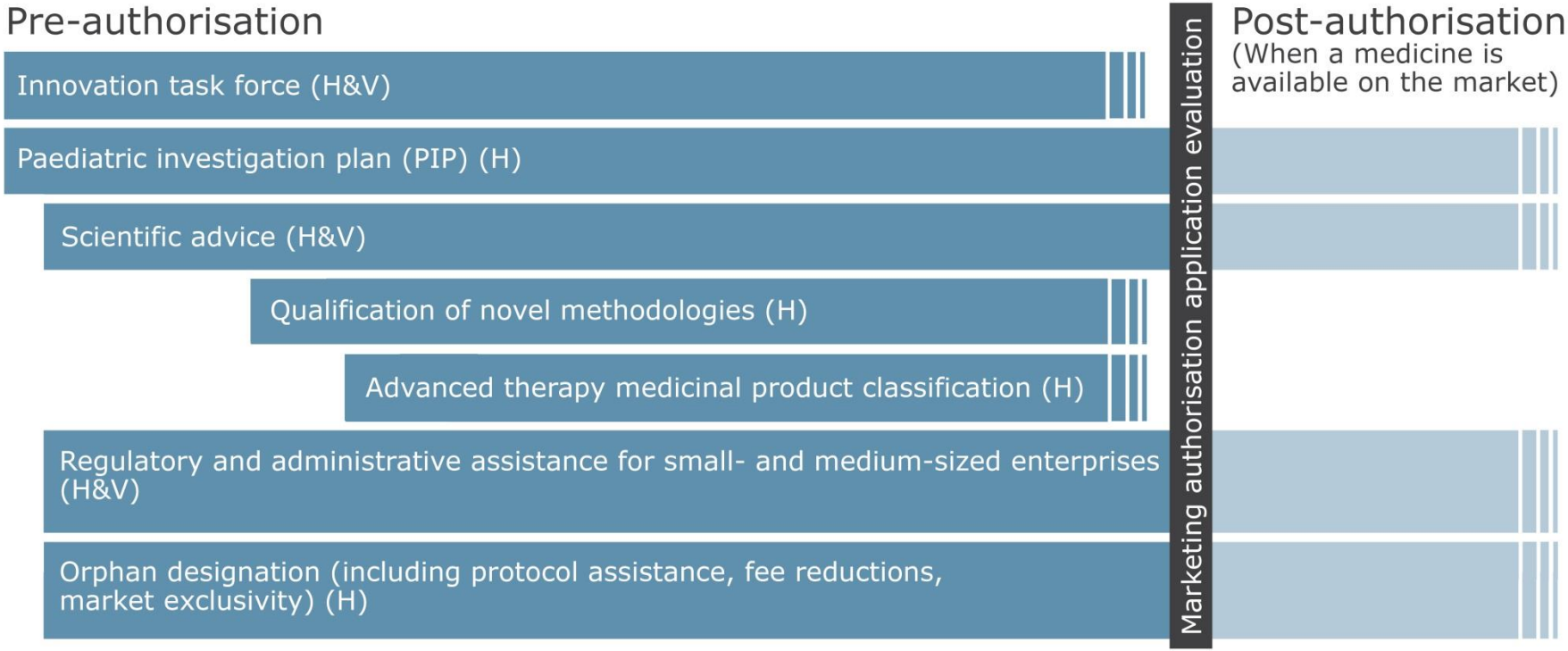
28 Working parties

~890 Staff members

Medicines Lifecycle: Development and Regulatory



Supporting research and innovation of medicines

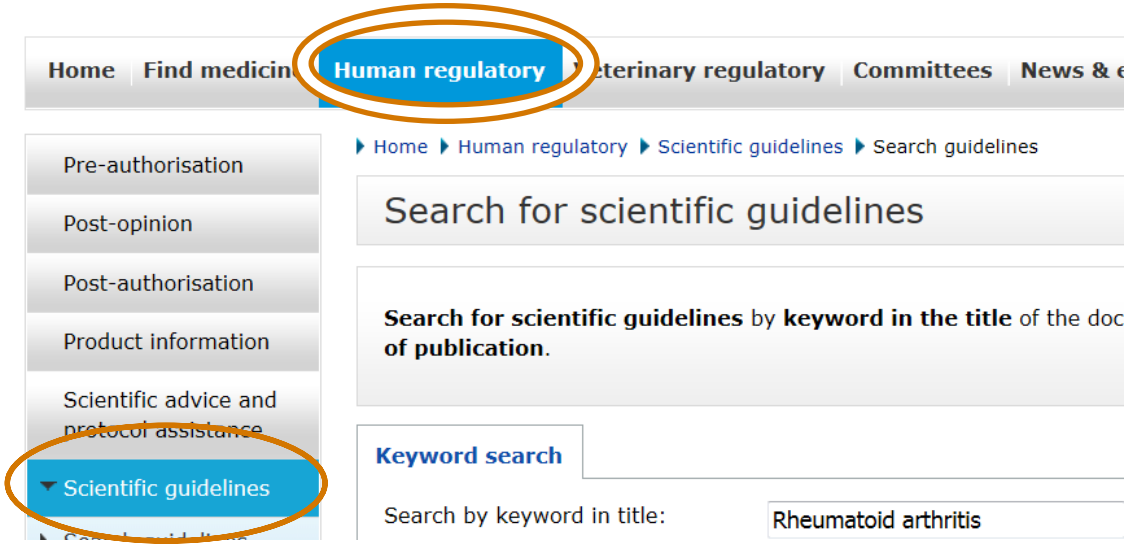


EMA guidelines in MSD

Adopted guidelines	Updates
Rheumatoid arthritis, 2003	Final guideline for adoption by end 2016
JIA, 2006	Published 2015
Axial spondyloarthritis, 2009	Publication by end 2016
Osteoarthritis 2010	Not foreseen
Psoriatic arthritis, 2006	Not foreseen
Lupus	Published 2015
New guidelines under development	
Gout	
Glucocorticoid-induced osteoporosis	

EMA Guidelines

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/landing/scientific_guideline_search.jsp&mid=WC0b01ac05804698db



Development of EU guidelines

Guideline in the pharmaceutical legislative framework

-harmonised EU approach

-based on the most up-to-date scientific knowledge

-to facilitate planning the overall pharmaceutical product development, the preparation of applications for marketing authorisations by the pharmaceutical industry and the assessment, approval and control of medicinal products in the European Union

It has no legal force (“soft law” non-legally binding but quasi-binding character). Alternative approaches may be taken, provided that these are appropriately justified.

EU guideline development steps

- Development, adoption and release for consultation of concept paper
- Preparation and release for consultation of draft guideline
- Preparation and adoption of final guideline for publication and its implementation

All steps are transparent, published on EMA website

RA guideline– Assessment of efficacy

Combined measures reflecting the different signs and symptoms are to be used

For this purpose diverse validated composite disease activity scores are available, such as

- DAS28,
- Simplified Disease Activity Index (SDAI)
- Clinical Disease Activity Index (CDAI))

with cut-off criteria for 'remission'

However, it is acknowledged that there are some limitations in these disease activity scores and patients may still have ongoing inflammation at remission. Therefore, more stringent remission criteria were developed by the ACR-EULAR in 2011. These criteria consist either of a Boolean definition, including tender and swollen joint counts ≤1, and CRP ≤1 mg/dl, or an index-based definition, with SDAI ≤3.3.

In addition, ACR response criteria (e.g. ACR20, ACR50, ACR70 reflecting improvement of signs and symptoms from baseline of 20, 50 or 70%) should be documented.

Outcome measures
JIA core set and response criteria

Core set:

1. Physician global assessment of overall disease activity
2. Parent or patient global assessment of overall well-being
3. Functional ability (CHAQ)
4. Number of joints with active arthritis
5. Number of joints with limited range of motion
6. Index of inflammation: ESR or CRP
7. Fever (only for systemic JIA)

ACR Ped Criteria for improvement:

3/6 core set variables improved ≥ 30% (50%, 70%) with no more than 1/6 worsened by >30%

Definition of flare:

3/6 core set variables worsened ≥ 30% with no more than 1/6 improved by ≥ 30%

Criteria for defining clinical inactive disease

in oligoarticular, polyarticular and systemic JIA

- No joints with active arthritis
- No fever, rash, serositis, splenomegaly, or generalised lymphadenopathy attributable to JIA
- No active uveitis as defined by the SUN Working Group (28)
- ESR or CRP level within normal limits in the laboratory where tested or, if elevated, not attributable to JIA
- Physician's global assessment of disease activity score of best possible on the scale used
- Maximum duration of morning stiffness 15 min

Arthritis Care & Research
Vol. 63, No. 7, July 2011, pp 929–936
DOI 10.1002/acr.20497

SPECIAL ARTICLE

American College of Rheumatology Provisional Criteria for Defining Clinical Inactive Disease in Select Categories of Juvenile Idiopathic Arthritis

CAROL A. WALLACE,[1] EDWARD H. GIANNINI,[2] BIN HUANG,[2] LUKASZ ITERT,[2] AND NICOLINO RUPERTO,[3] FOR THE CHILDHOOD ARTHRITIS AND RHEUMATOLOGY RESEARCH ALLIANCE (CARRA), THE PEDIATRIC RHEUMATOLOGY COLLABORATIVE STUDY GROUP (PRCSG), AND THE PAEDIATRIC RHEUMATOLOGY INTERNATIONAL TRIALS ORGANISATION (PRINTO)

Objective. To prospectively validate the preliminary criteria for clinical inactive disease (CID) in patients with select categories of juvenile idiopathic arthritis (JIA).

Methods. We used the process for development of classification and response criteria recommended by the American College of Rheumatology Quality of Care Committee. Patient-visit profiles were extracted from the phase III randomized controlled trial of infliximab in polyarticular-course JIA (i.e., patients considered to resemble those with select categories of JIA) and sent to an international group of expert physician raters. Using the physician ratings as the gold standard, the sensitivity and specificity were calculated using the preliminary criteria. Modifications to the criteria were made, and these were sent to a larger group of pediatric rheumatologists to determine quantitative, face, and content validity.

Results. Variables weighted heaviest by physicians when making their judgment were the number of joints with active arthritis, erythrocyte sedimentation rate (ESR), physician's global assessment, and duration of morning stiffness. Three modifications were made: the definition of uveitis, the definition of abnormal ESR, and the addition of morning stiffness. These changes did not alter the accuracy of the preliminary set.

Conclusion. The modified criteria, termed the "criteria for CID in select categories of JIA," have excellent feasibility and face, content, criterion, and discriminant validity to detect CID in select categories of JIA. The small changes made to the preliminary criteria set did not alter the area under the receiver operating characteristic curve (0.954) or accuracy (91%), but have increased face and content validity.

Wallace et al. 2011

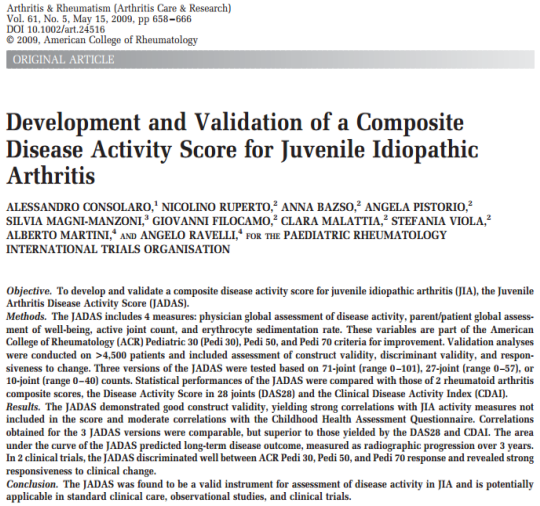
Juvenile Arthritis Disease Activity Score - JADAS

Components:

- Physician global assessment (0-10 cm VAS)
- Parent/patient global assessment (0-10 VAS)
- Active joint count (71 or 27 or 10 joints)
- Acute phase reactant (ESR or CRP)

Cutoff scores (with all versions of the JADAS)

- Inactive disease - 1
- Minimal disease activity - 2 for oligoarticular JIA
  - 3.8 for polyarticular JIA



Arthritis & Rheumatism (Arthritis Care & Research)
Vol. 61, No. 5, May 15, 2009, pp 658–666
DOI 10.1002/art.24516

ORIGINAL ARTICLE

Development and Validation of a Composite Disease Activity Score for Juvenile Idiopathic Arthritis

ALESSANDRO CONSOLARO,[1] NICOLINO RUPERTO,[2] ANNA BAZSO,[2] ANGELA PISTORIO,[2] SILVIA MAGNI-MANZONI,[3] GIOVANNI FILOCAMO,[2] CLARA MALATTIA,[2] STEFANIA VIOLA,[2] ALBERTO MARTINI,[4] AND ANGELO RAVELLI,[4] FOR THE PAEDIATRIC RHEUMATOLOGY INTERNATIONAL TRIALS ORGANISATION

Objective. To develop and validate a composite disease activity score for juvenile idiopathic arthritis (JIA), the Juvenile Arthritis Disease Activity Score (JADAS).
Methods. The JADAS includes 4 measures: physician global assessment of disease activity, parent/patient global assessment of well-being, active joint count, and erythrocyte sedimentation rate. These variables are part of the American College of Rheumatology (ACR) Pediatric 30 (Pedi 30), Pedi 50, and Pedi 70 criteria for improvement. Validation analyses were conducted on >4,500 patients and included assessment of construct validity, discriminant validity, and responsiveness to change. Three versions of the JADAS were tested based on 71-joint (range 0–101), 27-joint (range 0–57), or 10-joint (range 0–40) counts. Statistical performances of the JADAS were compared with those of 2 rheumatoid arthritis composite scores, the Disease Activity Score in 28 joints (DAS28) and the Clinical Disease Activity Index (CDAI).
Results. The JADAS demonstrated good construct validity, yielding strong correlations with JIA activity measures not included in the score and moderate correlations with the Childhood Health Assessment Questionnaire. Correlations obtained for the 3 JADAS versions were comparable, but superior to those yielded by the DAS28 and CDAI. The area under the curve of the JADAS predicted long-term disease outcome, measured as radiographic progression over 3 years. In 2 clinical trials, the JADAS discriminated well between ACR Pedi 30, Pedi 50, and Pedi 70 response and revealed strong responsiveness to clinical change.
Conclusion. The JADAS was found to be a valid instrument for assessment of disease activity in JIA and is potentially applicable in standard clinical care, observational studies, and clinical trials.

Consolaro et al 2009, 2012

EMA paediatric rheumatology guidelines

Guideline on clinical investigation of medicinal products for the treatment of systemic lupus erythematosus and lupus nephritis

Document details

Download document	Guideline on clinical investigation of medicinal products for the treatment of systemic lupus erythematosus and lupus nephritis
Reference number	EMA/CHMP/51230/2013
Status	adopted
First published	27/03/2015
Last updated	27/03/2015

Summary

This document is intended to provide guidance on the clinical investigation of medicinal products for the chronic treatment of systemic lupus erythematosus (SLE), a complex autoimmune disease that can affect multiple organs.

SLE outcome measures

- SLEDAI
- SELENA-SLEDAI
- BILAG
- BICLA
- ECLAM
- SLICC/ACR Damage index

PRINTO/ACR core set

The Pediatric Rheumatology International Trials Organization Criteria for the Evaluation of Response to Therapy in Juvenile Systemic Lupus Erythematosus

Prospective Validation of the Disease Activity Core Set

- Physician's global assessment of disease activity;
- A global disease activity measure (e.g. European Consensus Lupus Activity Measure (ECLAM), Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), Systemic Lupus Erythematosus Activity Measure (SLAM), British Isles Lupus Assessment Group (BILAG), or other global disease activity measures deemed appropriate for clinical trials)
- 24-hour proteinuria. Alternatively the spot urine protein
- Patient's/Parent's global assessment of the overall patient's wellbeing
- Health-related quality of life assessment (Child Health Questionnaire physical summary score)

Responders :

- at least 50% improvement from baseline in any 2 among 5 core set measures
- no more than 1 of the remaining worsening by more than 30%.

Ruperto et al, 2005

Crohn's disease – Assessment of efficacy

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/07/WC500211430.pdf

While Crohn's Disease Activity Index (CDAI), combining both patient reported data and surrogate markers of inflammation, has previously been used extensively in clinical trials in CD, both reliability and validity of this index has been questioned. The reproducibility of the CDAI may be limited, as significant inter-observer variability even in the hands of experienced clinicians has been observed. Furthermore, many of the components of the CDAI are subject to interpretation and may be biased. Consequently, the use of this index as a primary endpoint for future studies is discouraged.

Osteoporosis

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

4 September 2014
EMA/247433/2014

Report of the paediatric osteoporosis expert meeting
06 June 2014 – chaired by Viveca Odlind and Richard Veselý

7. Outcome measures

The frequency of fractures should be used as the primary outcome measure in paediatric studies. Use of bone mineral density (BMD) measurements and laboratory markers as surrogates has limitations, and the predictive value for future fractures needs to be further studied. **Development of a composite endpoint including number of fractures, bone mineral density and other parameters (quality of life including functioning, laboratory markers) might be useful to overcome methodological difficulties** in measuring a clinically relevant benefit in clinical trials in children with osteoporosis.

http://www.ema.europa.eu/docs/en_GB/document_library/Report/2014/09/WC500172407.pdf

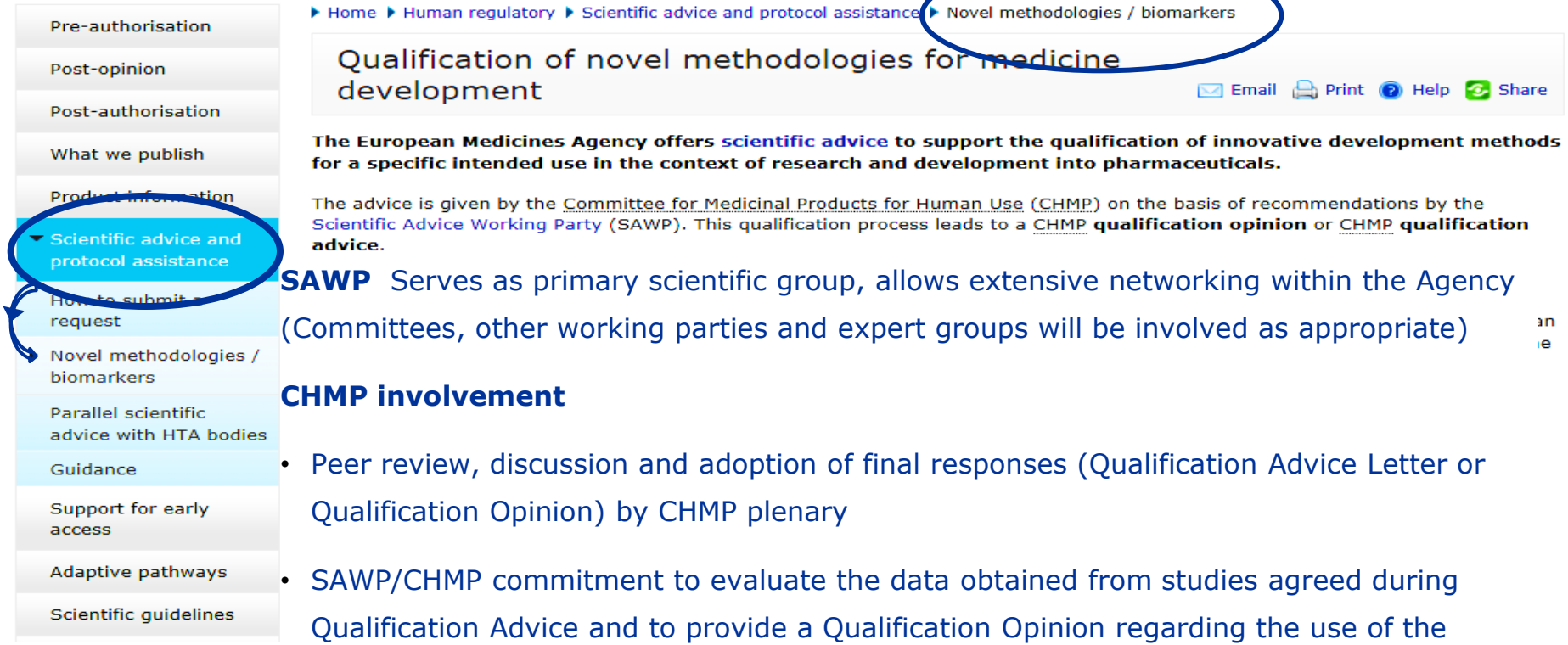
Cystic fibrosis

21 July 2016
EMA/CHMP/259918/2016
Committee for Medicinal Products for Human Use (CHMP)

Concept paper on the need for revision of the guideline on the clinical development of medicinal products for the treatment of cystic fibrosis (CHMP/EWP/9147/08)

Agreed by Respiratory Drafting Group	29 April 2016
Agreed by PDCO	17 May 2016
Adopted by CHMP for release for public consultation	21 July 2016
Start of public consultation	1 August 2016
End of consultation (deadline for comments)	31 October 2016

Qualification of novel methodologies for ~~medicine~~ development



SAWP Serves as primary scientific group, allows extensive networking within the Agency (Committees, other working parties and expert groups will be involved as appropriate)

CHMP involvement

- Peer review, discussion and adoption of final responses (Qualification Advice Letter or Qualification Opinion) by CHMP plenary
- SAWP/CHMP commitment to evaluate the data obtained from studies agreed during Qualification Advice and to provide a Qualification Opinion regarding the use of the method in R&D.

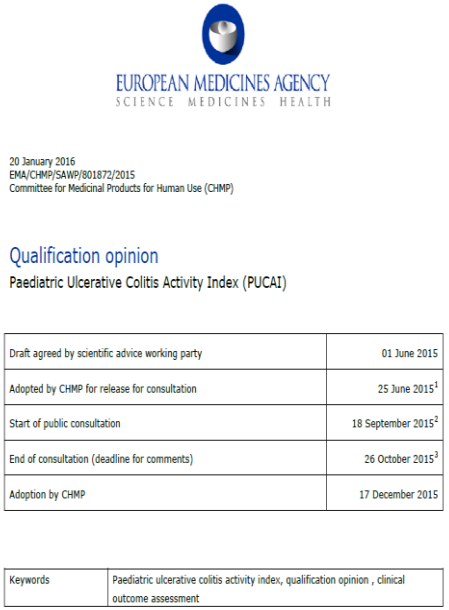
EMA website:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000319.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac0580022bb0

Qualification opinion - PUCAI

1. The paediatric ulcerative colitis activity index (PUCAI) can be used as the primary outcome measure in clinical trials of paediatric UC as a proxy for endoscopic assessment when colonoscopy is waived with appropriate justification

2. The PUCAI is suitable to be used as reliable efficacy evaluation in visits during which endoscopy is not performed in clinical trials of paediatric UC where endoscopy is used as primary outcome,

3. The PUCAI can be used to screen paediatric UC patients in order to grade disease activity into mild, moderate or severe.



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 January 2016
EMA/CHMP/SAWP/801872/2015
Committee for Medicinal Products for Human Use (CHMP)

Qualification opinion

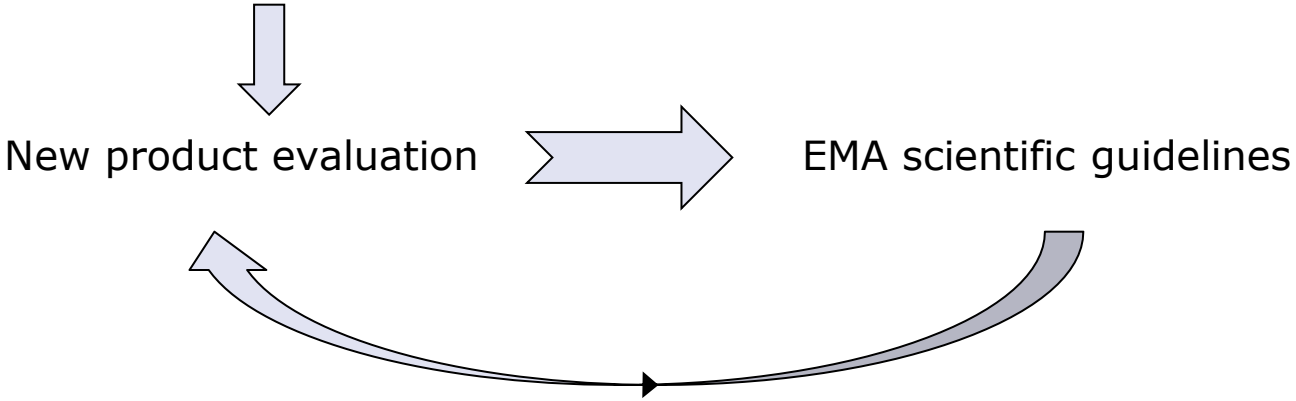
Paediatric Ulcerative Colitis Activity Index (PUCAI)

Draft agreed by scientific advice working party	01 June 2015
Adopted by CHMP for release for consultation	25 June 2015[1]
Start of public consultation	18 September 2015[2]
End of consultation (deadline for comments)	26 October 2015[3]
Adoption by CHMP	17 December 2015

Keywords	Paediatric ulcerative colitis activity index, qualification opinion , clinical outcome assessment

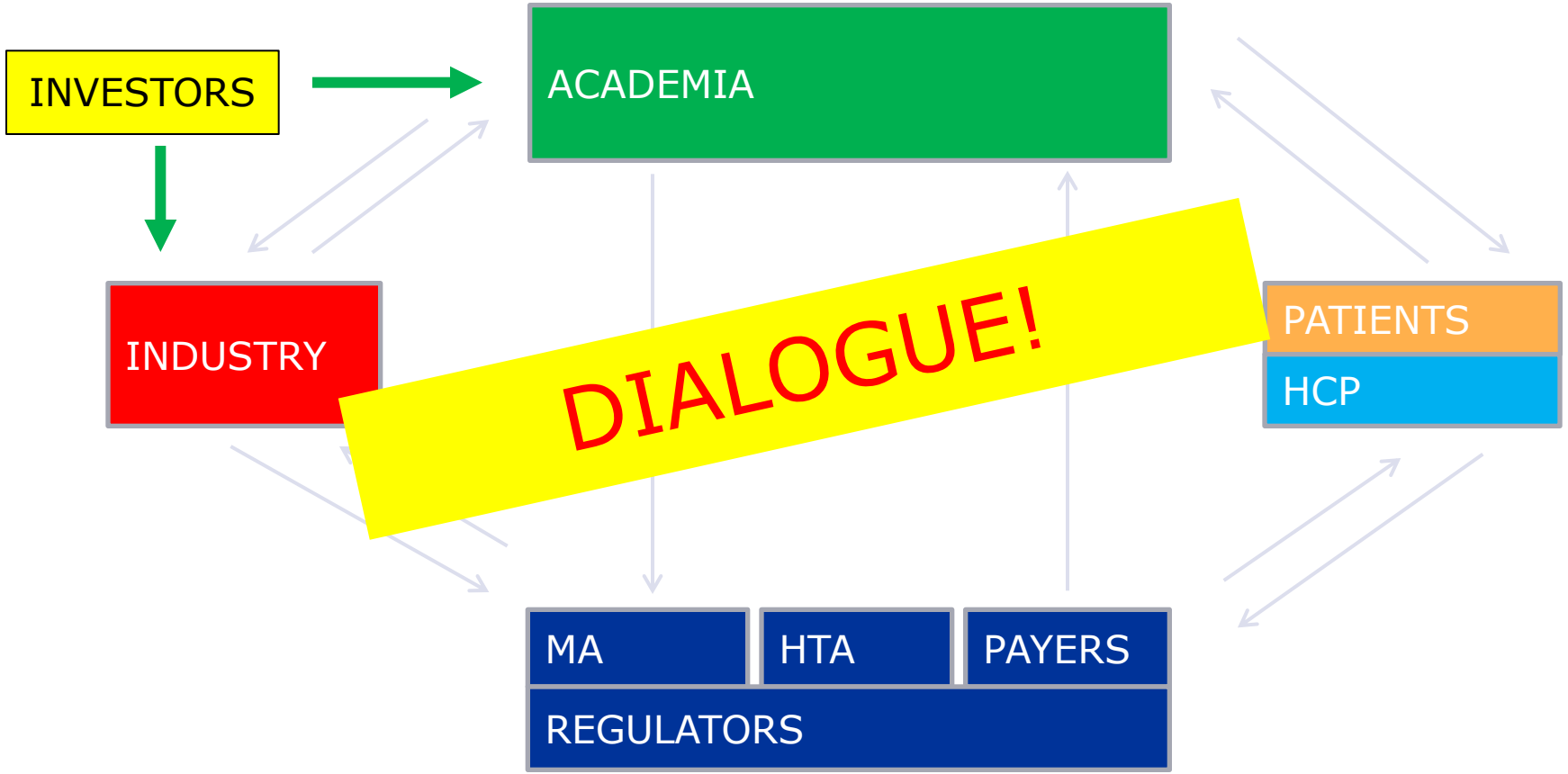
Implementation of new disease activity and treatment response evaluation instruments

Qualification procedure (advice or opinion)



Future trends and challenges

- Transparency - proactive publication of clinical reports
- Adaptive pathways
- Strengthening early dialogue with developers of medicines
- Patient participation in the assessment of medicines
- Ensuring safety of medicines in view of increasingly globalised development and manufacturing


INVESTORS
ACADEMIA
INDUSTRY
DIALOGUE!
PATIENTS
HCP
MA
HTA
PAYERS
REGULATORS

Achieving EMA's mission

EUROPEAN MEDICINES AGENCY

Foster scientific excellence in the evaluation and supervision of medicines, for the benefit of public health in the European Union

Evidenced-based decisions

Regulatory decision-making is based on assessment of:

- Valid scientific evidence generated by marketing authorisation applicants/holders
- Data and information available from alternative sources
  - ⇨ academic studies, public authority studies (including by regulators); use of data-sources on real-life use of medicines; clinical guidelines; reports in EudraVigilance and in the scientific literature

Feasible and proportionate decisions

- Incorporate clinical expertise and practical experience
- Address patient needs in real life (including values and preferences)
- Consider implementation in local healthcare contexts

Key elements underpinning collaboration with learned societies and academia

- EMA Stakeholder database
- EMA pool of experts
- Research and knowledge generation
- Multi-stakeholder platform
- Communication

EMA stakeholder relations management framework	
Inform – to enable feedback	*e.g.* dedicated web pages, relevant news items, Q&As, information days, information materials including videos and presentations
Consult – via written consultation	*e.g.* public consultation on policies, guidance, surveys
Consult and Involve – via direct interactions	*e.g.* multi-stakeholder meetings, workshops, conferences, public hearings, input into the development of regulatory guidelines and other regulatory procedures
Cooperate / participate – via direct interactions	*e.g.* participation to research projects, cooperation in activities of education and training, participation in scientific advisory groups and ad-hoc expert groups, cooperation with established EMA stakeholders and networks.

Thank you for your attention

Further information

[Insert relevant information sources or contact details as applicable.]

European Medicines Agency
30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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