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

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Outline

- PRINTO outline
- Scientific expertise and specialty level needed to design scientifically-sounded paediatric trials and research

Paediatric Rheumatic Diseases (PRD)

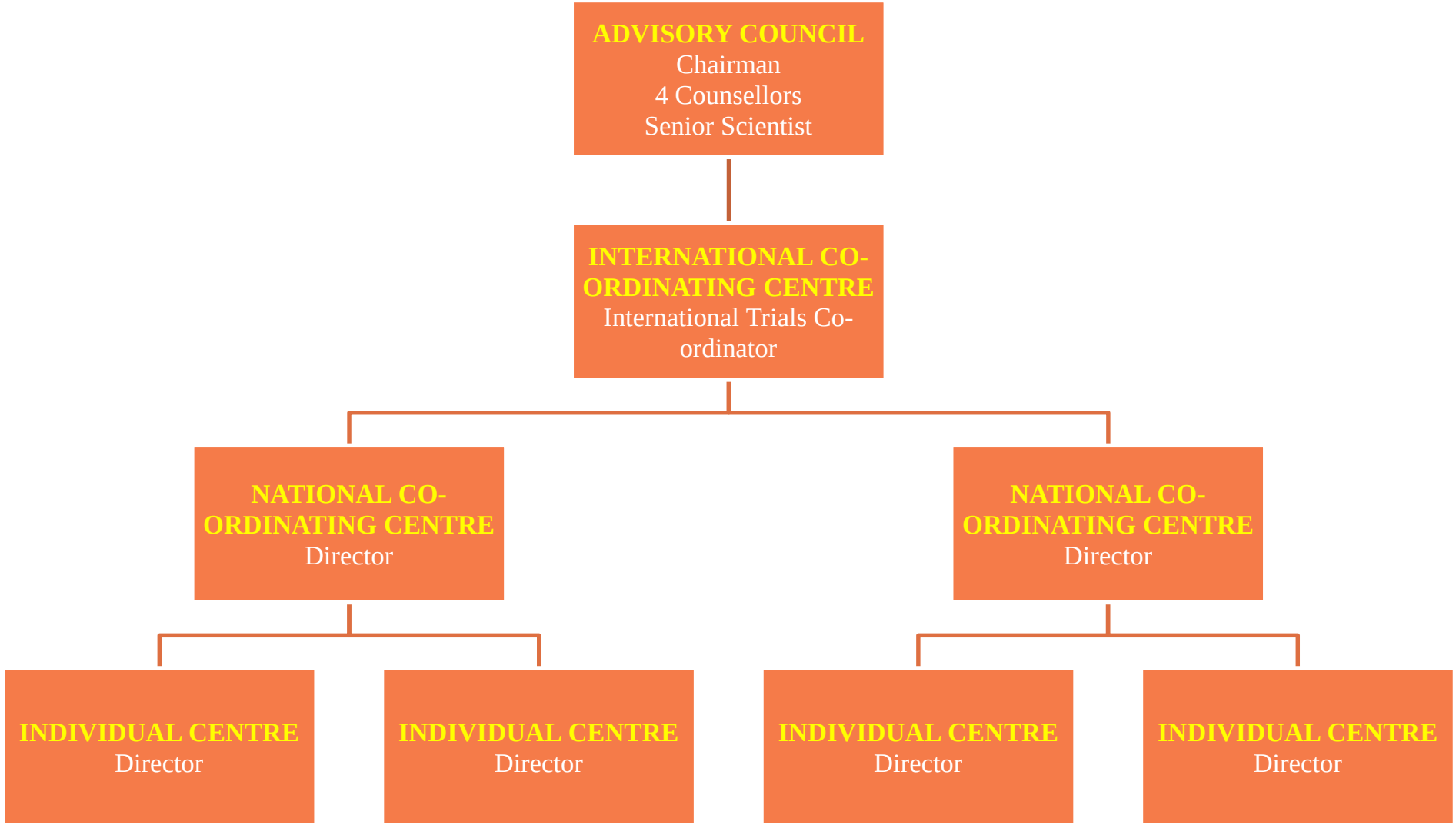
- PRD are rare diseases and the most common chronic illnessess in childhood
- PRD are highly debilitating and potentially affecting the entire life
- The most common diseases are
  - **Juvenile Idiopathic Arthitis (JIA)**
  - Juvenile Systemic Lupus Erythematosus (JSLE)
  - Juvenile Dermatomyositis (JDM)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

www.printo.it (> 60 countries)

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

PRINTO bylaws 1996

PRINTO Organisation Chart



PRINTO bottom up approach

- **Standardized criteria to evaluate response to therapy in JIA, JSLE and JDM**
  - ACR pediatric criteria in JIA (FDA, EMA
- Standardised web information to families
- Non for profit clinical trials (JIA, JDM, JSLE)
- Training to young researchers
- Liaisons with pharmaceutical industries
- Main source of funding European Union, AIFA, pharmaceutical companies

PRINTO not-for-profit studies (>36,000 pts)

	West Europe	East Europa	Latin America	North America	Others	Totals
MTX1	492	55	66	8	12	**633**
HRQOL	3,988	1,388	903		365	**6644**
JSLE	247	102	150	37	21	**557**
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MAS	519	99	74	148	271	**1111**
Pharmachild	4820	2377	515		333	**8045**

PRINTO publications

- 130 PRINTO manuscripts

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

Open questions

- Is there a role for academia for drug approval?
- Which are the problems encountered by academia?
  - **The case** of the MTX paradox for JIA and Regulation (EC) no 1901/2006 (pediatric legislation)
  - **The case** of the PRINTO JDM standard of care trial and the Clinical Trial Directive 2001/20/EC
  - **The case** of the ethical provision of drugs to chronically ill children especially from developing countries
  - **The issue** of funding for independent research

The paradox of Methotrexate

- Mainstream for treatment, proven efficacy and safety
  - NEJM 1992, Arthritis Rheum 2005, PRINTO Arthritis Rheum 2005-JAMA 2010
- Used in combination in several biologic agents trials (infliximab, adalimumab, abatacept, etc)
- No interest from companies (off patent, low cost)
- **It was not approved for use in JIA in many countries**
- **JIA pts treated with biologics required to fail MTX!**
- Now MTX finally approved by mutual recognition in many EU countries

Open questions

- Is there a role for academia for drug approval?
- Where are the paediatric centres?

www.pediatric-rheumatology.printo.it

edscape.com/

2016 new version

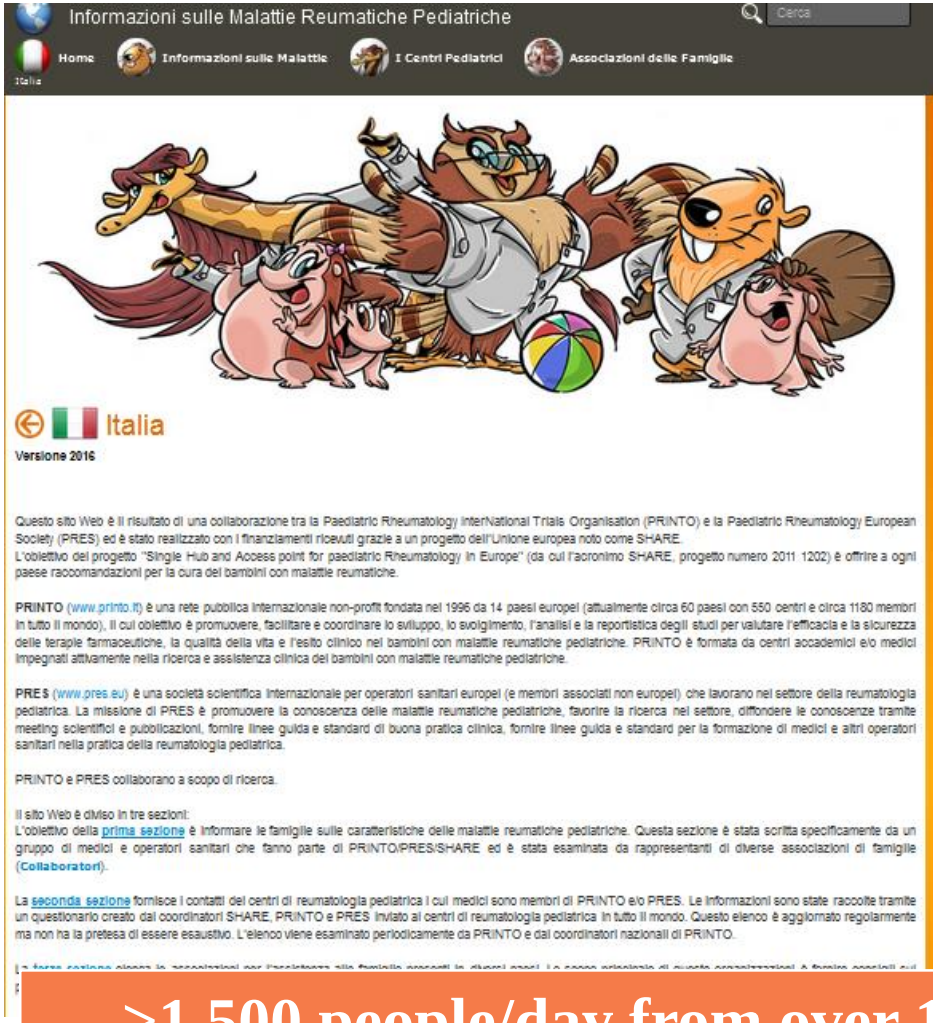
attel.medsch.ucla.edu/

relandclinic.org/

>1.500 people/day from over 130 countries

Ruperto Annals Rheum Dis. 2005

www.pediatric-rheumatology.printo.it



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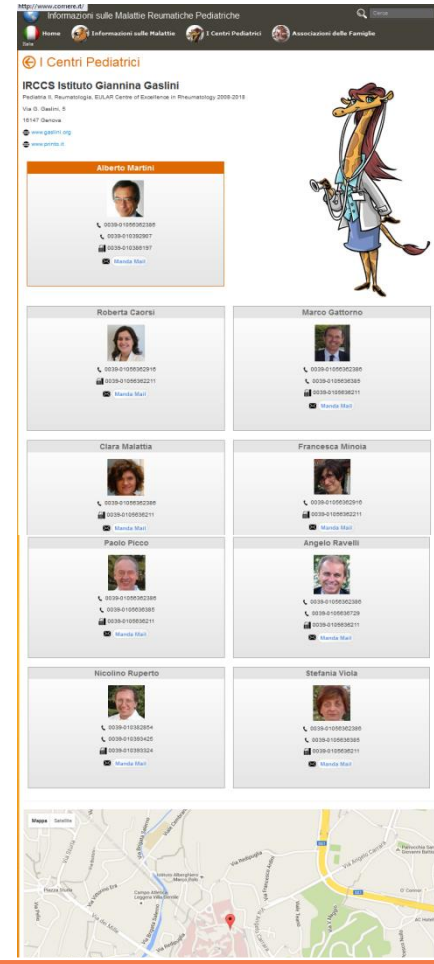
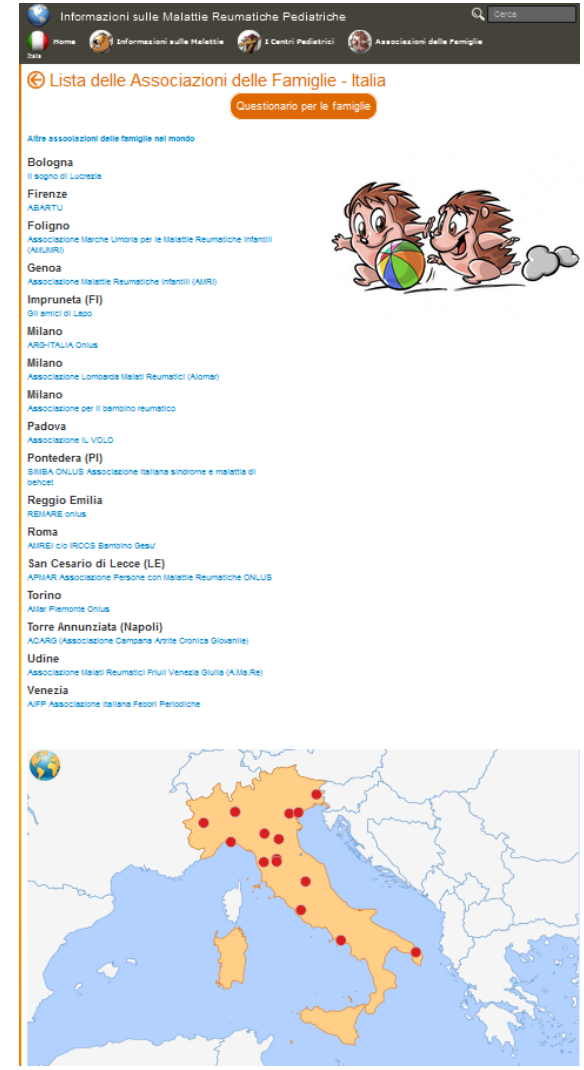




>1.500 people/day from over 130 countries

Open questions

- Is there a role for academia for drug approval?
- Where are the paediatric centres?
- Do we need standardised clinical trial training?

PRINTO research training

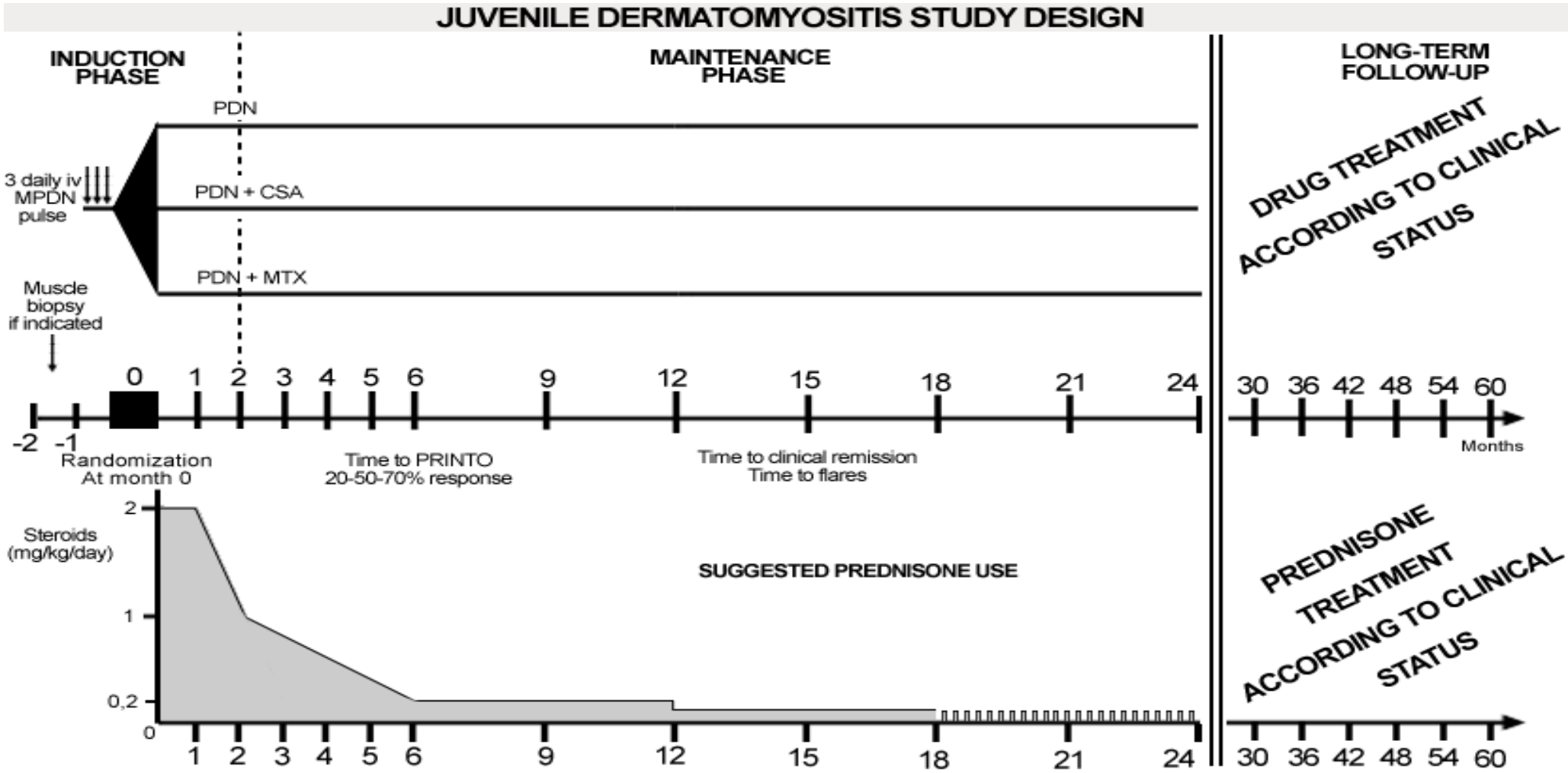
- Fellowships (1-12 months)
  - > 150 physicians from 24 countries
  - Funding: EU, EULAR, Government, self-financing
  - International PhD on-going

- PRINTO joint assessor certificate (required by FDA for clinical trials)

Open questions

- Is there a role for academia for drug approval?
- Where are the paediatric centres?
- Do we need standardised clinical trial training?
- Can we simplify ethics committee rules (at least for academic paediatric studies)?

The “standard of care” PRINTO JDM trial



Ruperto et al for PRINTO. **Lancet** 2015

Ethics evaluation or ethics bureaucracy?

Editorial

Ethics bureaucracy: a significant hurdle for collaborative follow-up of drug effectiveness in rare childhood diseases

Mats G Hansson,[1] Marco Gattorno,[2] Joanna Stjernschantz Forsberg,[1] Nils Feltelius,[3,4] Alberto Martini,[2] Nicolino Ruperto[2]

years performing phase II and III trials with biologic agents in juvenile idiopathic arthritis which eventually have been approved by regulatory authorities as well as other clinical studies regarding the more common paediatric rheumatic diseases.[9 10] Up to now PRINTO has gathered health information on more than 12 000 paediatric patients from over 40 countries.

Despite major improvements observed in the treatment of rare paediatric rheumatology disorders and the availability of a large network such as PRINTO a number of unsolved issues remain. These are listed below:

► the capacity of drugs to prevent the

Arch Dis Child June 2012 Vol 97 No 6

- In the new rules no specific provision for pediatric studies especially if run by academia

2000: a radical change

- 1999 FDA “pediatric rule”
- 2007 EMA and EU parliament: pediatric legislation
  - Mandatory to companies Pediatric Investigation Plan (PIP)
- **Pediatric networks**
  - PRCSG: USA
  - PRINTO: Europe and ROW (>60 countries)
- **PRINTO/PRCSG** response to therapy standardisation
- **Introduction of biologic agents**

Open questions

- Is there a role for academia for drug approval?
- Where are the paediatric centres?
- Do we need standardised clinical trial training?
- Can we simplify ethics committee rule (at least for academic paediatric studies)?
- Is there a role for an “academic” CRO?
- Opportunities/weakness of the pediatric legislation

Liaisons with pharma companies

- **Scientific collaboration:**
  - **PIP/Protocol/CRF drafting, feasibility for site selection,** training, **PRINTO/PRCSG primary outcome evaluation,** monitoring, analysis, reporting
- Clinical trials:
  - NSAIDs: meloxicam, rofecoxib
  - Biologic agents:
    - **Approved: etanercept, adalimumab, abatacept, tocilizumab, canakinumab**
    - On-going: certolizumab, belimumab, JAK3.
    - Not approved: infliximab, golimuma (??)
- **Starting point:** FDA, EU pediatric legislation

Drug development/PIP/PRINTO

PRINTO collaboration with pharmaceutical companies

PRINTO academic pharmacovigilance pharmachild

Phase I

Phase II

Phase III

Phase IV and post-marketing

PIP Submission

No specific pediatric requests by the legislation

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

An appraisal of the legislation

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.

PRINTO-PRCSG Enrollment (N~3000)

	West Europe	East Europa	Latin America	North America	Others	Totals
Etanercept				69		69
Etanercept	43	75	5		4	127
Infliximab	62	10	28	23		123
Adalimumab						171
Abatacept iv						190
Abatacept sc						207
Tocilizumab syst						112
Tocilizumab poly						188
Canakinumab PII						23
Canakinumab P III						190
Golimumab						173
Meloxicam						226
Adalimumab regi	274	60	3	303	9	849
Tofacitinib	10	7				17
Rilonacept	134	35	82	69	7	327

Primary data outcome evaluation independently performed by PRINTO/PRCSG and directly transferred to companies (database audited)

The issue of the «me-too drugs» (e.g. anti-TNF)

	West	East	Latin	North America	Total
Etanercept				69	**127**
Infliximab				11	**123**
Adalimumab				88	**171**
Abatacept				31	**214**
Tocilizumab 1				24	**112**
Tocilizumab 2				24	**188**
Canakinumab 1					**23**
Canakinumab 2-3				19	**190**
Golimumab	69	46	30	28	**173**
Certolizumab pegol			On going		

PRINTO/PRCSG proposal to perform «just» pK-dose finding/safety open label trials

The issue of the biosimilars (e.g. anti-TNF)

	West Europe	East Europe	Latin America	North America	Total
Etanercept				69	**127**
Infliximab				11	**123**
Adalimumab				88	**171**
Abatacept				31	**214**
Tocilizumab 1				24	**112**
Tocilizumab 2				24	**188**
Canakinumab 1					**23**
Canakinumab 2-3				19	**190**
Golimumab				28	**173**
Certolizumab pego					
Biosimilar anti-TN					
Biosimilar anti-TNF2					
Biosimilar anti-TNF3					

PRINTO/PRCSG proposal to perform «at least» pK-dose finding/safety open label trials

NO PROVISION FOR PAEDIATRICS

even for pK-dose finding studies

Are all studies needed or scientifically sounded?

- **Study 1:** strategies to limit/prevent safety events
- **Study 2:** graduated syringes to eliminate/reduce dosing error in children
  - Good questions but….agreed sample size 15-20 patients!
- **Study 3:** a proper formulation for little children
  - US: fixed dose regiment (half of the adult dose)
  - EU: initial marketing just for children > 12 years
- **Study 4:** adult dose to treat children
  - Study negative drug not registered for use in children but legislation requirements fullfilled

Other open questions

- Do we need all these «unsufficient and unsounded studies»?
- Do we have «just» to replicate in children what is useful in adults
- Could/should academia intervene on the choice of the PDCO approved list of studies for pharmaceutical companies?

Open questions

- Is there a role for academia for drug approval?
- Where are the paediatric centres?
- Do we need standardised clinical trial training?
- Can we simplify ethics committee rule (at least for academic paediatric studies)?
- Is there a role for an “academic” CRO?
- Opportunities/weakness of the pediatric legislation
- Ethics and other provisions?

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 and the disease relapsed
- **PRINTO/PRCSG ethical mandatory request:**
  - Provision of drug to patients until beneficial to child
  - Family reimbursement for travel related expenses

Other provisions

- Feasibilities for centre identifications through recognised networks:
  - European Network of Paediatric Research at the EMA (ENPr-EMA) Ruperto et al. Arch Dis Child 2012
- Central network contract negotiation (e.g. minimum per patient fee for all participating countries)
- Authorship for collaborative publication (122 papers with ~550 co-authors)
- The use of registries and link with pharma companies

The issue of public funding

- 3 millions € in public grants from 1998
  - PRINTO as support for academic research with reinvestement of funding coming from pharmaceutical industries

- CARRA (North American network) 33 millioni $ in 2 years!

Open questions

- Is there a role for academia for drug approval?
- Where are the paediatric centres?
- Do we need standardised clinical trial training?
- Can we simplify ethics committee rule (at least for academic paediatric studies)?
- Is there a role for an “academic” CRO?
- Opportunities/weakness of the pediatric legislation
- Ethics and other provisions?

Possible proposals for directive's/regulations' revision

- Strengthen the role of academia and independent research through regulation
- Simplify the ethics approval in **paediatrics** in conjunction with the clinical trial 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

PHARMAChild

Pharmacovigilance in juvenile idiopathic arthritis patients (Pharmachild) treated with

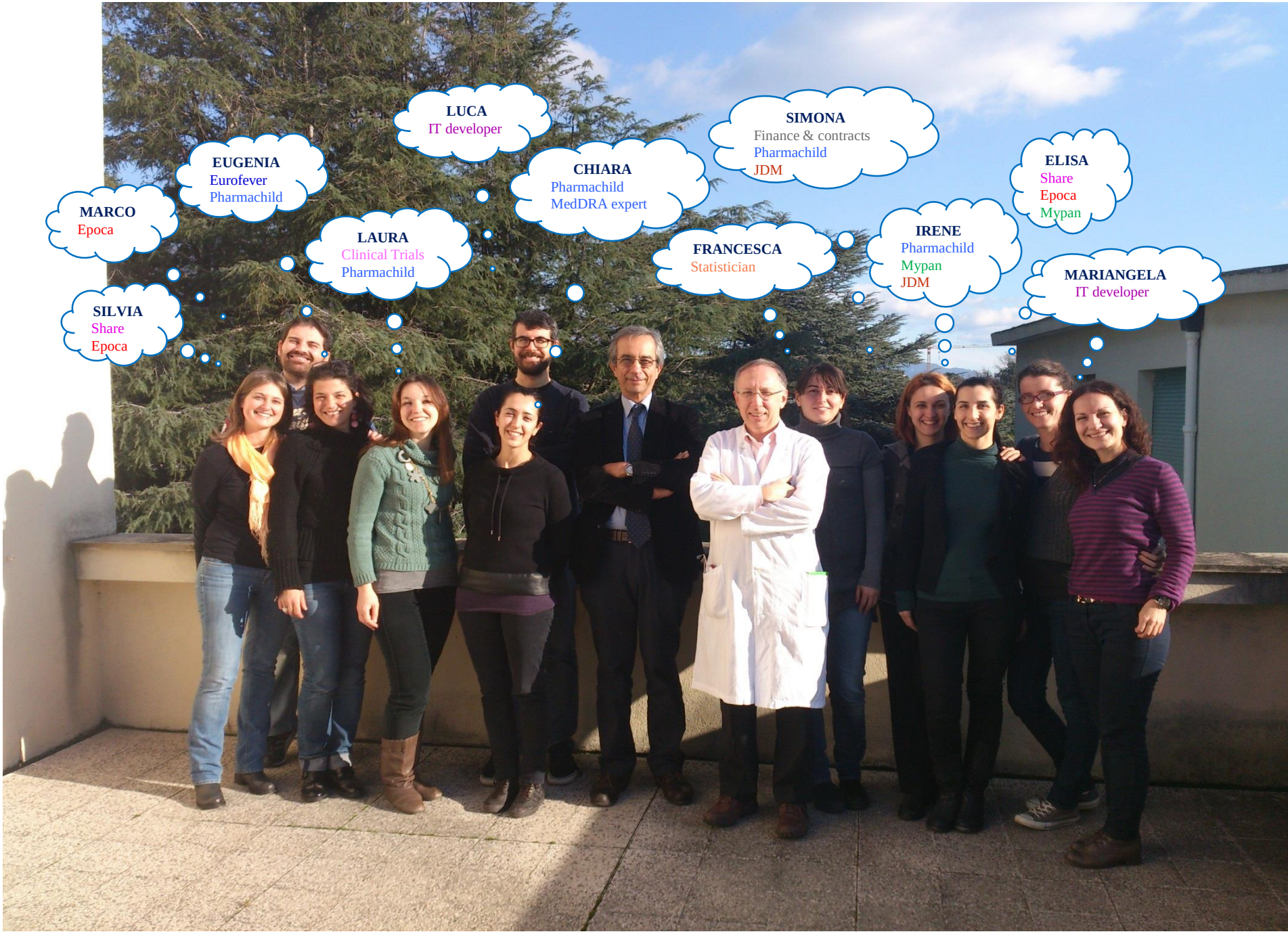
Study 5: pharmacovigilance study funded by EU.

Agreement with one company.

No mandatory request to for pediatric safety studies

9,536 patients enrolled in the retrospective/prospective part

(6171 retro 3365 retro+prosp)


LUCA
IT developer
SIMONA
Finance & contracts
Pharmachild
JDM
EUGENIA
Eurofever
Pharmachild
CHIARA
Pharmachild
MedDRA expert
ELISA
Share
Epoca
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Clinical Trials
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FRANCESCA
Statistician
IRENE
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- Back up

Patient Registries Workshop questions

- Identify the challenges faced by registries and industry when collaborating;
- Understand the **technical challenges** presented by disparate datasets;
- Identify **concrete solutions** to better facilitate relations to avoid duplication.

Academia and industry challenges

- Identify the challenges faced by registries and industry when collaborating;
  - Public support (e.g. Pharmachild)
  - **Private support (e.g. Pharmachild/abatacept but with PRINTO data property as per ENCEPP)**
    - Pharmachild platform accepted by industries (and potentially suggested by regulatory bodies)
  - Interaction of academia with regulatory authorities directly or indirectly (via companies)

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- Data Property of academia (PRINTO as per ENCEPP) with total academic independence
- Pharmachild platform used for regulatory purposes
- Funding
  - directly to centres (central negotiation PRINTO/Company)
  - Funding to PRINTO reinvested for the overall management of the registry (all drugs reported)

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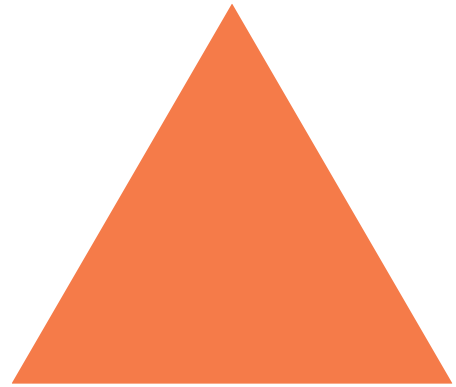
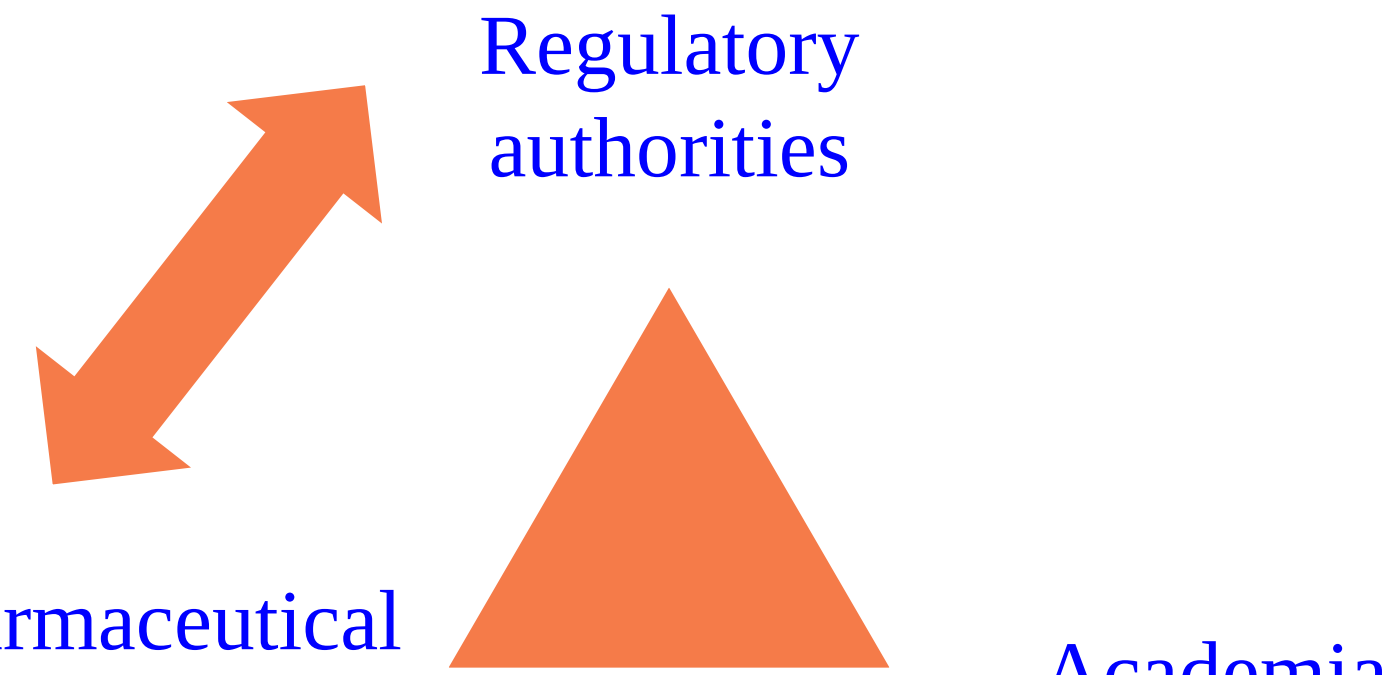
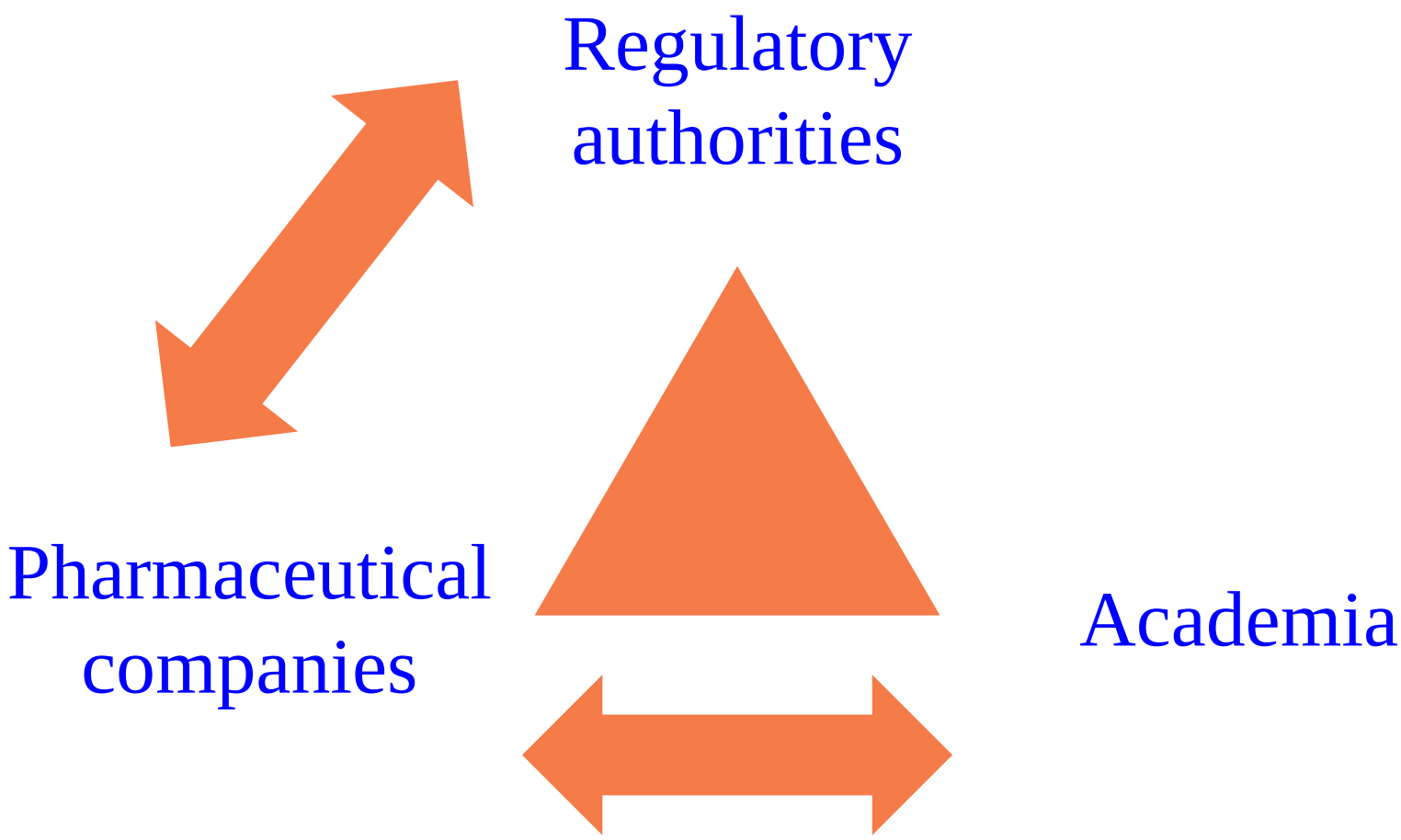
Regulatory authorities



Pharmaceutical companies

Academia


Regulatory authorities
Pharmaceutical companies
Academia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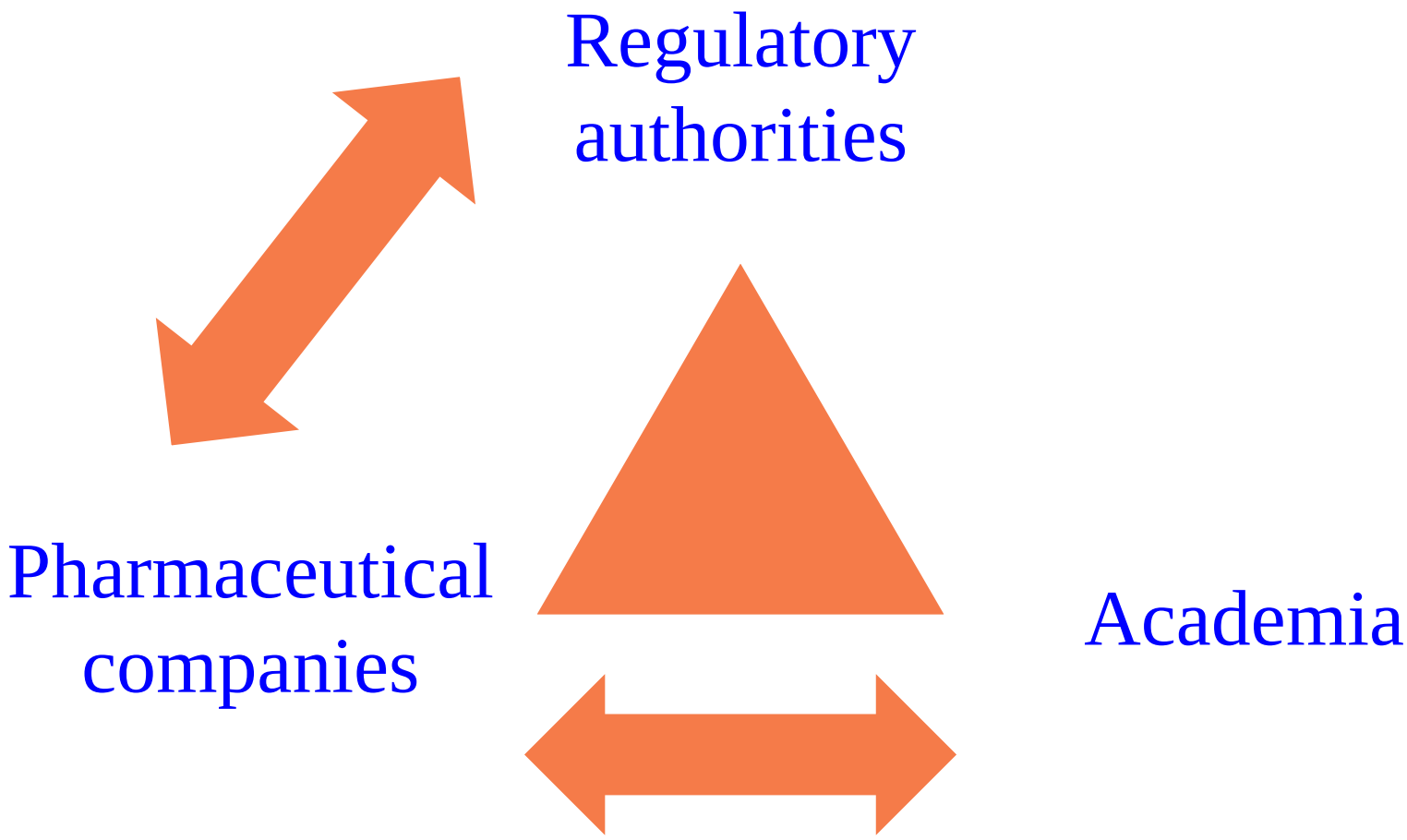
The "broken» triangle



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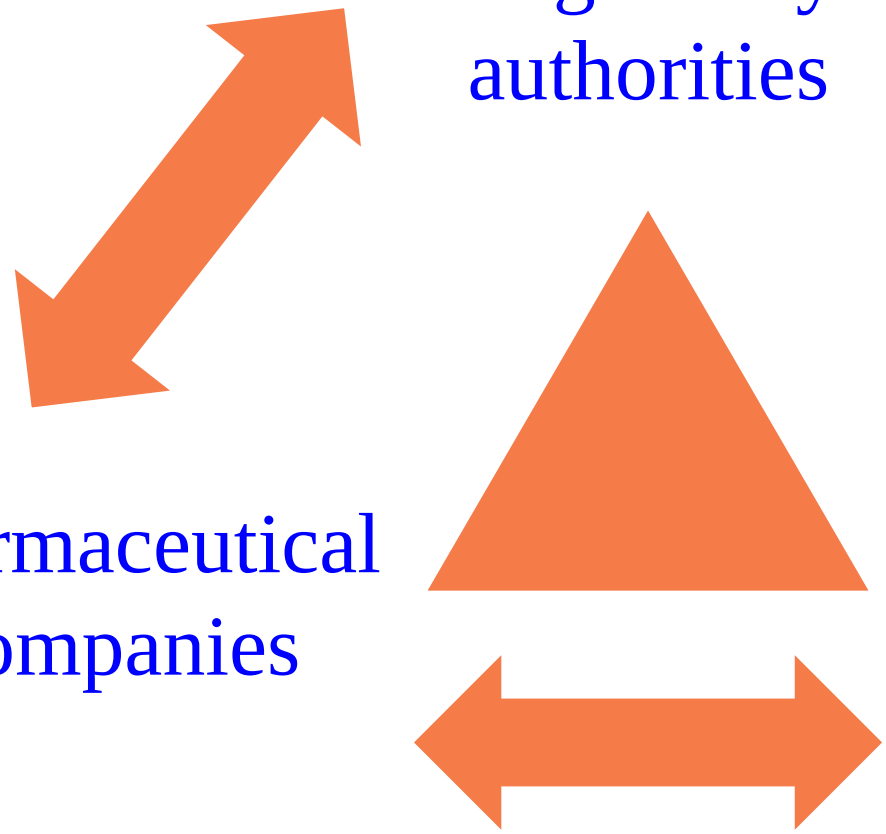


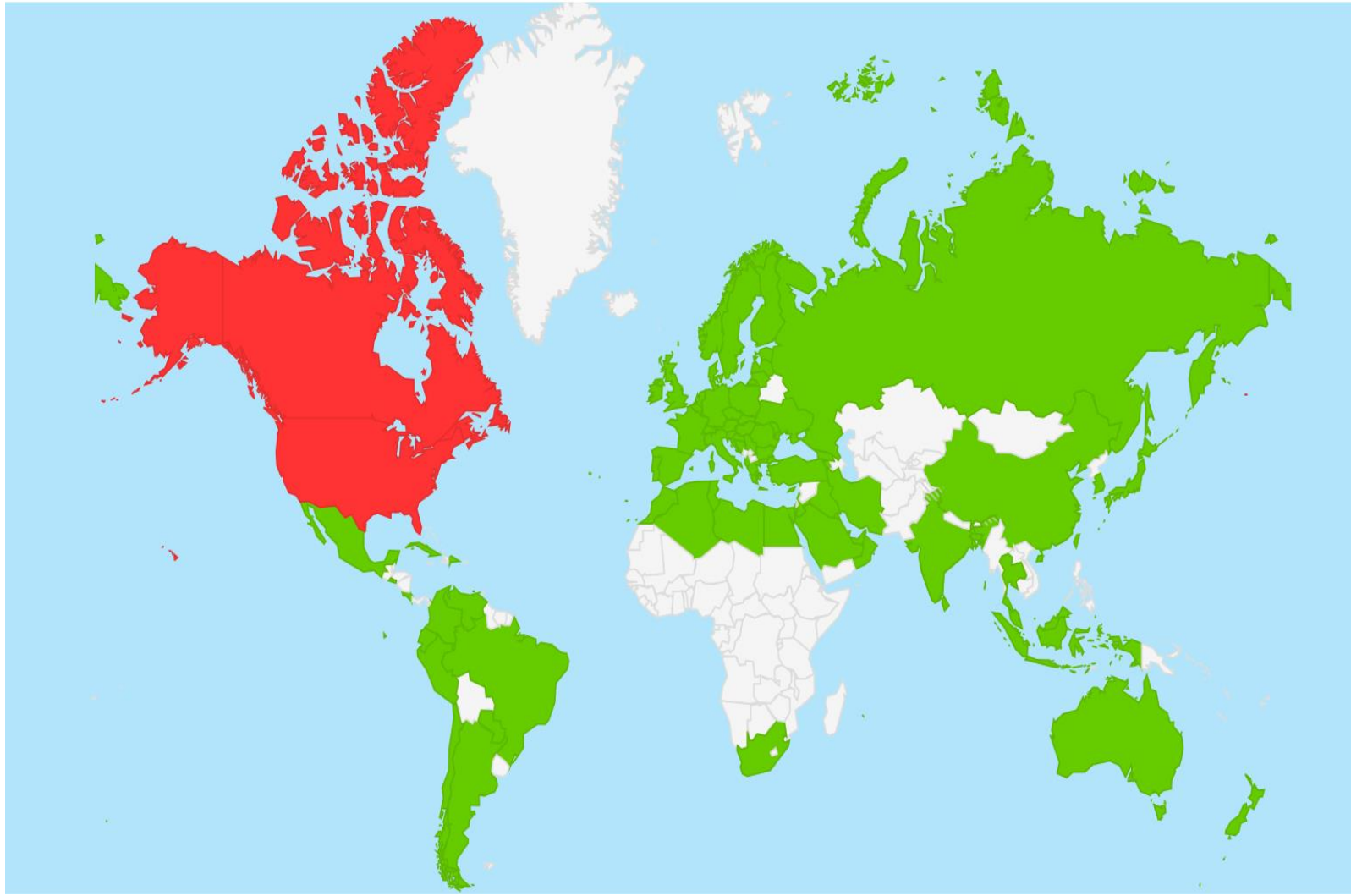
- **FDA «moral suasion» versus companies**
- **EMA link between PIP and pharmacovigilance**

Technical challenges

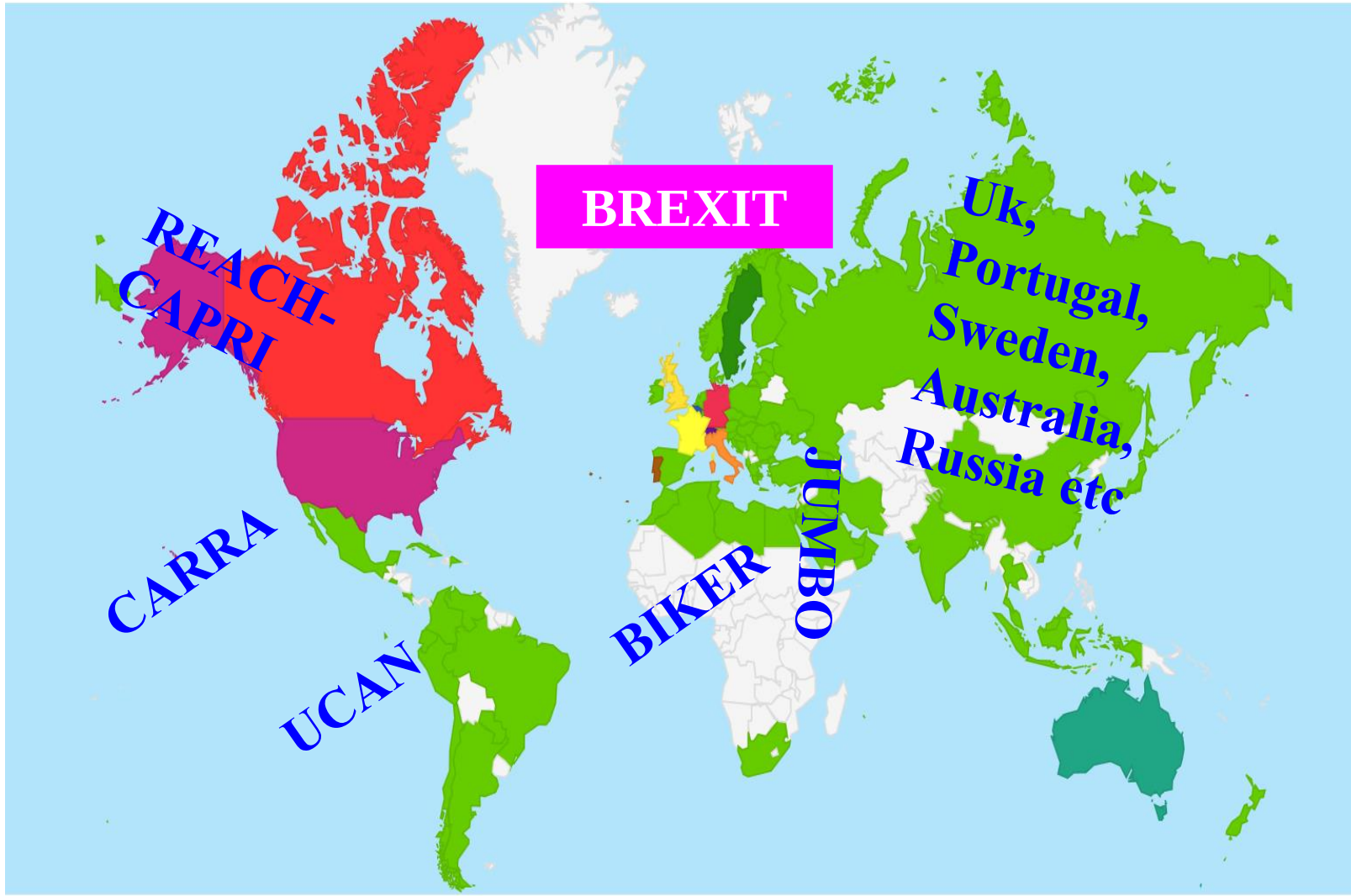
- Understand the technical challenges presented by disparate datasets;
  - Web platform health professionals/parents userfriendly with return
  - Combine national data (or avoid national data at least in pediatrics)

1996: PRINTO start

1996-2016: collaboration



National initiatives



How to combine data from different sources?

- Problems
  - Different data fields
  - Different data dictionaries
  - **Missing data**
- Possible solution
  - Combine the results for manuscripts, reports etc

How to combine data from different sources?

	Pharmachild N = 4959*	NR England N = 1537	NR Germany N = 3139#	NR Portugal N = 112	NR Swiss N = 632	TOTAL N =10379
Gender						
Female	3287 (66.3)	1041 (67.7)	2117/3136 (67.5)	70 (62.5)	421 (66.6)	6936/10376 (66.9)
Diagnosis:		N = 1510				N=10352
Systemic	604 (12.2)	199 (13.2)	202 (6.4)	14 (12.5)	84 (13.3)	1103 (10.7)
Oligoarticular	1792 (36.1)	399 (26.4)	1011 (32.2)	31 (27.7)	198 (31.3)	3431 (33.1)
Polyarticular RF-	1342 (27.1)	506 (33.5)	944 (30.1)	26 (23.2)	160 (25.3)	2978 (28.8)
Polyarticular RF+	177 (3.6)	140 (9.3)	199 (6.3)	21 (18.8)	15 (2.4)	552 (5.3)
Psoriatic	185 (3.7)	98 (6.5)	244 (7.8)	3 (2.7)	34 (5.4)	564 (5.5)
Enthesitis	607 (12.2)	100 (6.6)	438 (14.0)	17 (15.2)	124 (19.6)	1286 (12.4)
Undifferentiated	252 (5.1)	68 (4.5)	101 (3.2)	0 (0.0)	17 (2.7)	438 (4.2)
Age at onset	5.4 (2.4-10.0)	NA	7.2 (3.1-11.4) N=3094	6.3 (2.5-10.9)	NA	
Age at JIA Diagnosis	6.2 (2.8-11.0) N=4800	5.5 (2.1-10.2) N=1495	8.2 (4.0-12.3) N=2067	7.3 (3.3-12.3)	NA	
Disease duration at the last available follow up	4.9 (2.5-8.2)	5.4 (2.7 – 8.8) N=1383	5.2 (3.1-8.4) N=3090	3.0 (0.5-9.6)	NA	
Therapy:	N=4336	N=1537**	N=3134	N=112	N=567	N=9686
MTX only	1220 (28.1)	503 (32.7)	1132 (36.1)	0 (0.0)	36 (5.7)	2891 (29.9)
Only one Biologic Drug	181 (4.2)	307 (20.0)	104 (3.3)	1 (0.9)	127 (20.1)	1447 (14.9)
Only one Biologic Drug + MTX	2109 (48.6)	586 (38.1)	1545 (49.2)	27 (24.1)	286 (45.3)	3967 (41.0)
More than one Biologic	29 (0.7)	22 (1.4)	13 (0.4)	6 (5.4)	31 (4.9)	79 (0.8)
More than one Biologic + MTX	797 (18.4)	116 (7.5)	340 (10.8)	78 (69.6)	87 (13.8)	1302 (13.4)
Nr. patients with ESI or AE	942 (19.0)	1093 (71.1)	1163(37.1)	27 (24.1)	NA	3225 (31.1)
Nr. patients with ESI	446 (9.0)	230 (15.0)	249 (7.9)	5 (4.5)	NA	930 (9.0)
Nr. patients with AE	635 (12.8)	1075 (69.9)	1069 (34.1)	24 (21.4)	NA	2803 (27.0)

Possible solutions

- Identify concrete solutions to better facilitate relations to avoid duplication
  - Parternshipt academia/industries/regulators
  - «Provide advantages» to health professionals/families
  - Combine results from different sources

  - **Scientific reputation (authorship involvement)**
    - 130 manuscripts with 685 authors (40% on multiple publications)

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