Prioritising drug development for children with rhumatologic diseases The Paediatric Rheumatology InterNational Trials Organization (PRINTO) perspective

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Outline

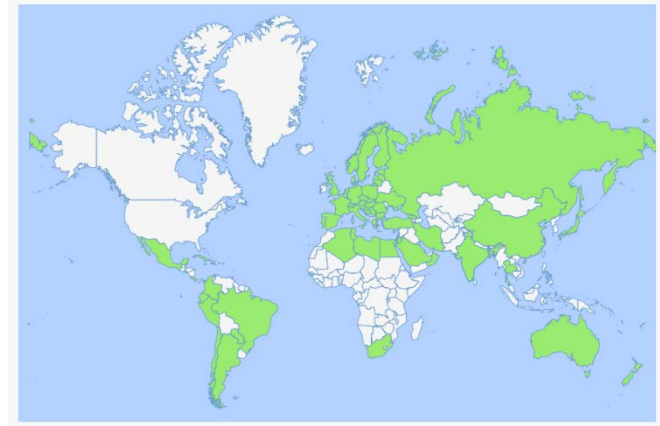
- PRINTO outline
- Liaisons with industries

Paediatric Rheumatic Diseases (PRD)

- PRD are rare diseases and the most common chronic illnessess in childhood
- PRD are highly debilitating and potentially affecting the entire life
- The most common diseases are
  - **Juvenile Idiopathic Arthitis (JIA)**
  - Juvenile Systemic Lupus Erythematosus (JSLE)
  - Juvenile Dermatomyositis (JDM) and others

www.printo.it (>60 countries, >500 centres)

www.pediatric-rheumatology.printo.it



- ***EULAR Centre of Excellence in Rheumatology 2008-2018***
- ***Category 1 ENPrEMA***

Italy, May 19, 1996

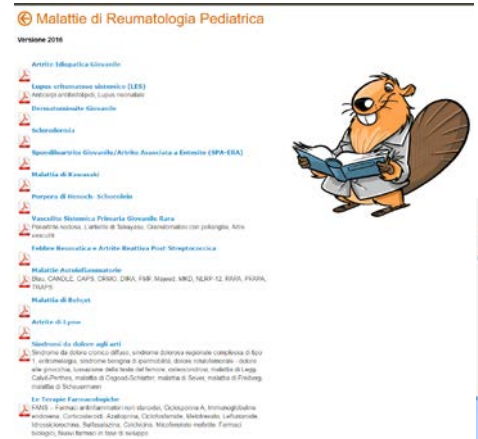
"...to foster, facilitate, and conduct high quality research in the field of paediatric rheumatology..."

PRINTO bylaws

Ann Rheum Dis. 2005 Arch Dis Child 2011-2012

2016 new version

www.pediatric-rheumatology.printo.it



- **Centres**
- **Family associations**

~4,500 people/day from over 180 countries

Ruperto Annals Rheum Dis. 2005

PRINTO academic not-for-profit studies

(>37,500 pts in 300 centres in 67 countries)

	No centres / countries 300/67	West Europe	East Europe	Latin America	North America	Others	Totals
MTX1	56/20	492	55	66	8	12	**633**
HRQOL	32/32	3,988	1,388	903		365	**6644**
JSLE	108/39	247	102	150	37	21	**557**
JDM	95/36	159	37	78	17	3	**294**
Cyclosporine	56/22	203	27	25	85	4	**344**
MTX2	61/29	193	80	80		11	**364**
Vasculitis	93/36	599	353	260	6	181	**1399**
JDM	53/20	89	10	39	1		**139**
Eurofever	100/35	2981	349	68	1	185	**3584**
EPOCA	120/49	6044	3635	1308	723	2175	**13885**
MAS	90/31	659	99	74	148	131	**1111**
Pharmachild	86/32	5252	2401	576		219	**8448**
Abirisk	24/12	115	33				**148**

PRINTO-PRCSG Enrollment

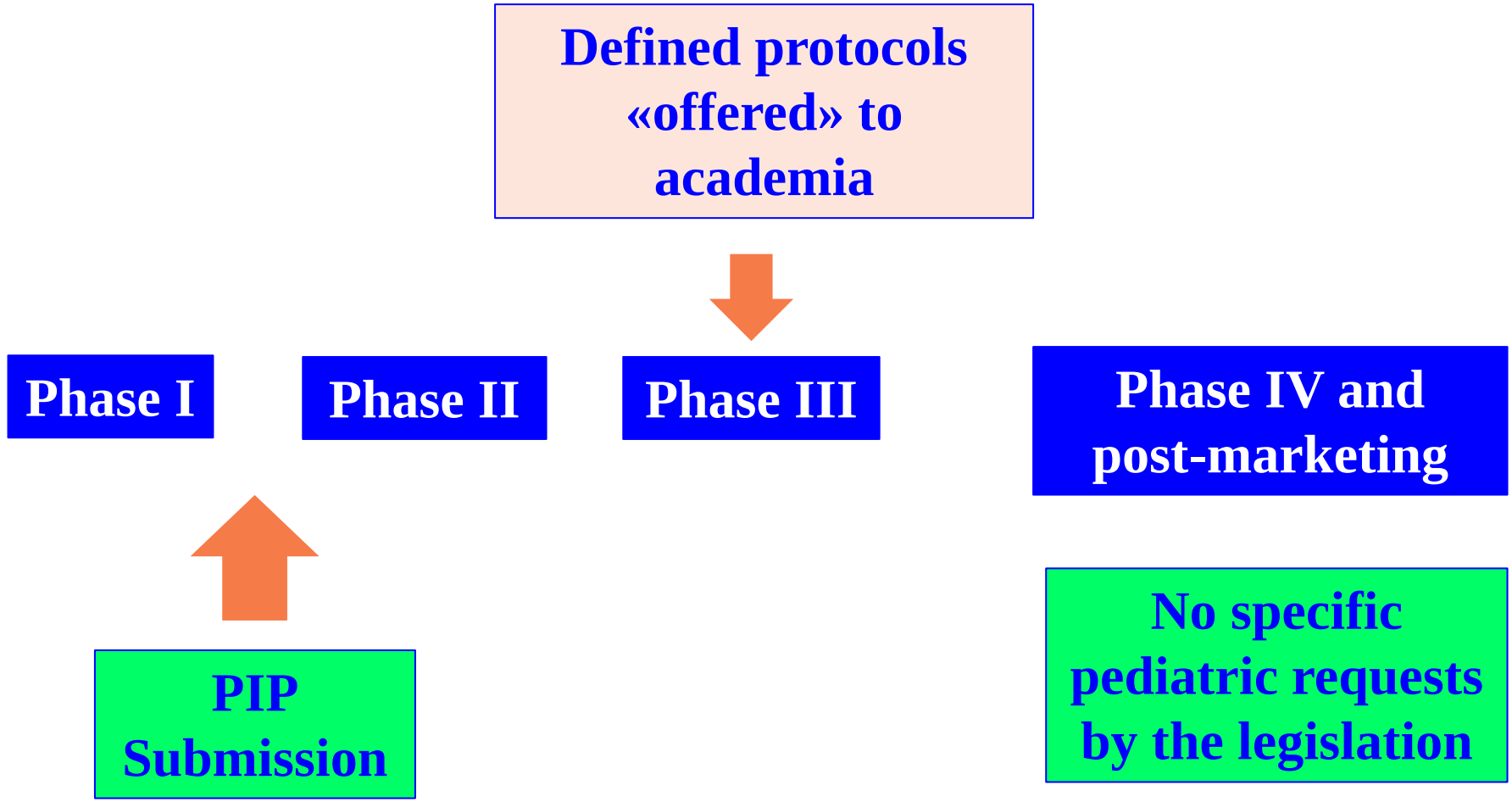
(3349 patients in 253 centres in 39 countries)

	No centres / countries 253/39	West Europe	East Europe	Latin America	North America	Others	Totals
Etanercept	9/2				69		69
Etanercept	38/19	43	75	5		4	127
Infliximab	31/14	62	10	28	23		123
Adalimumab							171
Abatacept iv							190
Abatacept sc							207
Tocilizumab syst							112
Tocilizumab poly							188
Canakinumab PI							23
Canakinumab P I							190
Golimumab							173
Meloxicam							226
Adalimumab regi	90/17	274	60	5	505	5	849
Abatacept registry	23/14	151	26	3		14	194
Rilonacept	59/22	134	35	82	69	7	327
Tofacitinib poly	6/3	10	7				17
Certolizumab Pegol	34/7		44	39	80		163

>90% of the PIP successfull through Phase II or III trials implemented with the PRINTO PRCSG networks

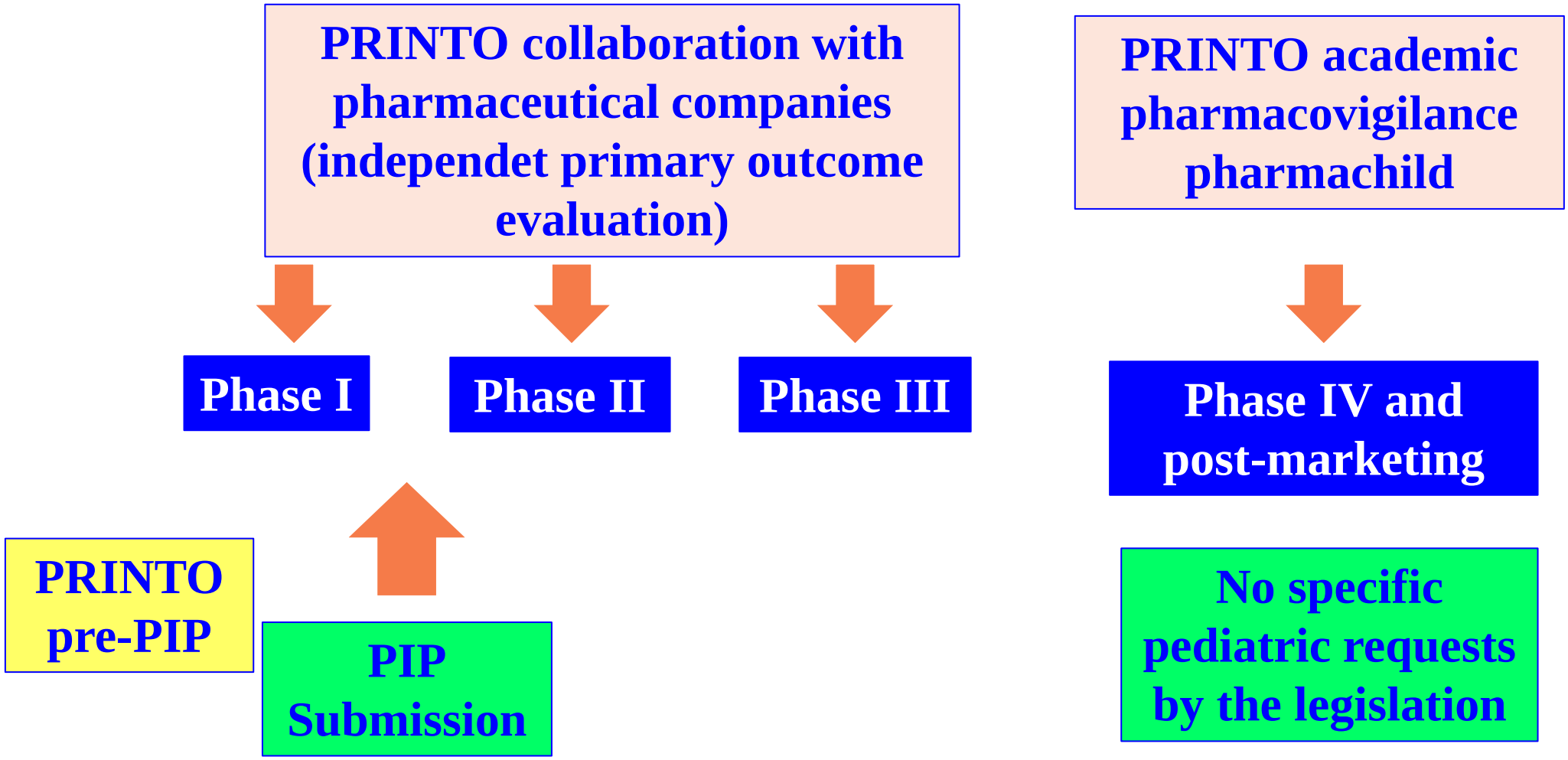
Is there a role for “academia”?

Drug development: «the central paradigm»



Is there a role for “academia”?

The «broken» paradigm



Liaisons with pharma companies

- **Scientific collaboration:**
  - Pediatric rheumatology concerns
  - PIP/Protocol/CRF drafting
    - Study design, inclusion/exclusion criteria
  - feasibility for site selection,
  - Training and investigator certification
    - Joint assessor certificate,
  - PRINTO/PRCSG primary outcome evaluation with real time monitoring and data transfer to companies
  - Analysis and reporting

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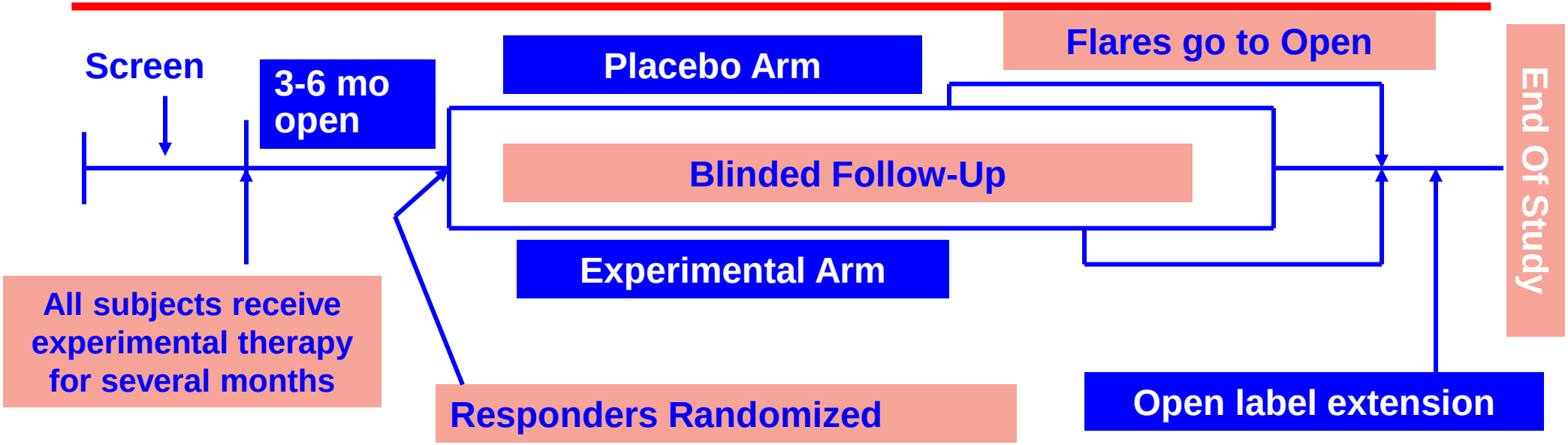
Concerns in ped rheumatic diseases (PRD)

- How to define ***response to therapy***
- Need to limit ***time on placebo*** (chronic disease)
- What are ***acceptable control*** *groups*?
- PRD are rare ***(feasibility)*** and therefore we need
  - a) to obtain *as much information as possible from every subject*
  - b) design trials to be as *efficient* as possible (low sample size).
- What is the **standard of care**?
- What we are interested in?
  - short-term
  - ***long-term outcomes*** **(especially for remission/safety)**

How to measure response

- JIA ACR criteria (30-**50-70-100% change**)
  - **FDA/EMA «approved» JIA ACR 30%**
  - PRINTO/ACR/EULAR criteria for juvenile SLE and JDM
    - Juvenile Arthritis Disease Activity Scores (JADAS): absolute level of disease activity
    - Inactive disease/**clinical remission** ACR provisional criteria and JADAS remission criteria
- Similar criteria for juvenile SLE, and JDM

BLINDED WITHDRAWAL STUDIES



Response to therapy

- JIA ACR 30/50-70-90 response and flare criteria (**FDA and EMA approved**)
- JIA clinically inactive disease/clinical remission (on or off therapy)
- Juvenile Arthritis Disease Activity Score (JADAS)
- CHAQ/CHQ and JAMAR in more than 50 languages

Trial design in JIA

- Parallel design
  - MTX (Giannini for PRCSG NEJM 1992, Woo A&R 2000, Ruperto for PRINTO A&R 2004)
  - Meloxicam (Ruperto for PRINTO A&R 2004)
  - Infliximab (Ruperto for PRINTO A&R 2007)
  - Tocilizumab and canakinumab in sJIA (De Benedetti/Ruperto for PRINTO/PRCSG NEJM 2012)
- Withdrawal design
  - Etanercept (Lovell for PRCSG NEJM 2000)
  - Adalimumab (Lovell, Ruperto for PRINTO/PRCSG NEJM 2008)
  - Abatacept (Ruperto, Lovell for PRINTO/PRCSG Lancet 2008)
  - Canakinumab in sJIA (on going for PRINTO/PRCSG)
  - Tocilizumab in poly JIA (Brunner for PRINTO/PRCSG ARD 2015)
  - Golimumab in poly JIA (submitted)
- Open Label: certolizumab pegol (5th anti-TNF) (in preparation)

JIA population (all but one with placebo)

- Different populations similar efficacy/safety profile
- Methotrexate: **NSAIDs non responders**
- Etanercept: **MTX non responders** (NR) (MTX stop)
- Infliximab: **MTX non responders**
- Adalimumab: (**MTX NR and MTX naive**)
- Abatacept: (**MTX NR and biologics NR**)
- Golimumab/certolizumab: **MTX non responders**
- Tocilizumab, canakinumab/sarilumab: **systemic JIA**
- Secukinumab: **spondyloarthropathies**

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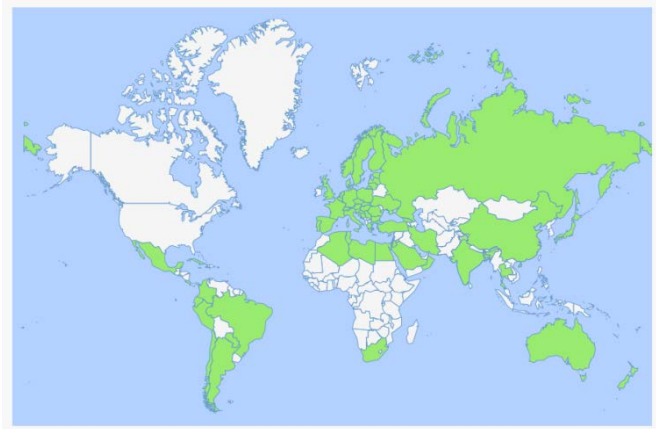
Feasibility and joint assessor certification



- Feasibility questionnaire with key points agreed with company
- Site feasibility among PRINTO members
- Provision of centre performance
- Final selection by the company among centres suggested by PRINTO

OVERVIEW
JOINT ASSESSORS FOR TRIALS PERFORMED BY THE PEDIATRIC RHEUMATOLOGY COLLABORATIVE STUDY GROUP (PRCSG) AND THE PEDIATRIC RHEUMATOLOGY INTERNATIONAL TRIALS ORGANISATION (PRINTO)
December 7, 2007

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

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Data Flow

Source document sent in real time

Double Data entry by the centre to PRINTO/PRCSG

Monitoring of source document of the centre

by PRINTO/PRCSG

Monitoring of source document of the centre/PRINTO-PRCSG

by Company

Regular transfer of clean data for data reconciliation

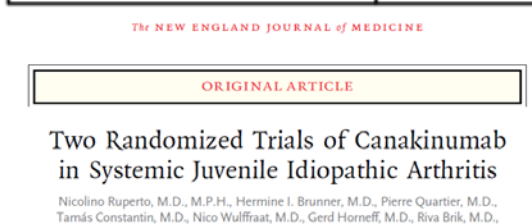
from PRINTO/PRCSG To Company

Independent PRINTO primary outcome real time assessment

Protocol
Site No. **1234** Subject ID No. **1234002** Date of Visit: **06-MAR-2017** Visit: **Week 1**

ACR Responder

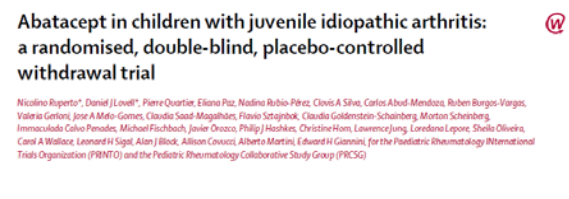
MODIFIED ACR SCORE Set	Value at Baseline	Value at Week 1	Absolute difference	Percent change	Note
Physician VAS	20	12	-8	-40%	
Joints with LOM	0	0	0	0%	
Active joints	4	2	-2	-50%	
Parent VAS	20	10	-10	-50%	
CHAQ score	2	1.25	-0.75	-37.5%	
CRP value	30	15	-15	-50%	
RESPONDER STATUS	ACR Responder 50				


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Two Randomized Trials of Canakinumab in Systemic Juvenile Idiopathic Arthritis

Nicolino Ruperto, M.D., M.P.H., Hermine I. Brunner, M.D., Pierre Quartier, M.D., Tamás Constantin, M.D., Nico Wulffraat, M.D., Gerd Horneff, M.D., Riva Brik, M.D.,


Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial

Nicolino Ruperto*, Daniel J Lovell*, Pierre Quartier, Eliana Paz, Nadina Rubio-Pérez, Clovis A Silva, Carlos Abud-Mendoza, Ruben Burgos-Vargas, Valeria Gerloni, Jose A Melo-Gomes, Claudia Saad-Magalhães, Flavio Sztajnbok, Claudia Goldenstein-Schainberg, Morton Scheinberg, Immaculada Calvo Penades, Michael Fischbach, Javier Orozco, Philip J Hashkes, Christine Hom, Lawrence Jung, Loredana Lepore, Sheila Oliveira, Carol A Wallace, Leonard H Sigal, Alan J Block, Allison Cavuoti, Alberto Martini, Edward H Giannini, for the Paediatric Rheumatology INternational Trials Organization (PRINTO) and the Pediatric Rheumatology Collaborative Study Group (PRCSG)


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Randomized Trial of Tocilizumab in Systemic Juvenile Idiopathic Arthritis

Fabrizio De Benedetti, M.D., Ph.D., Hermine I. Brunner, M.D., Nicolino Ruperto, M.D., M.P.H., Andrew Kenwright, B.Sc.,

Pharmacovigilance in juvenile idiopathic

Pharmacovigilance study EU funded

Agreement with one company with data property of PRINTO

No mandatory request to for pediatric safety studies

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  - PRINTO/PRCSG primary outcome evaluation with real time monitoring and data transfer to companies
  - **Analysis and reporting**

PRINTO publications: reason for success

- 130 PRINTO manuscripts
- 685 authors
  - 276 (40%) multiple publications
  - H-index 60

- *EULAR Centre of Excellence in Rheumatology 2008-2018*
- *Category 1 ENPrEMA*

Ann Rheum Dis. 2005 Arch Dis Child 2011-2012

PRINTO perspective

- **Early and repeated intervention by academia**
  - **Pre-PIP (attention to pK-dose finding)**
  - Pre-protocol finalisation
  - Prioritization (eg anti IL6-IL1 first in children)
  - Feasibility for centre identification
  - Assistance during the conduct of the trial
    - E.g. PRINTO/PRCSG as primary outcome independent certified assessors **(NEJM, Lancet editors added in the methods section)**
- (??) revision of definitive protocol by PDCO

Open problems

Viewpoint

Impact of the European paediatric legislation in paediatric rheumatology: past, present and future

Nicolino Ruperto,[1] Richard Vesely,[2] Agnes Saint-Raymond,[2] Alberto Martini,[1,3] for the Paediatric Rheumatology International Trials Organisation (PRINTO)

To cite: Ruperto N, Vesely R, Saint-Raymond A, *et al. Ann Rheum Dis* 2013;**72**:1893–1896.

- **Paradox:** too many studies too few patients
- **Me-too-drugs:** perform «just» pk-dose findings/safety open label trials
- **Biosimilars:** missing point in the legislation; perform «at least» pk-dose findings/safety open label trials
- **Study prioritisation:** not all studies are scientifically sounded→greater intervention from academia

Greater use of extrapolation

Juvenile Systemic Lupus erythematosus

- **Juvenile SLE is the same disease as adult SLE** but with different frequencies of disease manifestations (e.g. renal involvement more frequent and severe)
- **Peak around puberty in females**
- Very rare in young children or males
- Several PIP in SLE and juvenile SLE

DRUG TARGETS – PHASE 3 IN ADULTS WITH SLE

No longer	Currently under study for Registration	Currently under study but not for Registration
• Abetimus/toleragen • Ocrelizumab/ CD20 • Epratuzumab/CD22 • Rontiluzumab/ INFα • Tabalumab/ BCR • Tocilizumab, Sirukumab/ IL6	• Atacicept, Blisbimod, belimumab (LN) / BCR • Sifalumumab, anifrolumab / **Interferon alpha** • Abatacept/ **CTLA4** • Edratide (IPP-201101, Lupuzor **/ toleragen**	• Etanercept, infliximab • Rituximab • Cyclophosphamide • Steroid (stopping) • Mycophenolate • Tacrolimus • Tripterygium Wilfordii • Mizoribine

FDA approved for adults with SLE:
Hydroxychloroquine, aspirin, steroids, belimumab

Adapted from: Wallace, D. J. Nat. Rev. Rheumatol. 11, 616–620 (2015)

APC: Antigen presenting cells

Target	Cell types / pathways	Product(s)
CD19	B cell, follicular DC	XmAb®5871
CD28	T cells (costim)	TAB08, lulizumab
CD30	Activated T and B cells	Brentuximab vedotin
CD40	APC	BI 655064
CD40L (CD154)	T Helper cells	Dapirolizumab pegol (DZP0)
CD74	HLA-DR invariant chain	Milatuzumab
Chaperonin 10	Effects TLR signaling	INV103
IL 6	Pro-inflammatory cytokine	ALX-0061, PF-04236921, sirukumab
IL10	STAT 3 signaling	BT063
P40 unit of IL12/23	Block TH17 pathway	Ustekinumab
Sphingosine 1-phosphate 1 receptor	Anti- inflammatory via T cells and APC	ACT-334441, Amiselimod, Fingolimod
Ubiquitin ligase modulator	Down regulate NF-kappa beta	CC-220
Type 1 interferons	Interferon production	INF alpha kinoid (INF-K), RSVL-132
Janus Kinase	STAT 1,3,5 signaling	Fostamatinib, tofacitinib
Protease inhibition	APC function, T cell function	Nelfinavir
Estrogen receptor alpha	ERK-phosphorylation	ICI 182,780 (Faslodex)

DRUGS IN PHASE 2 STUDIES

The case: belimumab and juvenile SLE

- Pk phase II/III dedicated study dosing→
- Double-blind-placebo controlled 1 year study on top of current treatment(s)
- Trials just finished but with **great difficulties in recruitment (5 years)**
  - EULAR 2016 abstract
  - ClinicalTrials.gov Identifier: NCT01649765

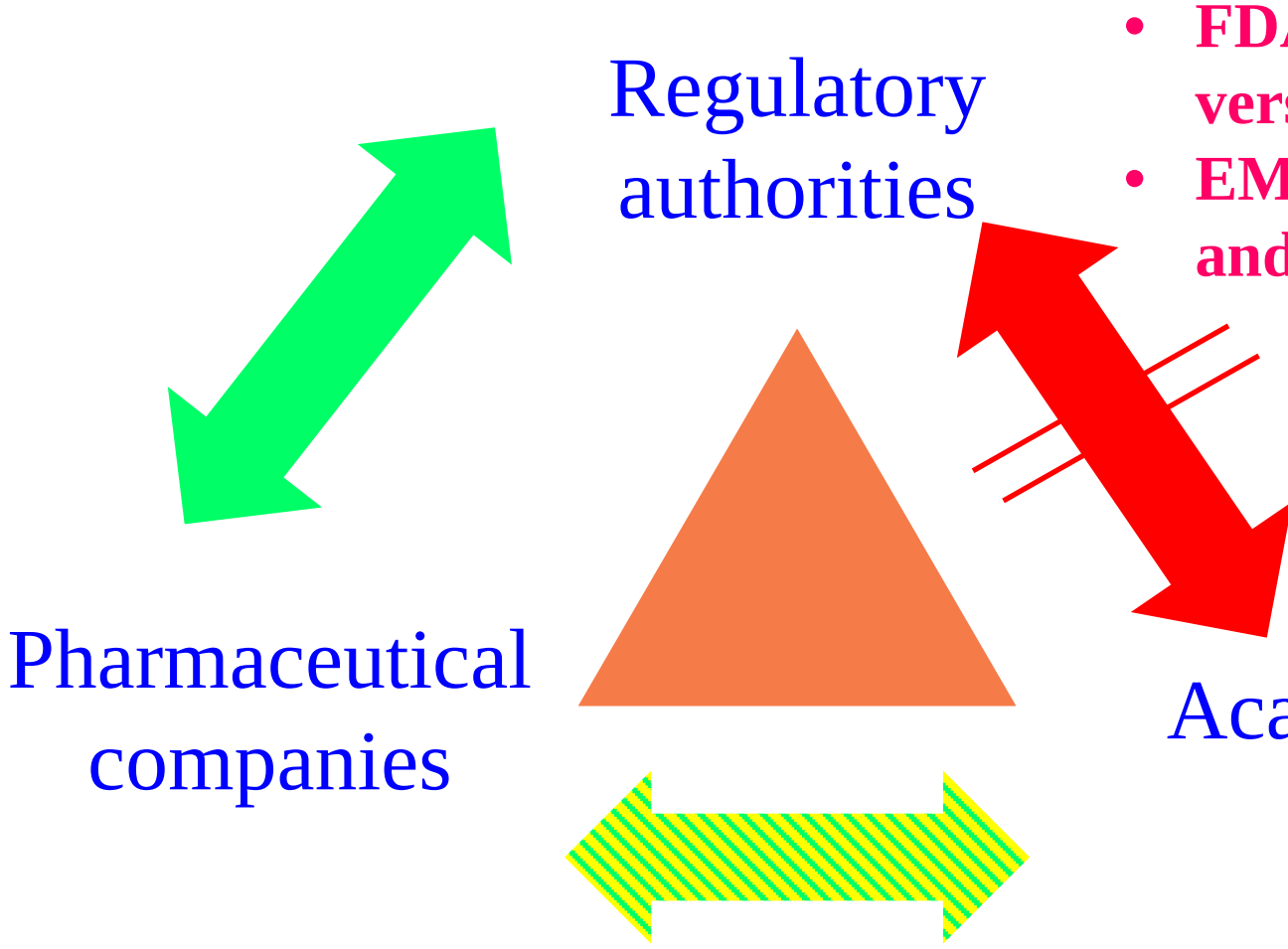
Lessons and proposal for juvenile SLE

- Given the overlapping clinical features of juvenile SLE and adult SLE and the greater incidence around puberty we proposed to companies and regulators
  - To perform **pk dose finding study** (starting from adult efficaceous and safe dose)
  - To evaluate **long term safety** in registry

Legislation appraisal
The “ethical” case

- **The case:** 35/190 children enrolled in a EMA/FDA approved clinical trial with biologic in JIA in Latin American countries.
- Drug provision stopped once drug approved for JIA.
- Most of the patients could not afford the drug (no insurance) and the disease relapsed
- **PRINTO/PRCSG ethical mandatory request:**
  - Provision of drug to patients until beneficial to child
  - Family reimbursement for travel related expenses

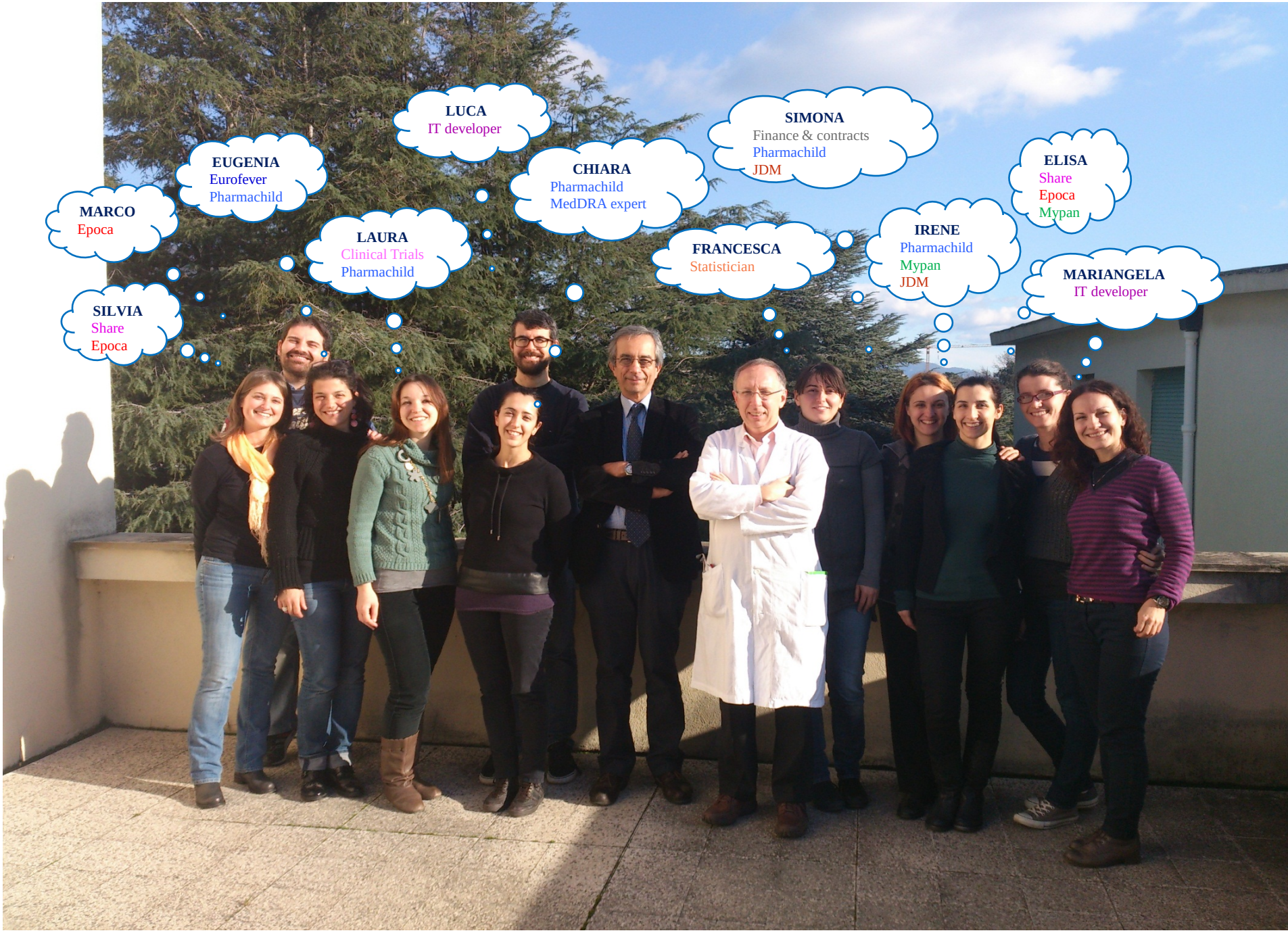
The "broken» triangle



- **FDA «moral suasion» versus companies**
- **EMA link between PIP and pharmacovigilance**

Possible proposals for directive's/regulations' revision

- Strengthen the role of academia and independent research through regulation
- Demand the provision of drugs to patients (especially children) until beneficial
- Self-maintaining mechanism for academic independent research through large scale patient's registries
- Provision for pharmacovigilance, «me-too», biosimilar, similar disease (JSLE)→extrapolation


LUCA
IT developer
EUGENIA
Eurofever
Pharmachild
CHIARA
Pharmachild
MedDRA expert
SIMONA
Finance & contracts
Pharmachild
JDM
ELISA
Share
Epoca
Mypan
MARCO
Epoca
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FRANCESCA
Statistician
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