
A pharmacovigilance project in Juvenile Idiopathic Arthritis (JIA): Pharmachild The PRINTo perspective

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Outline

- ◆ PRINTo brief introduction
- ◆ Juvenile idiopathic arthritis (JIA) and safety
- ◆ The Pharmachild project
- ◆ Methodological challenges



www.printo.it (> 60 countries)

The screenshot shows the PRINTO website interface. At the top is the PRINTO logo and name. Below it is a 'SITE MENU' with links to 'ABOUT PRINTO', 'RESEARCH PROJECTS', 'PUBLICATIONS', and 'CONTACT'. A 'MEMBER AREA' section includes a login form with fields for 'User ID' and 'Password', and a 'validate' button. A 'NEWS' section titled 'IN THE SPOTLIGHT' contains two articles: '16 AUG 2005 A new version of the website is online' and '16 AUG 2005 The survey about the JSL and JDM trials is online'. At the bottom, there is a photograph of a group of people outdoors and a copyright notice: 'Copyright PRINTO IRCCS Istituto G. Gaslini Pediatria II Largo Gaslini, 5 16147 Genova, Italy'.

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

PRINTO bylaws 1996



A large banner for PRINTO. At the top left is the PRINTO logo. To its right is the text 'SUPPORTED BY THE EUROPEAN UNION' with the European Union flag. Further right is the 'PRS paediatric rheumatology european society' logo. The main part of the banner displays a grid of flags from various countries, including Argentina, Australia, Belgium, Brazil, Bulgaria, Chile, China, Costa Rica, Cuba, Czech R., Denmark, Deutschland, Egypt, España, France, Germany, Greece, Hrvatska, India, Iran, Ireland, Israel, Italia, Japan, Latvia, Lithuania, Luxembourg, Magyarország, México, Nederland, Norge, Österreich, Polska, Portugal, Россия, المملكة العربية السعودية, Shqipëri, Singapore, Slovenija, Slovensko, Srbija i Crna Gora, Suomi, Sverige, Switzerland, تونس, Türkiye, and UK. Below the flags, there is a section titled 'Information on paediatric rheumatic diseases' with an image of three children running. At the bottom, it says 'To be listed on this website please download the SURVEY' and 'For any paediatric rheumatic disease...'. A large text overlay at the bottom right reads '>11,000 people/day'.



PRINTO not-for-profit studies (~30,000 pts)

	Western Europe	Eastern Europe	Latin America	North America	Other	Total
MTX1	492	55	66	8	12	633
HRQOL	3,988	1,388	903		365	6,644
JSLE	243	102	150	37	21	553
JDM	162	37	78	18	3	298
Cyclosporine	203	27	25	85	4	344
MTX2	180	80	90		10	360
Vasculitis	599	353	260	6	181	1,399
JDM	98	13	15	1	2	139
Eurofever	1952	590	48	6	240	2,836
EPOCA	3535	2504	968	220	1477	8,704
MAS	520	225	72	152	142	1,111
Pharmachild	3538	2538	418		84	6,762

The success of the EU pediatric legislation

Regulation (EC) no 1901/2006 (1080 pts)



	West Europe	East Europe	Latin America	North America	Total
Etanercept				69	69
Infliximab	61	10	28	11	110
Adalimumab	57	26		88	171
Abatacept	75		108	31	214
Tocilizumab	59	7	22	24	112
Tocilizumab	54	50	60	24	188
Canakinumab	26				26
Canakinumab	141	13	17	19	190

JIA definition

- ◆ Arthritis with
 - Onset before the age of 16
 - Unknown etiology
 - Persistent for at least 6 weeks
- ◆ Reported prevalence of 86.1-94 per 100,000 children
- ◆ Classification criteria
 - 1977-78: juvenile reumathoid arthritis (USA), juvenile chronic arthritis (Europe)
 - **1997 juvenile idiopathic arthritis (JIA)**

The anti-TNF hidden problem

- ◆ **2008 FDA black box warning:** a possible increased risk of lymphoma and other malignancies in children treated with anti-TNF agents.
 - 9 cases in registries (mainly lymphomas)
 - FDA Post-marketing 48 pediatric malignancies (**20 in JIA**, 28 in IBD), after a median of **2.5 years** (range 1 month-7 years), **50% lymphomas**, most while using **other drugs** (steroids, azathioprine, MTX, mercaptopurine)



Anti TNF and Malignancies

Juvenile Idiopathic Arthritis and Risk of Cancer

A Nationwide Cohort Study

J. F. Simard,¹ M. Neovius,¹ S. Hagelberg,² and J. Askling³

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Arthritis & Rheumatism

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www.arthritisrheum.org and www.interscience.wiley.com

EDITORIAL

Should the Food and Drug Administration Warning of Malignancy in Children Receiving Tumor Necrosis Factor α Blockers Change the Way We Treat Children With Juvenile Idiopathic Arthritis?

Malignancies in Juvenile Idiopathic Arthritis: A Preliminary Report

SASHA BERNATSKY, ALAN M. ROSENBERG, KIEM G. OEN, CIARAN M. DUFFY, ROSALIND RAMSEY-GOLDMAN, JEREMY LABRECQUE, YVAN ST. PIERRE, and ANN E. CLARKE
(J Rheum 2011; 28:1007-1011)
First Release Jan 15 2011; doi:10.3899/jrheum.100711

Tumor Necrosis Factor α Blockers and Malignancies: Forty-Eight Cases Reported

Hagelberg, Lois La

U.S. Department of Health and Human Services
www.hhs.gov

FDA U.S. Food and Drug Administration
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Drugs
Home > Drugs > Drug Safety and Availability > Postmarket Drug Safety Information for Patients and Providers

Drug Safety and Availability
Postmarket Drug Safety Information for Patients and Providers
Drug Safety Information

Early Communication About an Ongoing Safety Review of Tumor Necrosis Factor (TNF) Blockers (marketed as Remicade, Enbrel, Humira, and Cimzia)

JIA and Malignancies considerations

- ◆ the effect of biological therapies on cancer risk in JIA is controversial owing to confounding factors such as the use of concomitant immunosuppressants
- ◆ Questions still remain on the effect of the disease itself and biological therapies on cancer risk.
- ◆ A rigorous pharmacovigilance system with a very large sample size and an adequate follow-up period

Pharmachild registry question

- ◆ Are current available **drugs (biologics±MTX)** able, in the long run, to achieve
 - clinical remission
 - prevent/stop joint erosions development over time while
 - **maintaining an acceptable safety profile?**
- FP7 funding 4/2011-3/2014 (**PI Dr Nico Wulffraat**)
- **ENCEPP sealing:** 25 November 2011
- NCT number: NCT 01399281

Study design: retrospective

RETROSPECTIVE DATA COLLECTION OF ANONYMOUS JIA PATIENTS

Step 1: Census

data collection of limited key elements (e.g. initials, JIA subtype, drug treatment) of all JIA patients followed at each centre.

This step will include individual PRINTO/PRES centres and existing national/international registries

Step 2: one time safety anonymous data collection (written consent only if required by local ethics committee)

Study design: prospective

PROSPECTIVE DATA COLLECTION OF CONSENTING JIA PATIENTS

Longitudinal (up to 3-10 years and more) collection of safety/efficacy data of

- 1) inception cohort of newly treated children (biologic agents \pm MTX) after consent
- 2) patients from the retrospective cohort who will sign consent/assent

IMPORTANT for Group 2 enrollment in the prospective cohort will allow validation of the retrospective chart review

Choice of the control group

1. JIA treated with MTX alone
2. JIA treated with a combination of **MTX ±** **biologicals**/other drugs
3. JIA treated with **biologicals only**
4. (JIA treated only with NSAIDs and/or steroid injection with at least 3 years follow-up).

Safety

- ◆ Events of Special Interest (**ESI**)
- ◆ Other moderate/severe/serious adverse events (**AE**)) as per the MedDRA dictionary
 - Mild events excluded

Events of special interests (ESI)

The following adverse events have been classified as being of special interest (ESI) for the Pharmachild study:

1. Aplastic anemia	14. Lupus erythematosus systemic/lupus-like syndrome
2. Neutropenia	15. Lymphomas
3. Pancytopenia	16. Leukaemias
4. Congestive heart failure	17. Haematopoietic neoplasms (excl leukaemias and lymphomas)
5. Gastrointestinal ulcer/bleed/perforation	18. Macrophage activation syndrome
8. Inflammatory Bowel Disease (IBD)	19. Neoplasm (other)
9. Tuberculosis	20. Demyelination
10. Serious/targeted infections	21. Optic neuritis
11. Other autoimmune diseases	22. Multiple sclerosis
12. Infusion-related reaction	23. Pregnancy
13. Injection related reaction	

Status as of April 2014

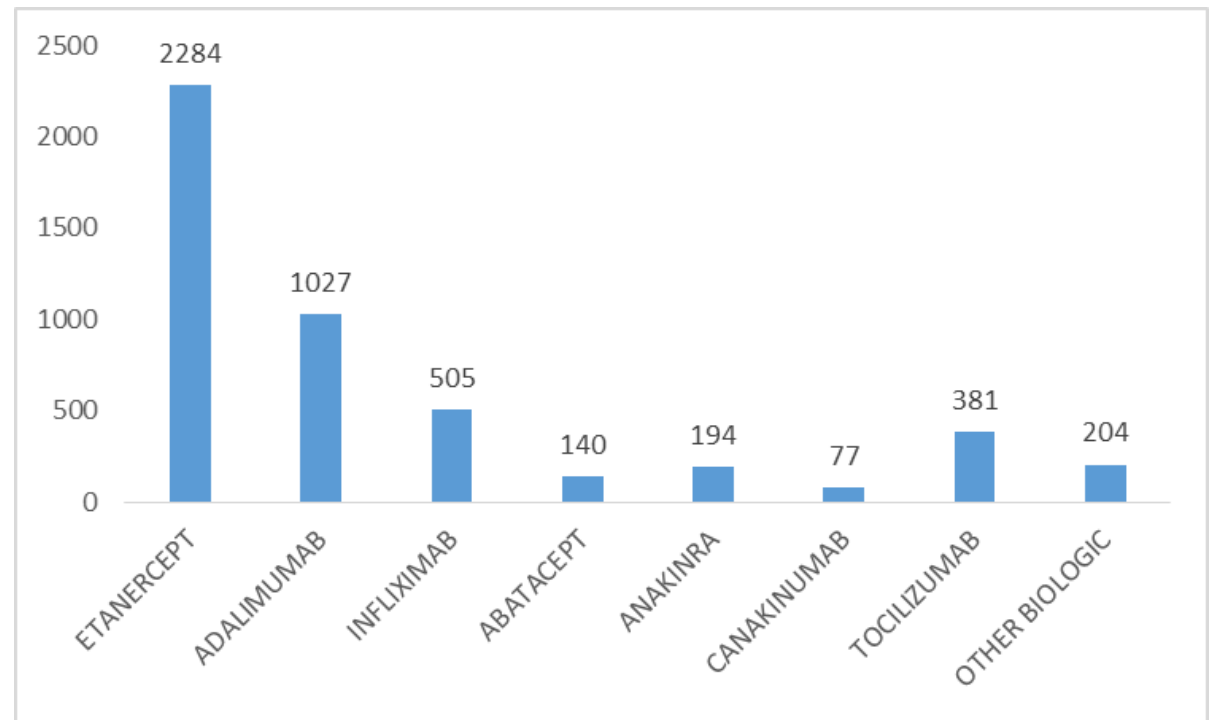
- ◆ 74 active sites from 24 countries
- ◆ Census 9359 patients
- ◆ Retrospective completed: **5529**
 - 4812 (biologics±MTX)
 - **1348 (MTX only)**
 - **654 (NSAIDs only)**
- ◆ Prospective completed: **428**

Retro demographic characteristics

	Systemic	Oligo articular	Poly articular RF-	Poly articular RF+	Psoriatic	Enthesitis	Undiffe- rentiated	Total
Sample	687 (12%)	2018 (36%)	1466 (27%)	202 (4%)	204 (4%)	659 (12%)	293 (5%)	5529
Age at onset	4.4 (2.5-8.5)	3.3 (2.0-6.9)	5.9 (2.4-10.1)	11.4 (7.4-13.5)	7.0 (2.8-12.0)	10.2 (8.2-12.7)	6.1 (2.5-11.0)	5.4 (2.4-10.0)
Age at JIA diagnosis	4.7 (2.7-9.0)	4.0 (2.3-7.9)	6.7 (2.9-11.2)	12.2 (8.3-14.3)	8.7 (3.4-13.3)	11.5 (9.4-13.9)	7.0 (3.2-11.8)	6.3 (2.8-11.0)
Disease duration	5.2 (2.4-9.0)	5.1 (2.4-8.7)	5.0 (2.7-8.2)	4.4 (2.6-7.4)	5.3 (2.8-8.8)	4.3 (2.4-6.9)	4.0 (2.0-7.3)	4.9 (2.5-8.2)
Female	368 (54%)	1551 (77%)	1111 (76%)	178 (88%)	142 (70%)	159 (24%)	184 (63%)	3693 (67%)

BIOLOGIC DRUGS (5529 RETRO PATIENTS)

BIOLOGIC DRUGS	N° PATIENTS	% PATIENTS
ETANERCEPT	2284	24.3
ADALIMUMAB	1027	10.9
INFLIXIMAB	505	5.4
ABATACEPT	140	1.5
ANAKINRA	194	2.1
CANAKINUMAB	77	0.8
TOCILIZUMAB	381	4.1
OTHER BIOLOGIC	204	2.2



History of drug treatment by JIA category

	Systemic	Oligoarticular	Polyarticular RF-	Polyarticular RF+	Psoriatic	Enthesitis	Undifferentiated	Total
No MTX and BIO	33 (4.8)	439 (21.8)	47 (3.2)	7 (3.5)	17 (8.3)	102 (15.5)	61 (20.8)	706
MTX only	65 (9.5)	645 (32.0)	373 (25.4)	42 (20.8)	50 (24.5)	106 (16.1)	67 (22.9)	1348
MTX + 1 Bio	294 (42.8)	702 (34.8)	779 (53.1)	110 (54.5)	90 (44.1)	286 (43.4)	107 (36.5)	2368
MTX + (2-8 Bio)	208 (30.3)	195 (9.7)	249 (17.0)	39 (19.3)	37 (18.1)	96 (14.6)	49 (16.7)	873
Only 1 Bio	64 (9.3)	33 (1.6)	15 (1.0)	2 (1.0)	10 (4.9)	66 (10.0)	7 (2.4)	197
More Bio	23 (3.4)	4 (0.2)	3 (0.2)	2 (1.0)	0 (0.0)	3 (0.5)	2 (0.7)	37
Total	687	2018	1466	202	204	659	293	5529

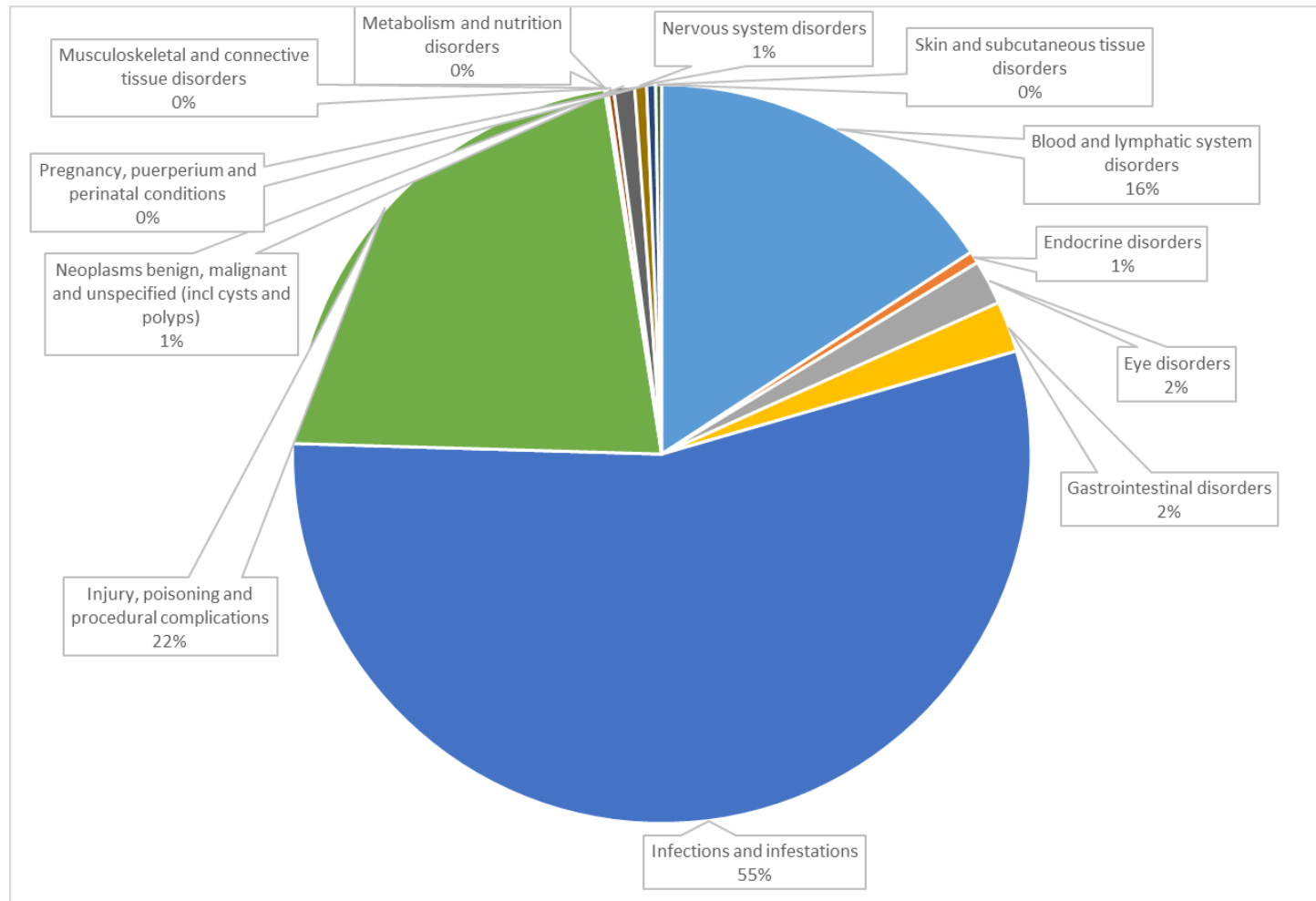
History of drug treatment by countries

	Western Europe	Eastern Europe	Latin America	Other	Total
MTX only	649 (48.15%)	504 (37.39%)	173 (12.83%)	22 (1.63%)	1348
MTX + 1 Bio	1183 (50.02%)	986 (41.69%)	82 (3.47%)	114 (4.82%)	2365
MTX + moreBio	509 (58.11%)	301 (34.36%)	35 (4%)	31 (3.54%)	876
Only 1 Bio	111 (56.35%)	63 (31.98%)	5 (2.54%)	18 (9.14%)	197
More Bio	31 (83.78%)	5 (13.51%)	0 (0%)	1 (2.7%)	37
Total	2483	1859	295	186	4823

ESI/other Adverse events

ESI / AE	N (%)
No of retrospective patients	5529
No of retrospective patients with ESI	493 (8.9%)
No of retrospective patients with AE	739 (13.4%)
No of retrospective patients with ESI or AE	1073 (19.4%)

ESI (766 NUMBER OF ESI)

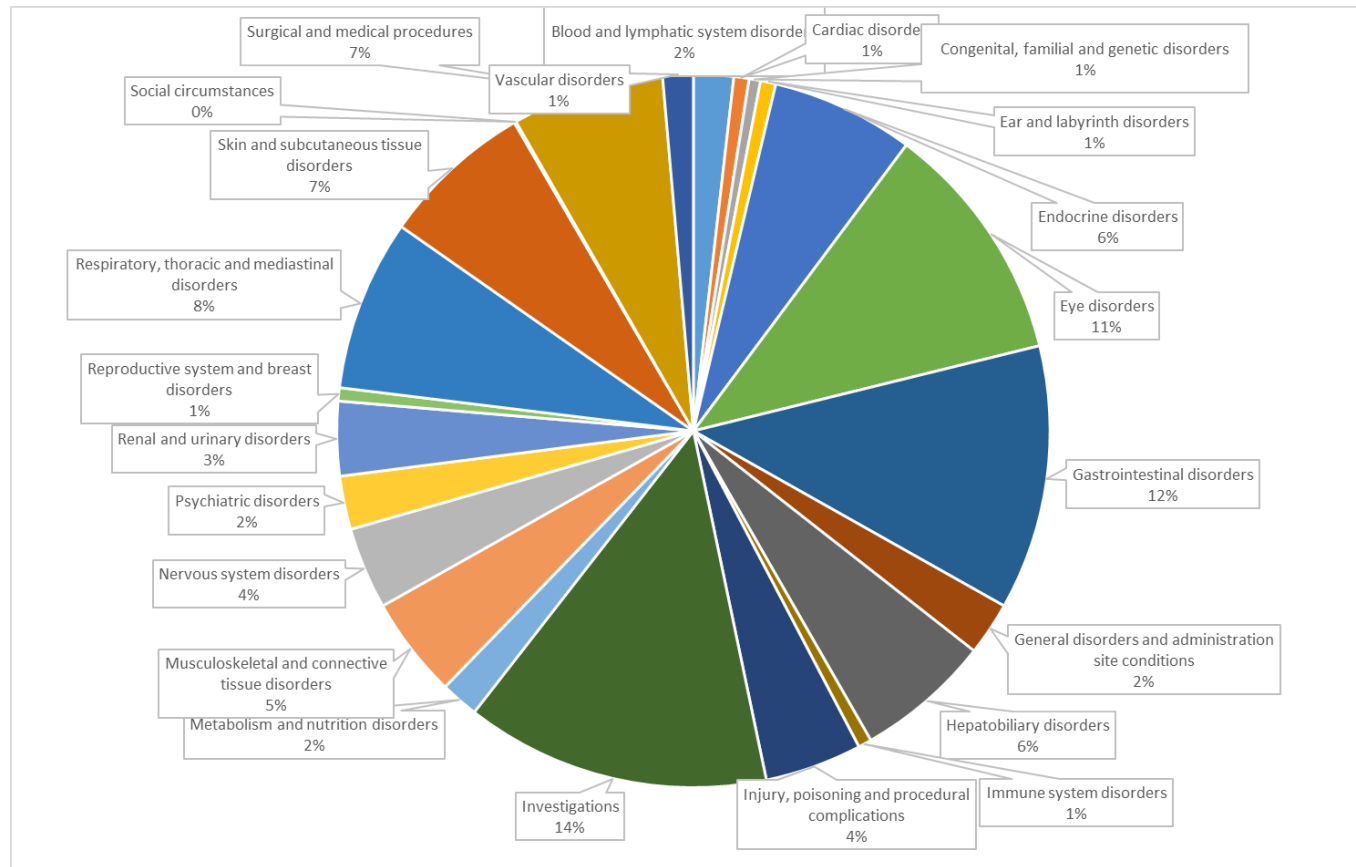


Example of ESI

◆ ESI

- ✓ 55% Infection and Infestations
(Varicella, Tuberculosis,...)
- ✓ 22% Injury, poisoning and procedural complications
(Infusion related reaction, injection related reaction,...)
- ✓ 16% Blood and lymphatic system disorders
(MAS, Neutropenia,...)

AE (1158 NUMBER OF AE)



Strategies vs challenges

◆ Strategies for success

- Service for physicians ((JADAS/Therapy graphs, data download, ILAR check, query and audit trail)
- Families involvement (languages barrier)

◆ Methodological challenges

- Ethics: approval process
- The issue of privacy
- Data Quality control and safety adjudication process
- Data merge/import and statistical analysis plan

Strategies for success

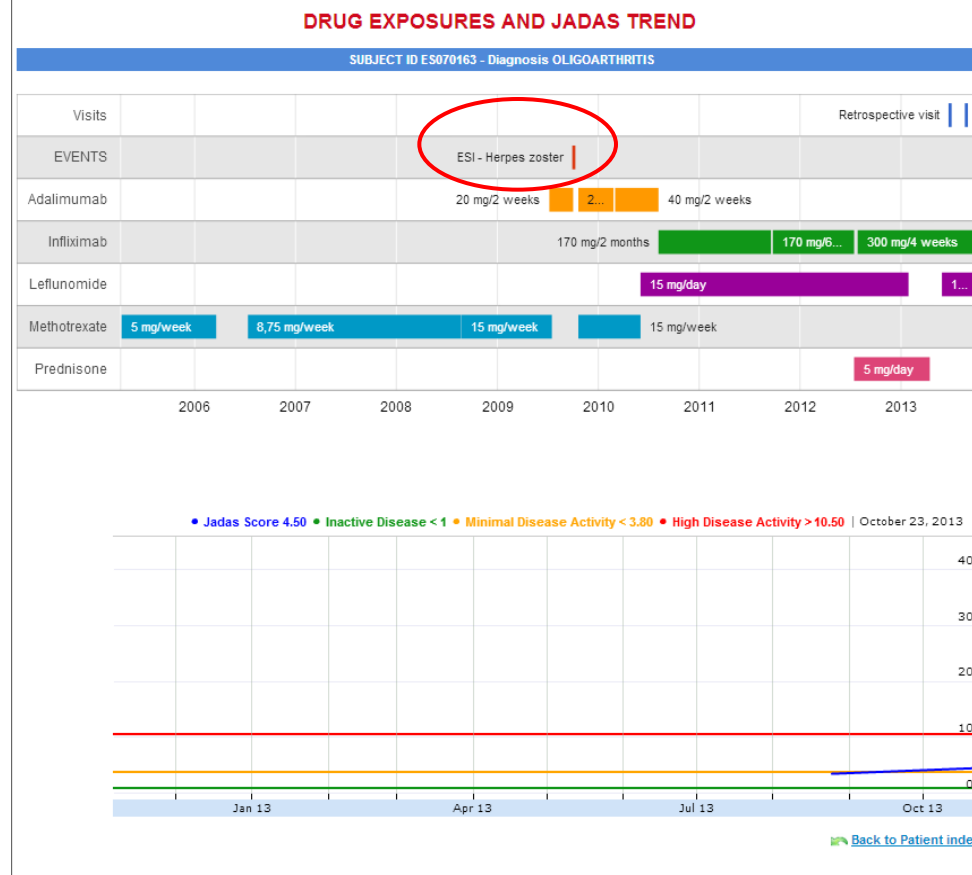
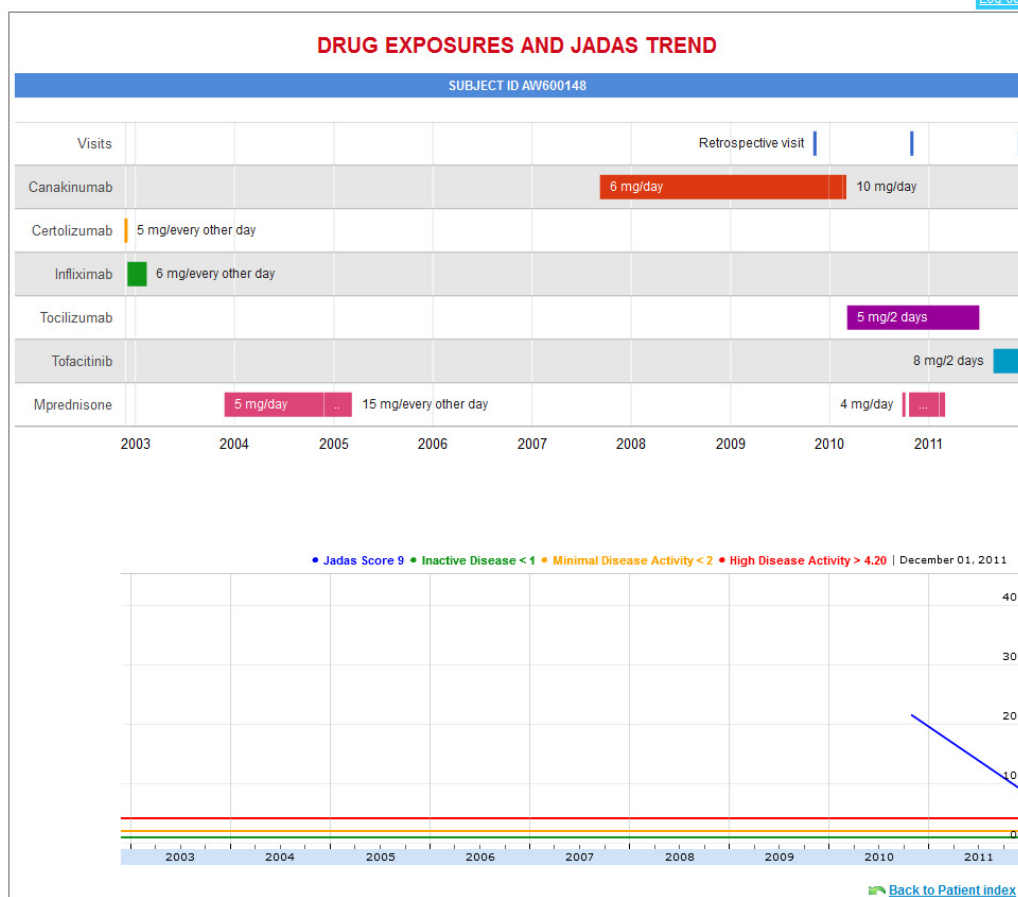
- ◆ **Census** of patients treated with MTX±biologics
- ◆ **Moderate to severe adverse events (AE) and Events of Special Interest (ESI)**
 - **Malignancies, serious infections, autoimmune dis., gastrointestinal events, growth failure etc**
- ◆ **Simplified*** and userfriendly web CRF
 - Patient chronicle (drug, flare, JADAS, remission, safety)
- ◆ **Family involvement** for AE/outcome reporting
- ◆ Regular update to MDs, families



Provide **advantages** for the physicians

- ◆ Immediate feed back by the system
- ◆ Use in routine clinical care with patient in visit room
 - Pre involvement of parents through **patient's reported outcome (PRO)**
- ◆ Patient's quantitative chronicle
 - Decision on patient management based on quantitative data
- ◆ No paper forms but web forms
- ◆ **A research and clinical service to the pediatric rheumatology community**

Patient disease activity and drugs





Patient reported outcome



admin

Log-out

RO - Traducere in romana-Romanian



Patient First Name or initial Encrypted Patient Last name or initial Encrypted

SUBJECT ID

RO010033

Date of visit 10-DEC-2012

JUVENILE ARTHRITIS MULTIDIMENSIONAL ASSESSMENT REPORT (JAMAR)

(last update : 26-APR-2013 by _____)

2 Traducere în română

Varianta pentru părinți

3 Numele și prenumele pacientului (sau inițiale):

Data: 10-DEC-2012

4 Părintele care completează chestionarul: **Tatăl**

5 Scopul acestui chestionar este de a aduna informații legate de starea actuală a bolii copilului Dvs.

6 Răspunsurile Dvs. ne vor ajuta să ne îmbunătățim evaluarea clinică.

7 Vă rugăm să citiți cu atenție întrebările de mai jos și să alegeți răspunsurile care se potrivesc cel mai bine copilului Dvs.

8 Dacă aveți nelămuriri sau aveți nevoie de precizări suplimentare, vă rugăm să ne solicitați ajutorul.

Juvenile Arthritis Multidimensionale Assessment Report (JAMAR) and AE



73 11. Since your child's last visit, has he/she had any disturbances which may be caused by the medication he/she is taking? Yes ☐ No ☐

74 If you answered "yes", please specify which in the table below

75	Fever	<input type="checkbox"/>	Pain or burning feeling in the stomach	<input type="checkbox"/>
76	Headache	<input type="checkbox"/>	Nausea	<input type="checkbox"/>
77	Skin rash	<input type="checkbox"/>	Vomiting	<input type="checkbox"/>
78	Mouth sores	<input type="checkbox"/>	Constipation	<input type="checkbox"/>
79	Swollen/bleeding gums	<input type="checkbox"/>	Diarrhoea	<input type="checkbox"/>
80	Increased body hair	<input type="checkbox"/>	Black or bloody stools	<input type="checkbox"/>
81	Weight gain	<input type="checkbox"/>	Blood in the urine	<input type="checkbox"/>
82	Weight loss	<input type="checkbox"/>	Swelling, bruising, pain, redness, etc., at the injection site	<input type="checkbox"/>
83	Mood swings (excitement, depression, anxiety)	<input type="checkbox"/>	Other (please describe) _____	<input type="checkbox"/>
84	Sleep disturbances	<input type="checkbox"/>	Other (please describe) _____	<input type="checkbox"/>

Safety from parents/children



Download your own data (25/61; 41%)



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Patients status and generic visit information
Drug therapy
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Disease activity status
Jamar
Events of Special Interest
Pregnancy Form
Adverse Events
JADI, Radiographs, Growth, Biologic Samples

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PATIENT ID													
A	B	C	D	E	F	G	H	I	J	K	L	M	N
PATIENT ID	VISIT DATE	AnaDa1st	AnaDa2nd	Ana1stDe	Ana1stSp	Ana2ndDe	Ana2ndSp	AnaDeMet	AnaDeMSp	AnaDeMet2	AnaDeMSp2	RF1st	RF2nd
1	IT010479	05/04/2012		99	titer:								0
2	IT010478	13/09/2012		99	titer:								99
3	IT010477	04/04/2012	15/02/2005	06/04/2010	1	titer: 1:320	1	titer: 1:320	0	0			0
4	IT010476	04/04/2012	14/07/2010	1	titer: 1:160	99	titer:	0					99
5	IT010475	03/04/2012	01/10/2010	10/10/2011	0	titer:	0	titer:	0	0			0
6	IT010474	03/04/2012	27/07/2011	1	titer: 1:320	99	titer:	0					99
7	IT010473	11/04/2012	15/11/2008	0	titer:	99	titer:	3					1
8	IT010472	23/11/2011	29/03/2008	1	titer: 1:80	99	titer:	3					1
9	IT010471	05/04/2011	29/03/2007	1	titer: 1:320	99	titer:	0					0
10	IT010470	22/06/2011	05/06/1998	15/09/1998	1	titer: 1:640	1	titer: 1:640	3	3			0
11	IT010469	05/06/2012	15/07/2005	19/09/2005	0	titer:	0	titer:	0	0			99
12	IT010468	20/11/2012		99	titer:			titer:					0
13	IT010467	11/09/2012	16/05/2002	06/07/2004	0	titer:	0	titer:	0	0			0
14	IT010466	16/04/2013	23/10/2002	13/11/2003	1	titer: 1:320	1	titer: 1:320	0	0			99
15	IT010465	23/11/2009	20/01/2005	17/01/2008	1	titer: 1:160	1	titer: 1:320	0	0			99
16	IT010464	09/07/2012	04/08/2009	0	titer:	99	titer:	0					0
17	IT010463	06/12/2012	19/09/2005	29/09/2008	1	titer: 1:320	1	titer: 1:160	0	0			99
18	IT010462	15/07/2011	15/05/2008	15/06/2008	0	titer:	0	titer:	0	0			0
19	IT010461	01/02/2013	24/01/2007	14/11/2007	1	titer: 1:160	0	titer:	0	0			99
20	IT010460	14/02/2013		99	titer:			titer:					99
21	IT010459	21/05/2012	05/07/2004	13/07/2005	1	titer: 1:320	1	titer: 1:160	0	0			0
22	IT010458	22/11/2012	04/02/2010	19/05/2010	1	titer: 1:320	1	titer: 1:320	3	0			0
23	IT010457	04/03/2011	15/10/2007	1	titer: 1:160	99	titer:	3					0
24	IT010456	03/12/2012	06/09/1995	12/01/2012	1	titer: 1:320	1	titer: 1:320	0	0			99
25	IT010455	17/05/2012	18/03/2005	30/11/2005	1	titer: 1:160	1	titer: 1:160	0	0			99
26	IT010454	21/06/2012	07/07/2005	23/09/2009	1	titer: 1:80	1	titer: 1:160	0	0			0
27	IT010453	10/07/2012	12/12/2006	1	titer: 1:320	99	titer:	0					99
28	IT010452	13/03/2013	13/06/2005	0	titer:	99	titer:	0					0
29	IT010451	20/09/2012	28/09/2004	27/03/2006	1	titer: 1:320	1	titer: 1:80	0	0			99
30	IT010450	08/08/2012	11/10/2005	10/02/2010	1	titer: 1:320	1	titer: 1:320	0	0			99
31	IT010449	30/08/2012	18/01/2006	0	titer:	99	titer:	0					0
32	IT010447	15/05/2012	02/10/2008	22/07/2011	0	titer:	0	titer:	0	0			0

Strategies vs challenges

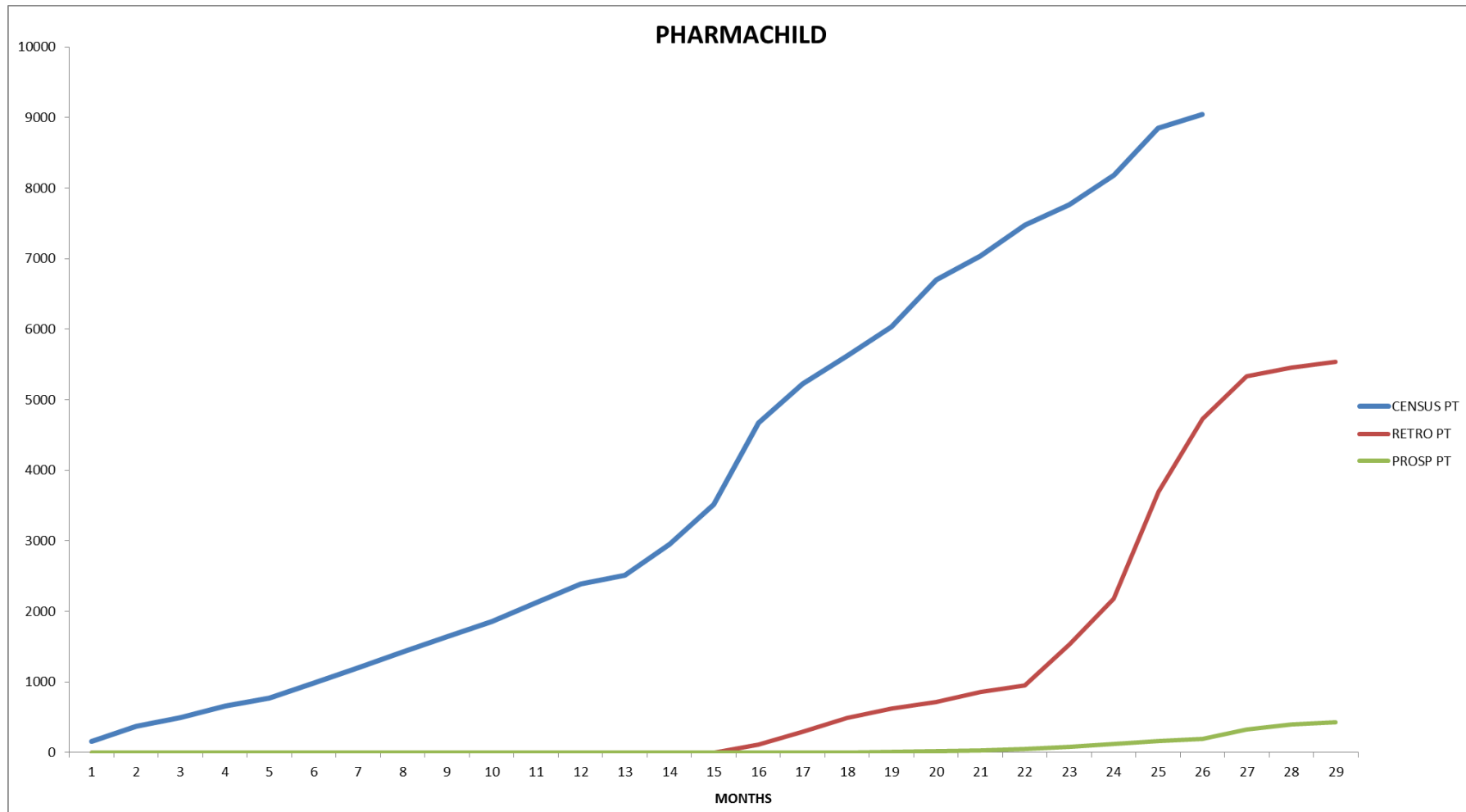
◆ Strategies for success

- Service for physicians ((JADAS/Therapy graphs, data download, ILAR check, query and audit trail)
- Families involvement (languages barrier)

◆ **Methodological challenges**

- Ethics: approval process
- The issue of privacy
- Data Quality control and safety adjudication process
- Data merge/import and statistical analysis plan

Enrollment status (5529 retro pts)



Ethics committees documents



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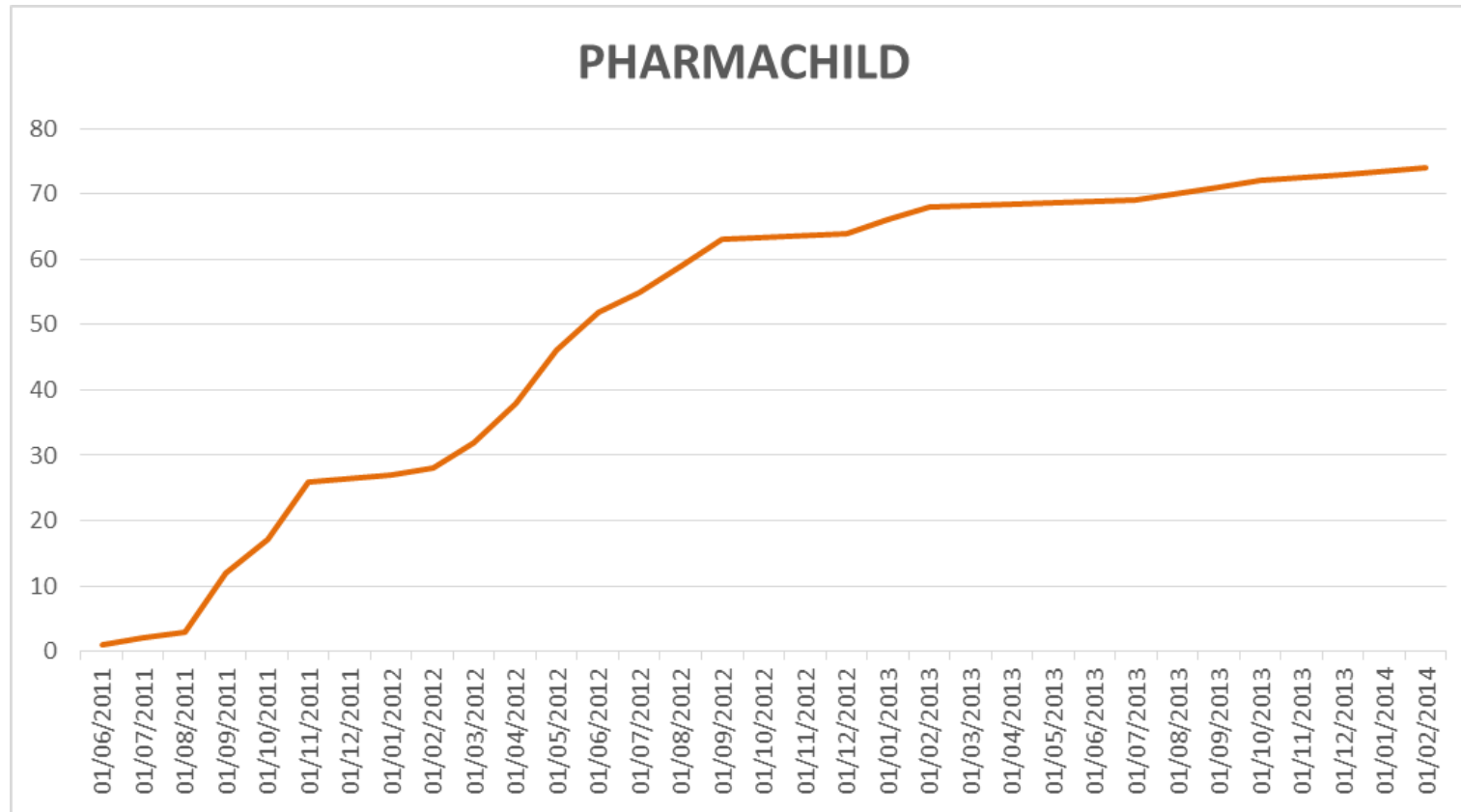
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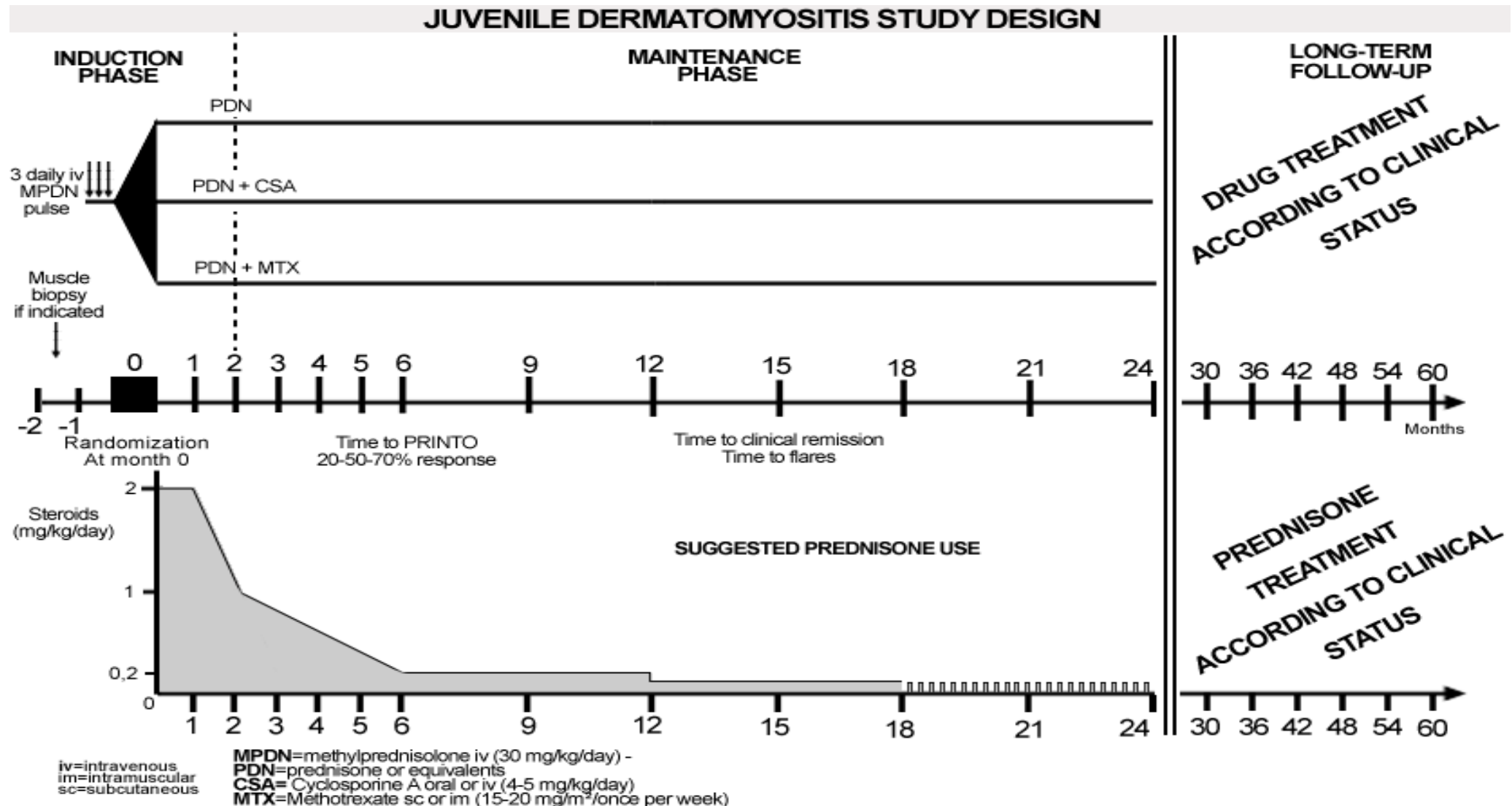
Consents / Assents, Protocols, JAMAR translations and CRFs English version

Country		1. Protocol full/synopsis	2. Consent/Assent forms	3. JAMAR parents/child	4. CRFs
PRINTO English version		Full protocol PDF 	Consent parents PDF 	JAMAR parents PDF 	CRF retrospective PDF 
		Synopsis PDF 	Consent 18+ PDF 	JAMAR child PDF 	CRF prospective PDF 
			Assent minor PDF 		CRF safety PDF 
Belgium 		Full protocol PDF 	Consent parents PDF 	JAMAR parents	CRF retrospective PDF 
		Synopsis PDF 	Consent 18+ PDF 	JAMAR child	CRF prospective PDF 
			Assent minor PDF 		CRF safety PDF 
Bulgaria 		Full protocol PDF 	Consent parents PDF 	JAMAR parents PDF 	CRF retrospective PDF 
		Synopsis PDF 	Consent 18+ PDF 	JAMAR child PDF 	CRF prospective PDF 
			Assent minor PDF 		CRF safety PDF 
Czech Republic 		Full protocol PDF 	Consent parents PDF 	JAMAR parents	CRF retrospective PDF 
		Synopsis PDF 	Consent 18+ PDF 	JAMAR child	CRF prospective PDF 

Ethics committee (72 centres on 2/2014)



The “standard of care” PRINTO JDM trial



Ethics committee documentation (EU directive)



Country	National approval	Local approval	CA approval	Insurance	GCP monitoring	Drug supply/no authorization off-label	EudraC T	Financial Agreement	EC payment
Austria		X							
Belgium	X	X	X				X		
Bulgaria	X	X		X	X				
Croatia	X	X				X			X
Czech Republic		X							
Denmark	X		X				X		
Finland	X	X	X						
France	X		X	X			X		X
Germany		X		X					X
Greece		X							
Hungary		X	X			X			
Italy		X		X			X	X	

Ethics committee documentation (EU directive)



Country	National approval	Local approval	CA approval	Insurance	GCP monitoring	Drug supply/no authorization off-label	EudraCT	Financial Agreement	EC payment
Latvia		X							
Netherl.	X	X			X		X		
Norway	X		X				X		
Poland		X							
Romania		X							
Slovakia		X							
Slovenia		X							
Spain	X	X						X	
Sweden	X						X		
United Kingdom	X	X	X	X			X	X	

Ethics committee documentation (EU directive)



Country	National approval	Local approval	CA approval	Insurance	GCP monitoring	Drug supply/no authorization off-label	EudraCT	Financial Agreement	EC payment
Extra EU countries									
Argentina		X							
Australia		X							
Brazil	X	X							
Georgia		X							
Israel						X			
Mexico		X						X	
Serbia		X							
Switzerland	X	X	X						
Turkey	X	X		X		X			
USA		X						X	

**Standardization and simplification
of ethics committee approval is a
key especially for paediatric
international collaborative
academic studies**

The issue of privacy



PHYSICIAN AREA

Username Password

[Forgot your password?](#)

[HELP](#)



**Pediatric Rheumatology
International
Trials Organisation**

PRINTO
Istituto G. Gaslini, Università di Genova, Pediatria II, Reumatologia
EULAR Centre of Excellence in Rheumatology 2008-2013
Largo Gaslini, 5 - 16147 Genova ITALY
Phone: 0039-010-38-28-54 / 0039-010-39-34-25
Fax: 0039-010-4211018 / 0039-010-393324
Email: printo@ospedale-gaslini.ge.it



ENTER CENTRE PASSWORD

Click [here to bypass the centre password](#) and continue with patients' personal data encrypted.
Consider that without the correct centre password it is not possible to enter/modify patients data.

[Lost your Centre password?](#)

[Log-out](#)

[HELP](#)



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Email: printo@ospedale-gaslini.ge.it

Privacy

- ◆ Personal information (first and last name, date of birth and the national patient unique identifier).
 - To be seen ONLY on the local computer screen.
 - On the central PRINTO database ONLY one way encrypted data will be saved.
- ◆ **Impossible for PRINTO to decrypt or disclose to anyone the personal information**
- ◆ Info exchange PRINTO↔local centres through the PRINTO PRINTO patient id (country-centre-patient number e.g. IT-01-0010)

Patient list encrypted on PRINTO server



INVESTIGATOR MENU
[HOME](#) [DOCUMENTS](#) [SUBJECTS LIST](#) [QUERY TICKET](#) [INSTRUCTIONS](#) [EXPORT DATA](#)

[Log-out](#)
[HELP](#)

SUBJECTS LIST FOR CENTRE IT01
[Insert centre password to decrypt personal data](#)


Displayed results:
 Page number: [Go to page](#)

Subject ID ↕↕	First name No Sort	Last name No Sort	Age (Y) No Sort	Gender ↕↕	ILAR Category ↕↕	CENSUS ↕↕	RETRO ↕↕	PROSP ↕↕	ACTION
IT01 <input type="text"/>	No Filter	No Filter	No Filter	All <input type="text"/>	Category: All <input type="text"/> Prov: All <input type="text"/>	All <input type="text"/>	All <input type="text"/>	All <input type="text"/>	Filter Reset
(in red provisional diagnosis)									
IT01-0479	Encrypted	Encrypted	Encrypted	F	SYSTEMIC	✓	✓	✗	summary
IT01-0478	Encrypted	Encrypted	Encrypted	M	ENTHES	✓	✓	-	summary
IT01-0477	Encrypted	Encrypted	Encrypted	F	POLY (RF-)	✓	✓	✗	summary
IT01-0476	Encrypted	Encrypted	Encrypted	M	OLIGO PERSISTENT	✓	✓	✗	summary
IT01-0475	Encrypted	Encrypted	Encrypted	F	OLIGO PERSISTENT	✓	✓	✗	summary
IT01-0474	Encrypted	Encrypted	Encrypted	F	OLIGO PERSISTENT	✓	✓	✗	summary
IT01-0473	Encrypted	Encrypted	Encrypted	M	ENTHES	✓	✓	✗	summary
IT01-0472	Encrypted	Encrypted	Encrypted	F	POLY (RF+)	✓	✓	✗	summary
IT01-0471	Encrypted	Encrypted	Encrypted	F	OLIGO EXTENDED	✓	✓	-	summary
IT01-0470	Encrypted	Encrypted	Encrypted	M	OLIGO EXTENDED	✓	✓	✗	summary
IT01-0469	Encrypted	Encrypted	Encrypted	F	OLIGO EXTENDED	✓	✓	-	summary

Quality control: systematic automatic check



TEST







INVESTIGATOR MENU

[HOME](#) [DOCUMENTS](#) [SUBJECTS LIST](#) [QUERY TICKET](#) [INSTRUCTIONS](#) [EXPORT DATA](#)

Log-out



SUBJECT AW600160 has a diagnosis of ENTHERS . However the diagnosis is provisional due to the following reasons.
You should resolve these issues at this or following visits.

	Query code	Description	Action
✗	ILAR011	ILAR exclusion criteria D is marked as NO, but RF results are not done/unknown in LAB form	Change criteria D to NA, diagnosis is considered provisional until RF exam will be performed
✗	ILAR016	Diagnosis = Enthesitis related with classification criteria onset of Arthritis in a male > 6 years, but age at onset < 6	Verify the information entered and make the proper correction to ILAR form or date of onset

 [back](#)

Audit trail



- ◆ An audit trail is a chronological set of records that provide documentary evidence of the sequence of activities that have affected data.
- ◆ In Pharmachild, to be FDA compliant, the audit trail is provided through stored procedures present in the database that save original data in a dedicated archive table
- ◆ Author and timestamp of every action performed are saved too

Audit trail



TEST



admin

[Log-out](#)

SECTIONS

USERS

[Users / Centres](#)
[User Photo \(!\)](#)

Participation

[Quest Pharma](#)
[Quest ABA](#)
[CV list](#)
[site LOG list](#)

Contracts

[Centre PSW](#)

SUBJECTS

[Patient list](#)
[Visits list](#)
[Check List](#)
[Retro Prog List](#)
[Prosp Prog List](#)
[Center Enroll](#)
[Duplicated Patients](#)

SAFETY

[Authorize MD review](#)
[MD Review status list](#)

TICKETS

[Ticket list](#)
[New Ticket](#)

NEWSLETTERS

[Newsletter list](#)

ADMIN

[Add contact for panel](#)
Sessione Log 2966
[Query System](#)

RETROSPECTIVE VISIT FORMS

SUBJECT IT980586 - Encrypted Encrypted date of birth Encrypted
Diagnosis OLIGOARTHRITIS **Provisional**

[Visit archive](#)






Age at Disease Onset	Age at JIA Diagnosis	Age at first visit at your centre	Age at RETROSPECTIVE visit at your centre	
5,3 years	5,4 years	5,4 years	9,3 years	

FORMS	New	Modify	View
<input checked="" type="checkbox"/> Subject status		modify	view
DEMOGRAPHIC AND DIAGNOSIS			
<input checked="" type="checkbox"/> Demographic and subject history (as of 07-JAN-2014)		modify	view
<input checked="" type="checkbox"/> ILAR category PROVISIONAL (as of 05-DEC-2013)		modify	view
<input checked="" type="checkbox"/> Laboratory and clinical information (as of 05-DEC-2013)		modify	view
OTHER FORMS TO BE COMPLETED			
EFFICACY			
<input checked="" type="checkbox"/> Drug therapy history since disease onset		modify	view
SAFETY			
<input checked="" type="checkbox"/> Events of Special Interest (ESI)		to be completed	
<input checked="" type="checkbox"/> Adverse events (AE)		to be completed	
1. CENTER DATA CONFIRMATION			
2. PRINTO CHECK			
3. PRINTO MD REVIEW			
<input checked="" type="checkbox"/> All required forms are NOT completed. Please check for any <input checked="" type="checkbox"/> above.	<input checked="" type="checkbox"/> Center data confirmation is required	<input checked="" type="checkbox"/> Visit still to be checked by PRINTO	
LOCK / UNLOCK MANAGEMENT		TICKETS ON THIS PATIENT	
		Open a ticket	

- Deleted and modified data are visible from the Admin section

Audit trail



AUTHOR	LAST UPDATE	ACTION TYPE	DATE ACTION	ORIGIN	DETAILS
	05-DEC-2013	UPDATE	05-DEC-2013	NA	 view
	07-JAN-2014	UPDATE	07-JAN-2014	NA	 view
	07-JAN-2014	UPDATE	07-JAN-2014	NA	 view
	07-JAN-2014	UPDATE	07-JAN-2014	NA	 view
	07-JAN-2014	UPDATE	07-JAN-2014	NA	 view

 [Back to retrospective index](#)

- For every form the list of all the different versions of the form is available, each with its author and timestamp

Audit trail



[Log-out](#)

DEMOGRAPHIC DATA AND SUBJECT HISTORY

(last update : 05-DEC-2013 by)

☒ Parents/legal guardian consent or minor assent or adult subject consent NOT REQUIRED for retrospective visit

☐ Parents/legal guardian consent or minor assent or adult subject consent OBTAINED for retrospective visit (if yes please specify below)

☐ Parent/legal guardian consent

☐ Minor assent

☐ Adult subject consent

Date

Date

Date

Subject First Name or initials

Encrypted

Subject Last Name or initials

Encrypted

If for confidentiality reasons you cannot put subject's name or initials, please write an incremental number or leave blank.

Sex

☐ Male ☒ Female

Country of Birth

Encrypted

Birth date (dd-mmm-yyyy)

Encrypted

NATIONAL SUBJECT UNIQUE IDENTIFIER

This number should identify the subject within the border of your country in a unique way. Examples of such number are the Social Security Number in the USA (nine digit number), fiscal code in Italy (16 alphanumeric code)

Encrypted

IMPORTANT: the personal information (first and last name, date of birth and the national subject unique identifier) will be seen ONLY on the local computer screen. The PRINTO web system will automatically ENCRYPT the personal data and ONLY the encrypted data will be saved on the PRINTO central database on an https platform . The PRINTO website will automatically assign a subject number (SUBJECT ID) to be used for communication with the centre. The PRINTO encrypting algorithm is designed in a way by which it is impossible for PRINTO to decrypt the personal information and disclose to anyone the subject first/last name, the date of birth and the national subject unique identifier.

SUBJECT ID

country code, centre code, progressive subject number e.g IT 01 0001

Country code

Centre code

Subject number

IT

98

0586

Subject ethnicity

Caucasian (European)

Ethnicity specify

Family socio-economic status (provide a rough assessment based on your knowledge of the family and of the socio-economic standards in your country)

☐ Cannot be reported ☐ Low ☒ Average ☐ High

Access to health care

☐ Cannot be reported ☒ Public ☐ Private ☐ Health insurance ☐ Personal funds

Education level (of the parent who completes the JAMAR)

☐ Elementary or lower ☒ High school ☐ Degree ☐ Unknown

[Log-out](#)

DEMOGRAPHIC DATA AND SUBJECT HISTORY

(last update: 07-JAN-2014 by)

☒ Parents/legal guardian consent or minor assent or adult subject consent NOT REQUIRED for retrospective visit

☐ Parents/legal guardian consent or minor assent or adult subject consent OBTAINED for retrospective visit (if yes please specify below)

☐ Parent/legal guardian consent

☐ Minor assent

☐ Adult subject consent

Date

Date

Date

Subject First Name or initials

Encrypted

Subject Last Name or initials

Encrypted

If for confidentiality reasons you cannot put subject's name or initials, please write an incremental number or leave blank.

Sex

☒ Male ☐ Female

Country of Birth

Encrypted

Birth date (dd-mmm-yyyy)

Encrypted

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Query ticket system



✓ Demographic and subject history (as of 09-SEP-2013) [modify](#) [view](#)

✓ ILAR category **PROVISIONAL** (as of 09-SEP-2013) [modify](#) [view](#)

✓ Laboratory and clinical information (as of 09-SEP-2013) [modify](#) [view](#)

FORMS TO BE COMPLETED AT EACH VISIT

EFFICACY

✗ Drug therapy history since previous visit [new](#)

✗ Standard joint assessment form [new](#)

✓ Disease activity status [modify](#) [view](#)

JAMAR

JAMAR	Child	Mother	Father
✓ Jamar questionnaire	Not done as declared on disease status		

SAFETY

✗ Events of Special Interest (ESI) drug first

✗ Adverse events (AE) drug first

OPTIONAL (ANNUAL) ASSESSMENTS

✗ JADI [new](#)


✗ Radiographs [new](#)

✓ Growth [modify](#) [view](#)

✗ Biologic Samples [new](#)

DMARDS	BIOLOGIC	AE	ESI	Disease status	JADAS 10
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Missing	NA

1. CENTER DATA CONFIRMATION




Visits data are official only after confirmation.
So visits must always be confirmed!
Confirmation of this visit is not possible until completion of all mandatory forms.
Please check for any ✗ above.

LOCK / UNLOCK MANAGEMENT

TICKETS ON THIS PATIENT

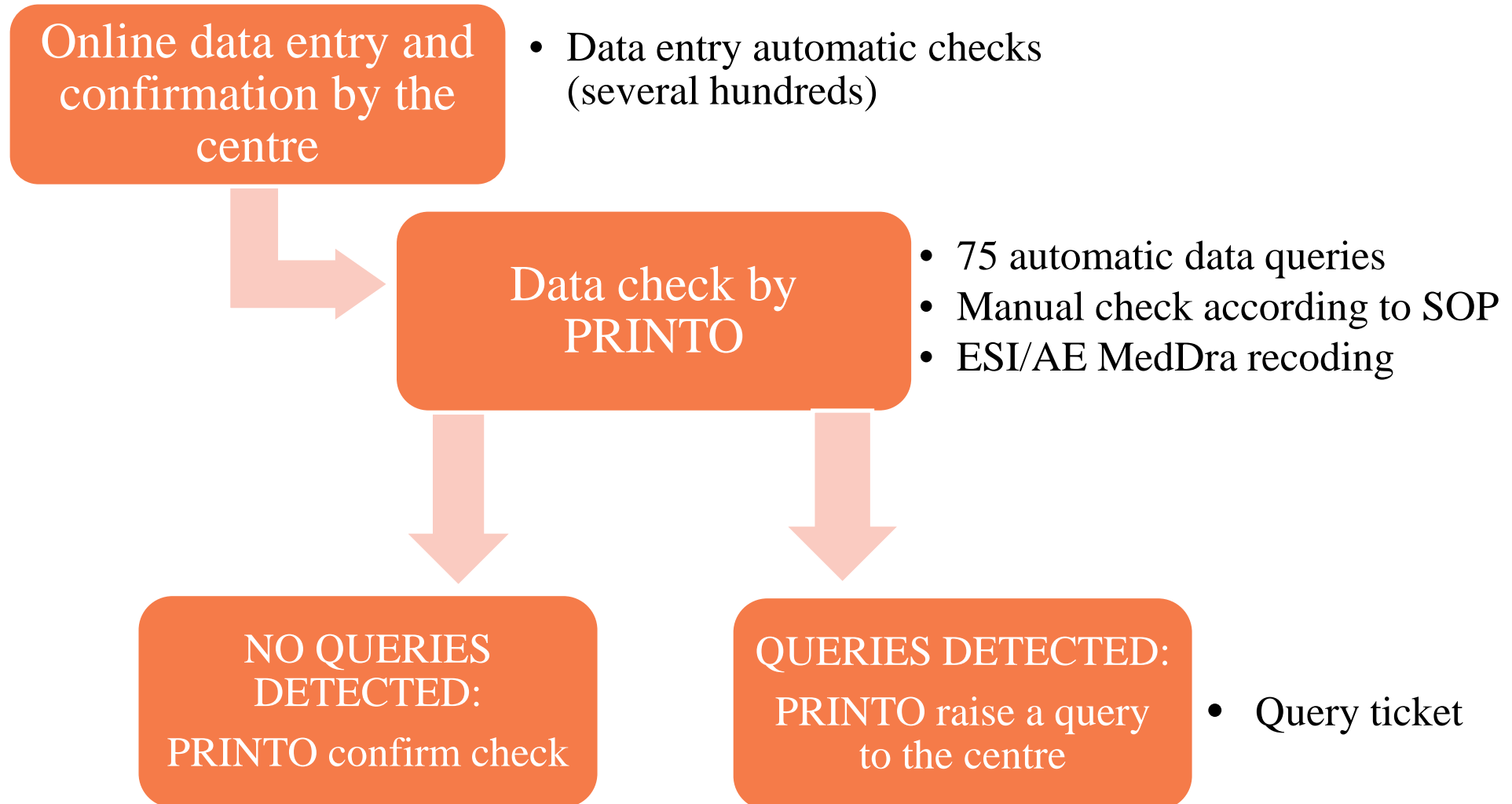
[Open a NEW ticket](#)

 **OPEN TICKETS TO BE CHECKED**

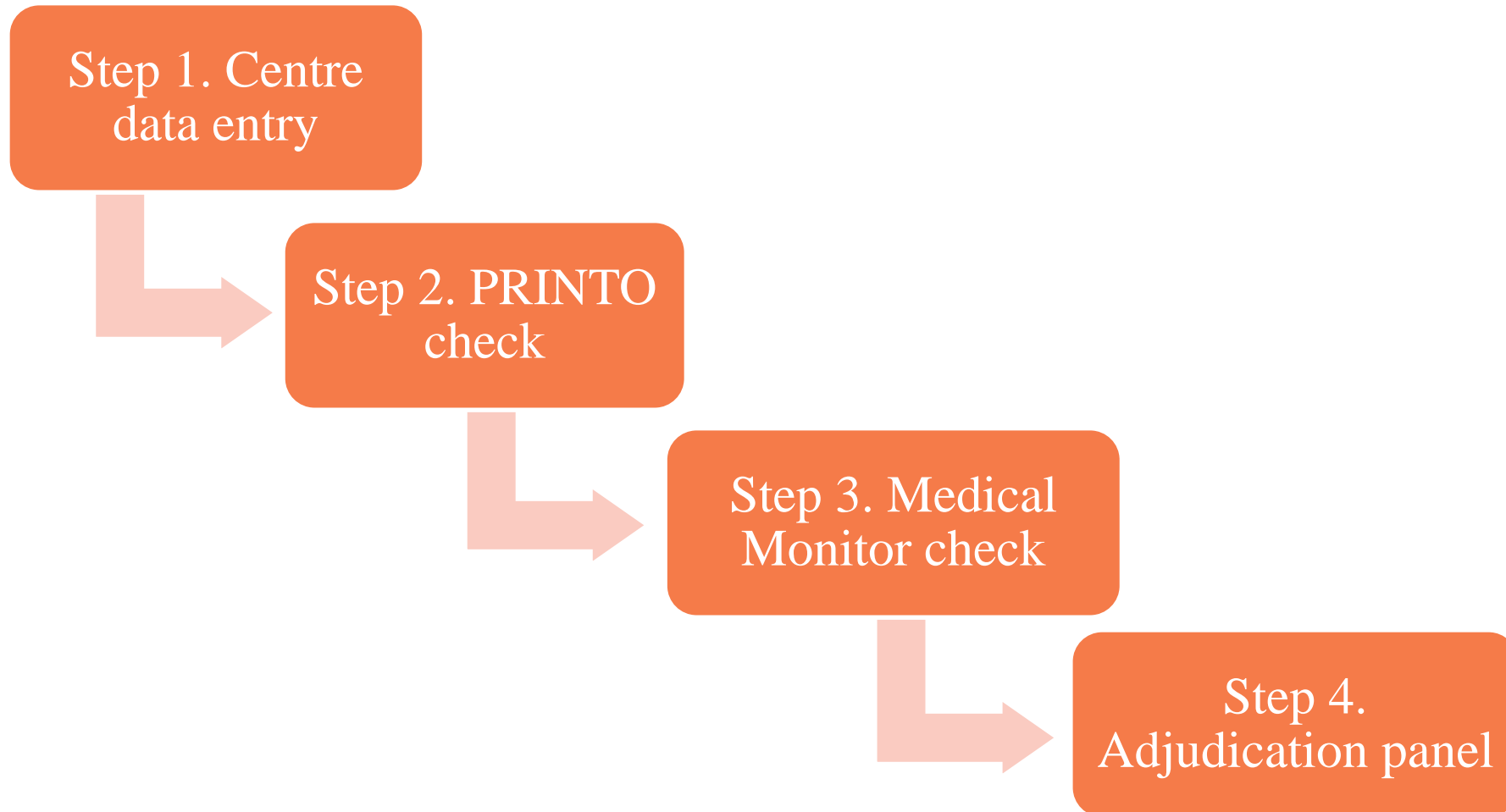
Open date	Ticket subject	Details
09-SEP-2013	Patient AW600116	see detail
08-OCT-2013	Patient AW600116	see detail

- Closed communication system for audit purposes
- System to discuss issues about Pharmachild data raised from both CC and the centres
- Possibility to reply until the ticket status is “open”
- Attachments are allowed
- Open tickets related to a subject are highlighted and available below the visit forms and on the home page of the system

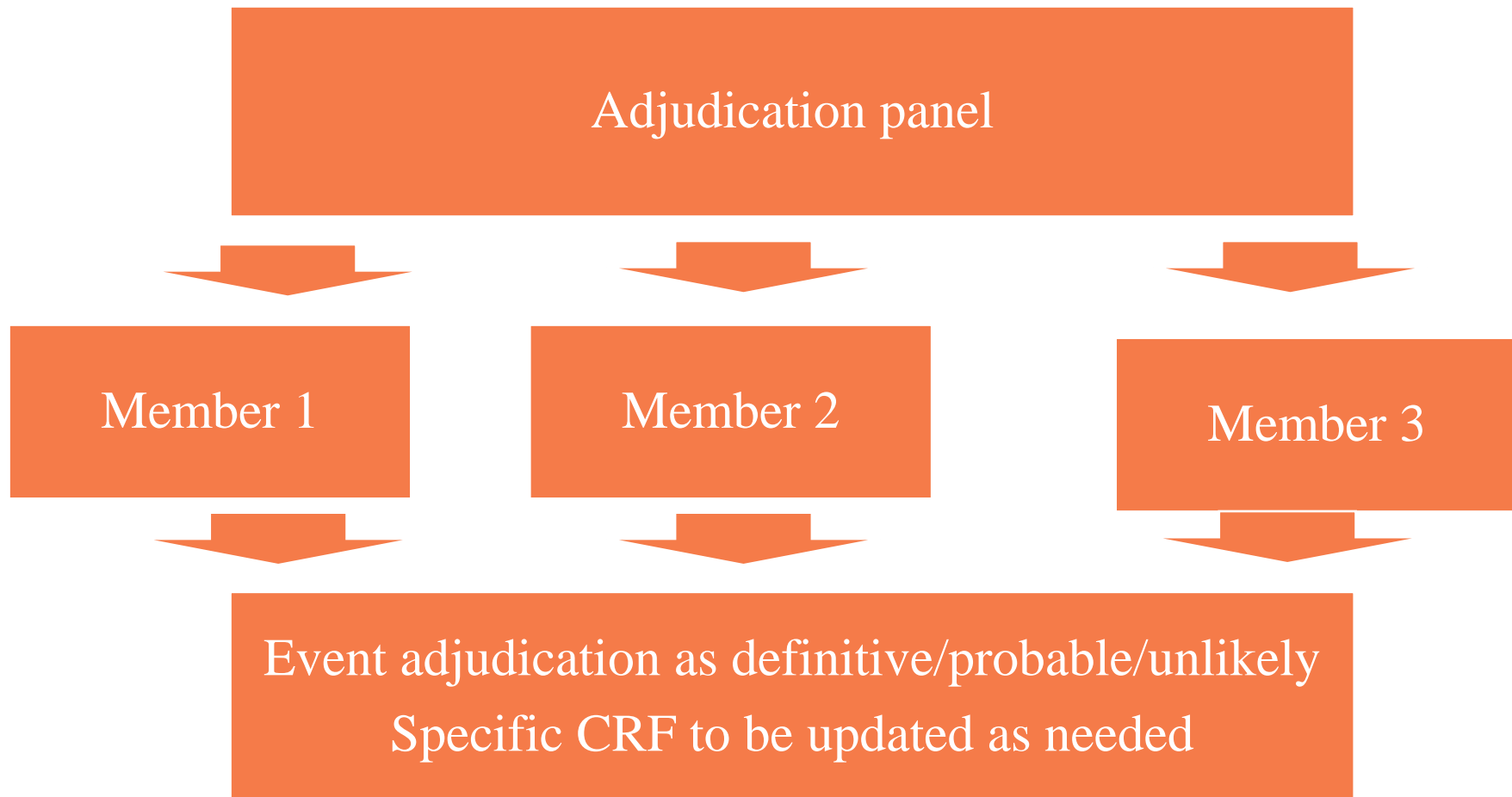
Data checking process



4 steps safety Adjudication process



Adjudication panel



Registries merging

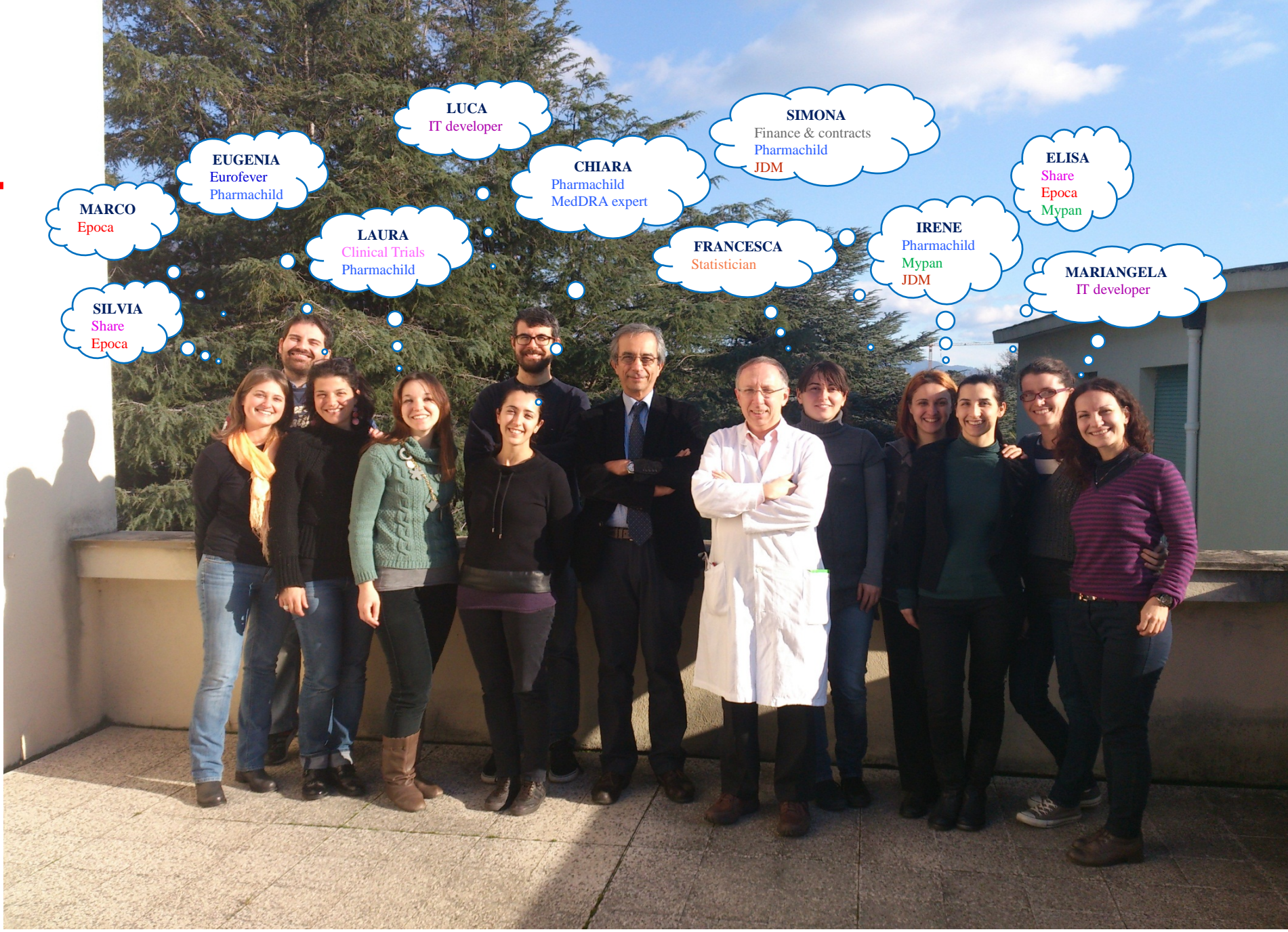
- ◆ Option 1: raw data merging (adaptation by individual registries)
- ◆ Option 2: data results merging with merging of raw data for few key variables
- ◆ **PRINTo view: Option 2 suggested best method**

>10,000 with EU registries merging

	Pharmachild N = 5529*	NR England N = 1537	NR Germany N = 3139 [#]	NR Portugal N = 112	NR Swiss N = 632	TOTAL N = 10949	p-value
Gender							
Female	3693 (66.8)	1041 (67.7)	2117/3136 (67.5)	70 (62.5)	421 (66.6)	7342/10946 (67.1)	0.76
Diagnos:		N = 1510				N=10922	<.0001
Systemic	687 (12.4)	199 (13.2)	202 (6.4)	14 (12.5)	84 (13.3)	1186 (10.9)	
Oligoarticular	2018 (36.5)	399 (26.4)	1011 (32.2)	31 (27.7)	198 (31.3)	3657 (33.5)	
Polyarticular	1466 (26.5)	506 (33.5)	944 (30.1)	26 (23.2)	160 (25.3)	3102 (28.4)	
RF-							
Polyarticular	202 (3.7)	140 (9.3)	199 (6.3)	21 (18.8)	15 (2.4)	577 (5.3)	
RF+							
Psoriatic	204 (3.7)	98 (6.5)	244 (7.8)	3 (2.7)	34 (5.4)	583 (5.3)	
Enthesitis	659 (11.9)	100 (6.6)	438 (14.0)	17 (15.2)	124 (19.6)	1338 (12.3)	
Undifferentiated	293 (5.3)	68 (4.5)	101 (3.2)	0 (0.0)	17 (2.7)	479 (4.4)	
Age at onset	5.4 (2.4 – 10.0)	NA	NA	6.3 (2.5 – 10.9)	NA		0.42
Age at JIA Diagnosis	6.3 (2.8 – 11.0) N=5354	5.5 (2.1 – 10.2) N=1495	NA	7.3 (3.3 – 12.3)	NA		<.0001
Disease duration	4.9 (2.5 – 8.2)	NA	NA	3.0 (0.5 – 9.6)	NA		0.0044
Therapy:	N=5529	N=1537	N=3134	N=112	N=567	N=10173	<.0001
MTX only	1348 (24.4)	503 (32.7)	1132 (36.1)	0 (0.0)	36 (5.7)	3019 (29.7)	
Only one Biologic Drug	197 (3.6)	1034 (67.3)	104 (3.3)	1 (0.9)	127 (20.1)	1463 (14.4)	
Only one Biologic Drug + MTX	2368 (42.8)	0 (0.0)	1545 (49.2)	27 (24.1)	286 (45.3)	4223 (41.5)	
More than one Biologic	37 (0.7)	0 (0.0)	13 (0.4)	6 (5.4)	31 (4.9)	87 (0.9)	
More than one Biologic + MTX	873 (15.8)	0 (0.0)	340 (10.8)	78 (69.6)	87 (13.8)	1381 (13.6)	
Nr. patients with ESI	493 (8.9)			5 (4.5)			0.10
Nr. patients with AE	739 (13.4)			24 (21.4)			0.013

Proposal in a nutshell

- ◆ One single international JIA registry for **MTX±biologics**
- ◆ Combination of existing registries for safety
 - non-profit (Germany, UK, France, Italy, Netherlands, etc)
 - for profit
- ◆ Establishment of a **common platform** for an active pharmacovigilance system
- ◆ Main goals: **safety** and effectiveness (e.g. erosions, efficacy, remission, retention on treatment)



MARCO
Epoca

EUGENIA
Eurofever
Pharmachild

LUCA
IT developer

CHIARA
Pharmachild
MedDRA expert

SIMONA
Finance & contracts
Pharmachild
JDM

ELISA
Share
Epoca
Mypan

LAURA
Clinical Trials
Pharmachild

FRANCESCA
Statistician

IRENE
Pharmachild
Mypan
JDM

MARIANGELA
IT developer

SILVIA
Share
Epoca