THE PHARMACHILD PROJECT: A PRINTO/PRES REGISTRY IN JUVENILE IDIOPATHIC ARTHRITIS

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Istituto G. Gaslini Genova

Pediatric Rheumatology International Trials Organisation (PRINTO)

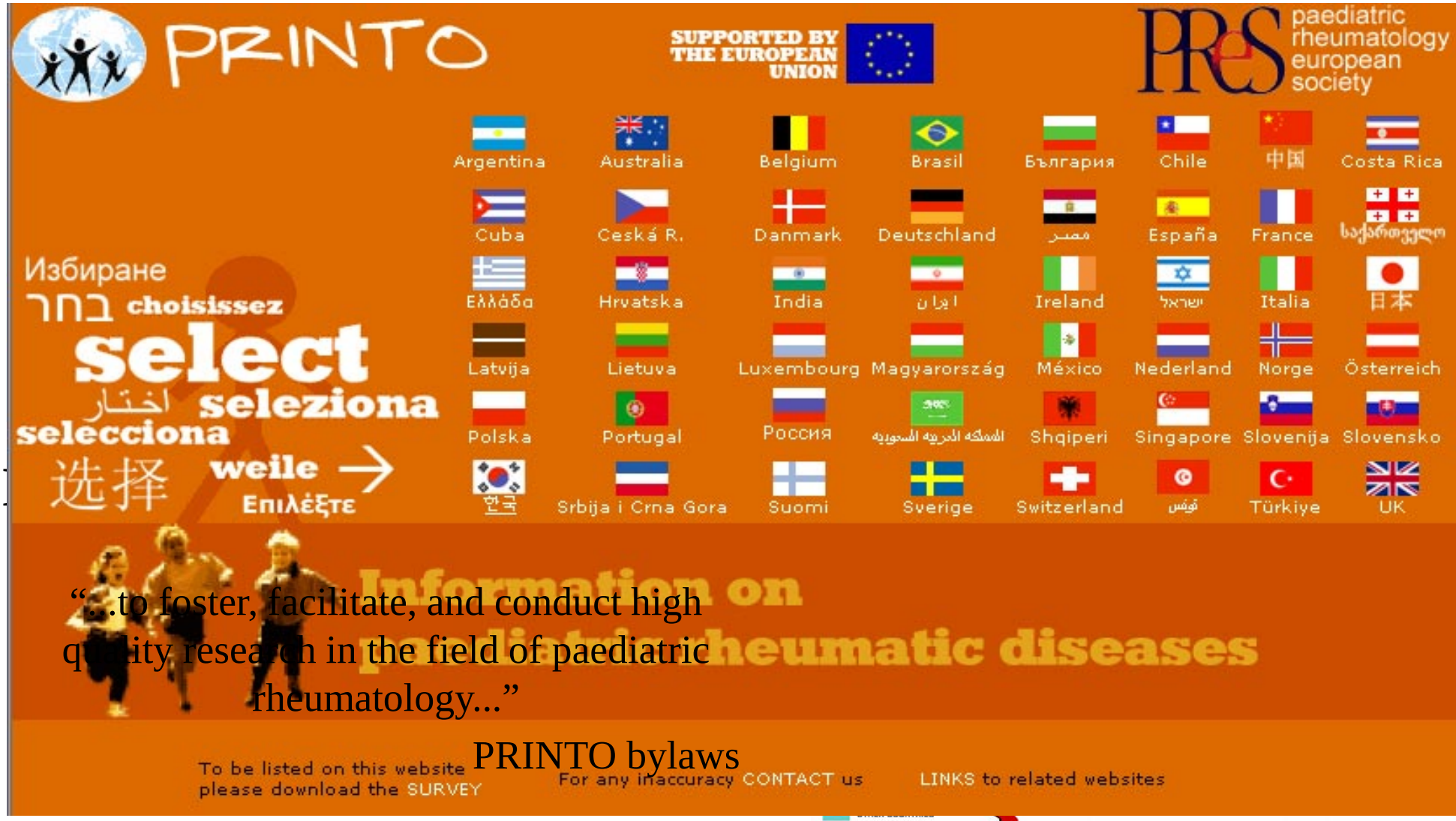
EULAR Centre of Excellence in Rheumatology 2008-2013

Outline

- PRINTO and juvenile idiopathic arthritis (JIA)
- Safety of biologicals in JIA
- The Pharmachild
  - Protocol
  - Websystem
  - Very preliminary results
- Problems with international collaboration
  - Ethics
  - Funding

www.printo.it (56 countries)

www.pediatric-rheumatology.printo.it



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

PRINTO bylaws

PRINTO no profit studies

	Western Europe	Eastern Europa	Latin America	North America	Other	Total
MTX	492	55	66	8	12	**633**
QOL	3,988	1,388	903		365	**6,644**
JSLE	243	102	150	37	21	**553**
JDM	162	37	78	18	3	**298**
CSA	203	27	25	85	4	**344**
MTX2	180	80	90		10	**360**
Vascul.	599	353	260	6	181	**1399**
Autoin	750	133	24		96	**1003**
JDM	98	13	15	1	2	**139**

The success of the EU pediatric legislation

Regulation (EC) no 1901/2006

	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
  - Unkown 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. Askling[3]

ARTHRITIS & RHEUMATISM
Vol. 62, No. 12, December 2010, pp 3776–3782

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Tumor Necrosis Factor α Bl

Forty-Eight Cases Rep

Peter Di

Drug Administrati

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. Epub Ahead of Print Jan 15 2011; doi:10.3899/jrheum.100711)

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EDITORIAL

Arthritis & Rheumatism

An Official Journal of the American College of Rheumatology
www.arthritisrheum.org and www.interscience.wiley.com

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?

U.S. Department of H

www.hhs.gov

U.S. Food and Drug Administration

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Drugs

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Drug Safety and Availability

Postmarket Drug Safety Information for Patients and Providers

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

Ruperto N, Martini. Nature Rheumatol 2011

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 2011/2014 **(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 ± 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

4. (JIA treated only with NSAIDs and/or steroid injection with at least 3 years follow-up).

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***

4. (JIA treated only with NSAIDs and/or steroid injection with at least 3 years follow-up).

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

*The KISS principle. Pincus et al J Rheumatol 2009

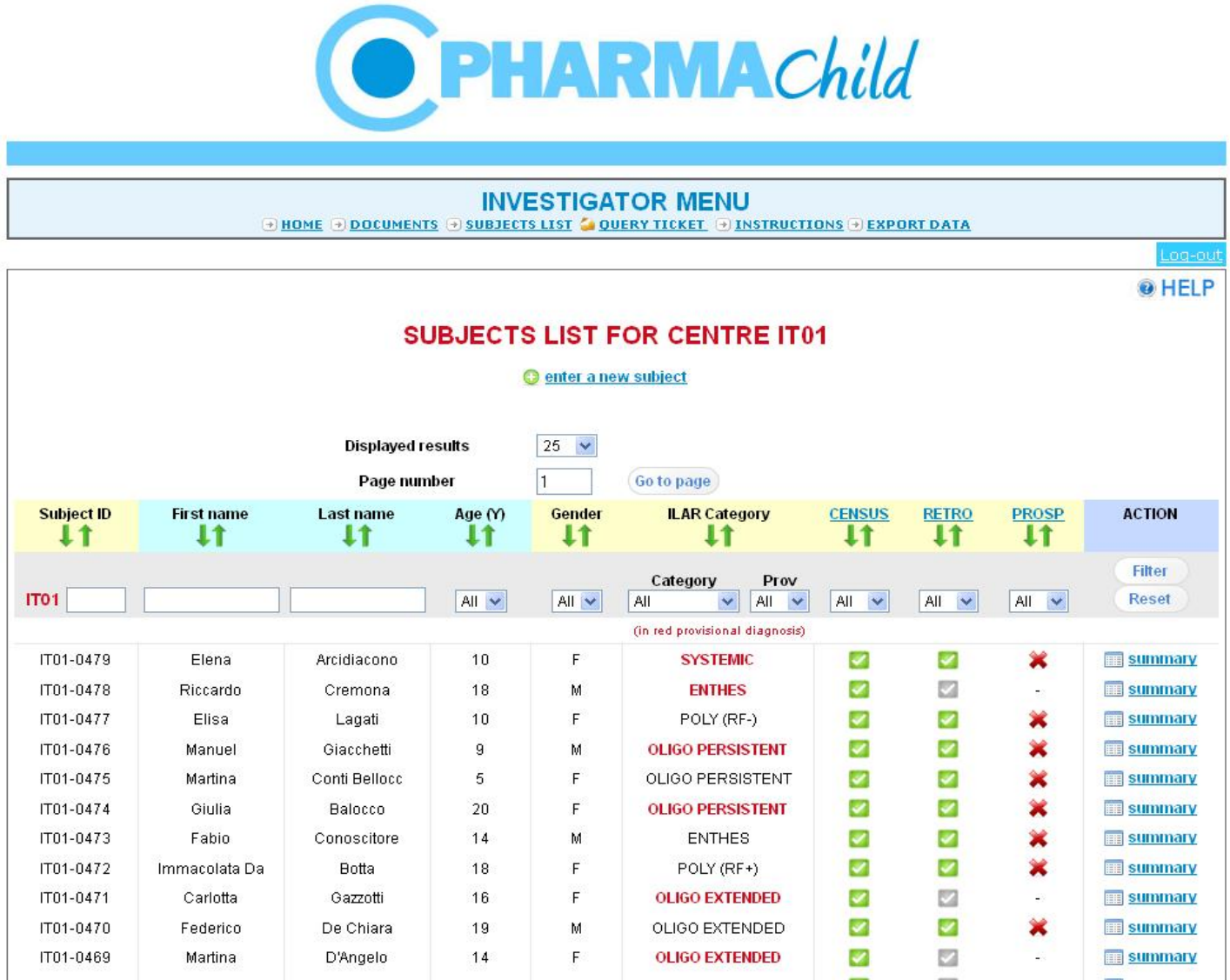
https://www.printo.it/pharmachild/investigator/

https://www.printo.it/pharmachild/investigator/

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 decripted



PHARMAchild

INVESTIGATOR MENU

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HELP

SUBJECTS LIST FOR CENTRE IT01

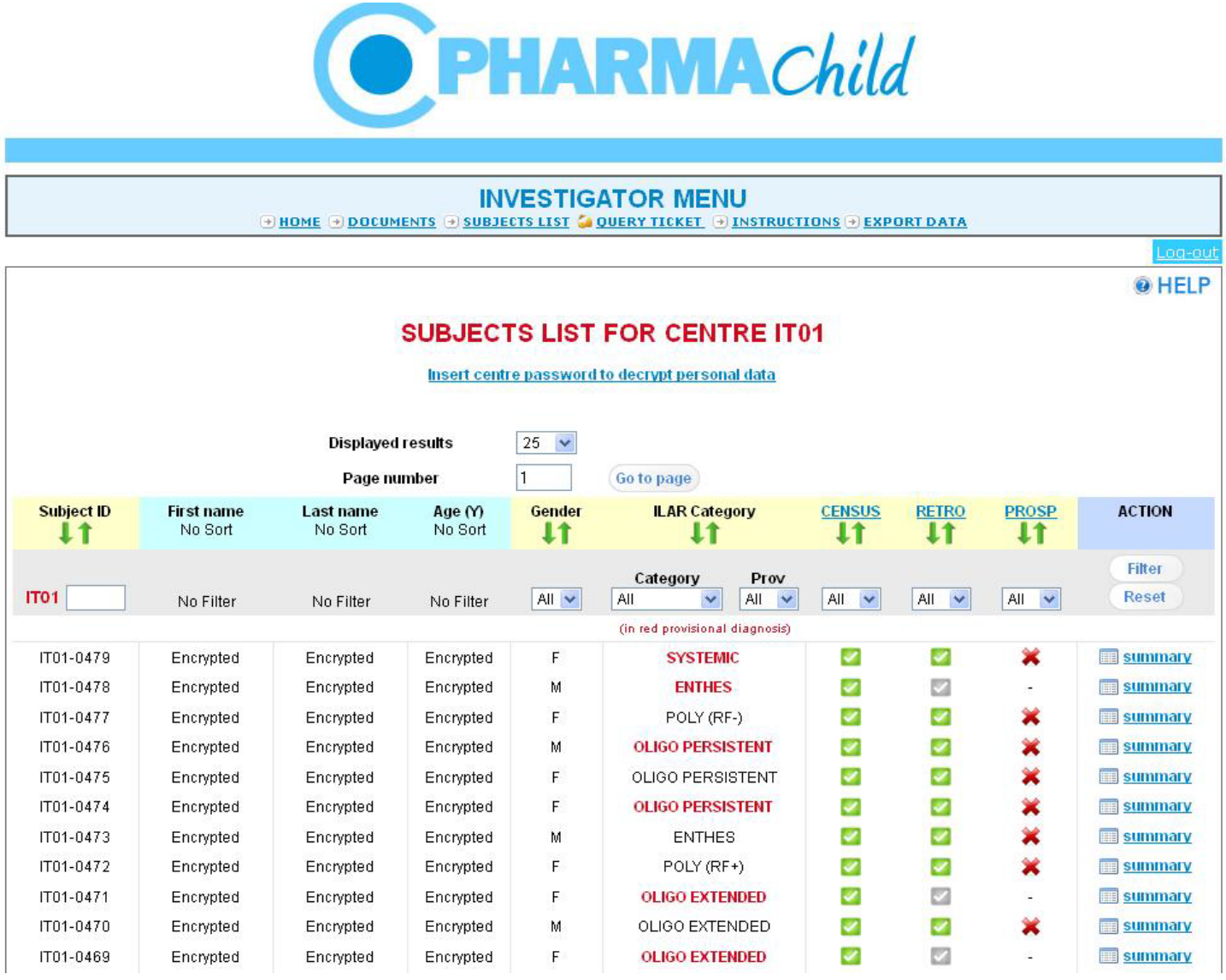
enter a new subject

Displayed results: 25

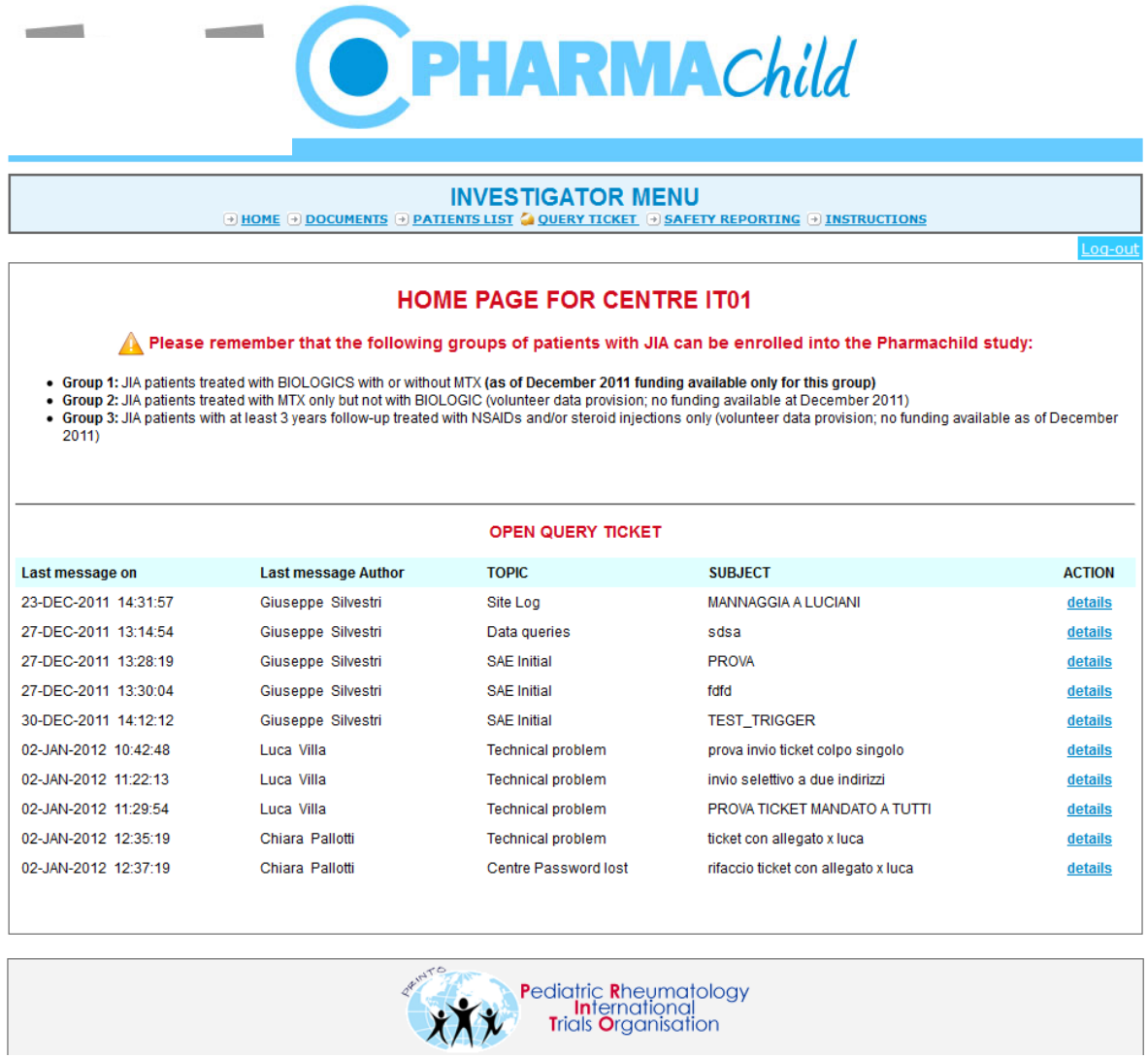
Page number: 1 Go to page

Subject ID	First name	Last name	Age (Y)	Gender	ILAR Category	CENSUS	RETRO	PROSP	ACTION
IT01			All	All	Category: All / Prov: All	All	All	All	Filter / Reset
					(in red provisional diagnosis)				
IT01-0479	Elena	Arcidiacono	10	F	SYSTEMIC	✓	✓	✗	summary
IT01-0478	Riccardo	Cremona	18	M	ENTHES	✓	✓	-	summary
IT01-0477	Elisa	Lagati	10	F	POLY (RF-)	✓	✓	✗	summary
IT01-0476	Manuel	Giacchetti	9	M	OLIGO PERSISTENT	✓	✓	✗	summary
IT01-0475	Martina	Conti Bellocc	5	F	OLIGO PERSISTENT	✓	✓	✗	summary
IT01-0474	Giulia	Balocco	20	F	OLIGO PERSISTENT	✓	✓	✗	summary
IT01-0473	Fabio	Conoscitore	14	M	ENTHES	✓	✓	✗	summary
IT01-0472	Immacolata Da	Botta	18	F	POLY (RF+)	✓	✓	✗	summary
IT01-0471	Carlotta	Gazzotti	16	F	OLIGO EXTENDED	✓	✓	-	summary
IT01-0470	Federico	De Chiara	19	M	OLIGO EXTENDED	✓	✓	✗	summary
IT01-0469	Martina	D'Angelo	14	F	OLIGO EXTENDED	✓	✓	-	summary

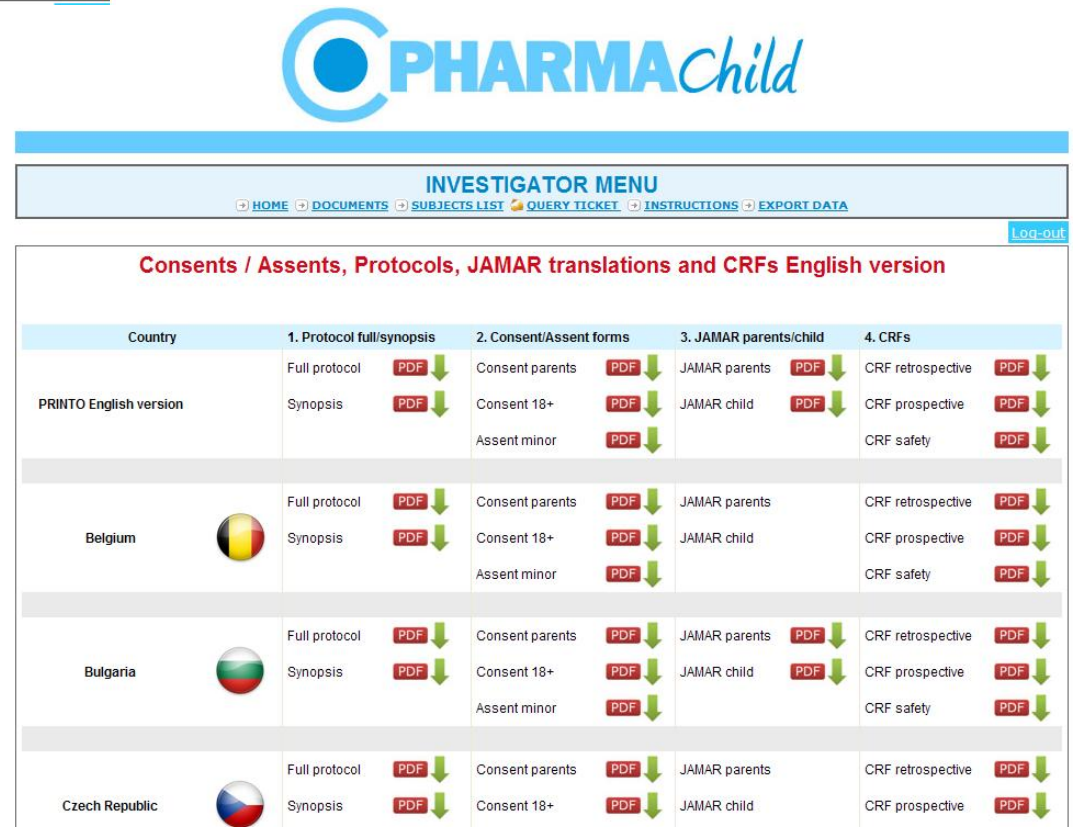
Patient list encrypted



Home page: communication tracking



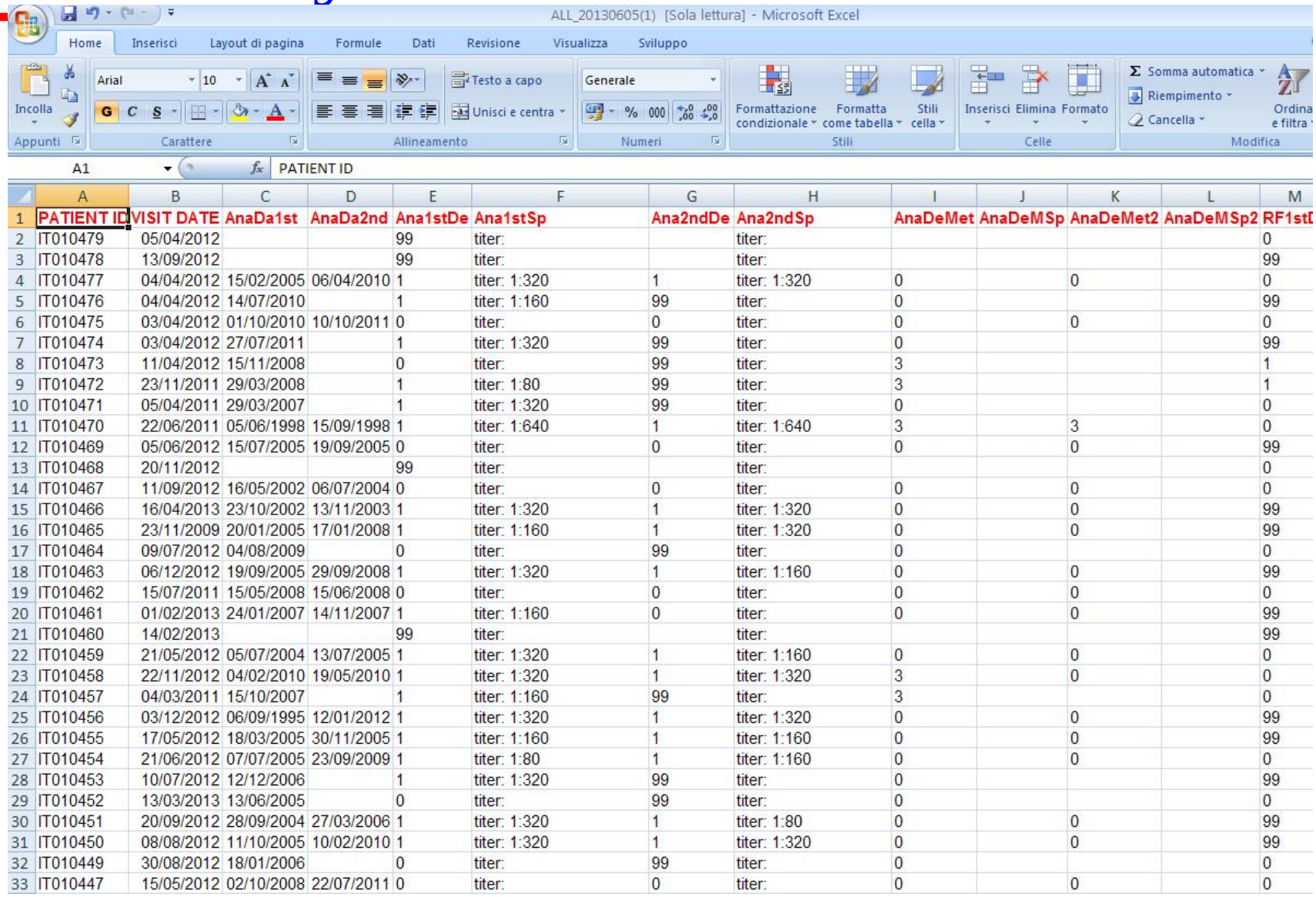
Ethics committees documents



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 quantitave chronicle
  - Decision on patient management based on quantitative data
- No paper forms but web forms
- **A research and linical service to the pediatric rheumatology community**

Download your own data



	A	B	C	D	E	F	G	H	I	J	K	L	M
1	PATIENT ID	VISIT DATE	AnaDa1st	AnaDa2nd	Ana1stDe	Ana1stSp	Ana2ndDe	Ana2ndSp	AnaDeMet	AnaDeMSp	AnaDeMet2	AnaDeMSp2	RF1stD
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3	IT010478	13/09/2012			99	titer:		titer:					99
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5	IT010476	04/04/2012	14/07/2010		1	titer: 1:160	99	titer:	0				99
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7	IT010474	03/04/2012	27/07/2011		1	titer: 1:320	99	titer:	0				99
8	IT010473	11/04/2012	15/11/2008		0	titer:	99	titer:	3				1
9	IT010472	23/11/2011	29/03/2008		1	titer: 1:80	99	titer:	3				1
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21	IT010460	14/02/2013			99	titer:		titer:					99
22	IT010459	21/05/2012	05/07/2004	13/07/2005	1	titer: 1:320	1	titer: 1:160	0		0		0
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Patient disease activity and drugs

PHARMAChild

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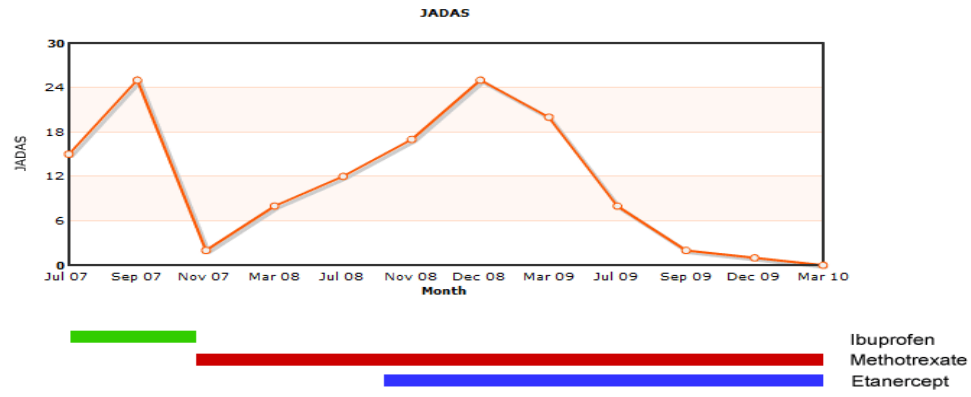
Patients list > Patient IT010075 summary > statistics

PROSPECTIVE STATISTICS

PATIENT IT010069 - mario rossi date of birth 02-MAY-2011



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Pediatric Rheumatology International Trials Organisation

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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	

PRINTO Feasibility (refer to 2008 – updated 2013)

	Western Europe	Eastern Europe	Latin America	Other	Total
No of centres	87	35	38	37	**197**
Methotrexate					
Prevalent	**10,663**	**4,276**	**4,231**	**3,438**	**22,608**
Incident	**2,148**	**845**	**960**	**740**	**4,693**
Biologic agents					
Prevalent	5,538	2,296	1,152	1,030	**10,016**
Incident	1,682	569	409	365	**3,025**

Methodology versus logistic hurdles

- 103 approvals from 30 different countries for JDM trial (essentially no comments) in two years
  - **3 refused approval because drugs were “not approved” for use in children!**
  - **Some request insurance for a “standard of care study” (20,000€ or 8% of the budget from AIFA)**
- **Move from directive to regulation for**
  - **Insurance not required for “ standard of care “ studies**
  - **“logistic management” of ethics approval: eg one per the entire EU or one per country**

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]

Arch Dis Child June 2012 Vol 97 No 6

Funding

- FP7 funding 2011/2014 **(PI Dr Nico Wulffraat)**
- Pharmaceutical companies
  - One project agreed (**PRINTO data property**, data collected for EMA/FDA company requirements)
  - Two under discussion

Funding: a negative history

- …3 applications to FP7 for MTX comparator within the framework of the paediatric priority list of off-patent drugs
  - 2010 total score 9,5/15 with a threshold of 10/15 (lack of industrial partner)
  - 2011 total score 2/15 (out of the scope of the call)
  - 2012 (two step procedure): rejected for lack of scientific significance

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)