

## ABIRISK

**Anti-Biopharmaceutical Immunization: Prediction and analysis of clinical relevance to minimize the risk**

**“Achievements 2013 and plan for 2014”**

**Marc Pallardy, INSERM UMR 996, France (IMI JU managing entity)  
Dan Sikkema, GSK (Overall Project Coordinator)**

**EIP Meeting, Lisbon, 2014**



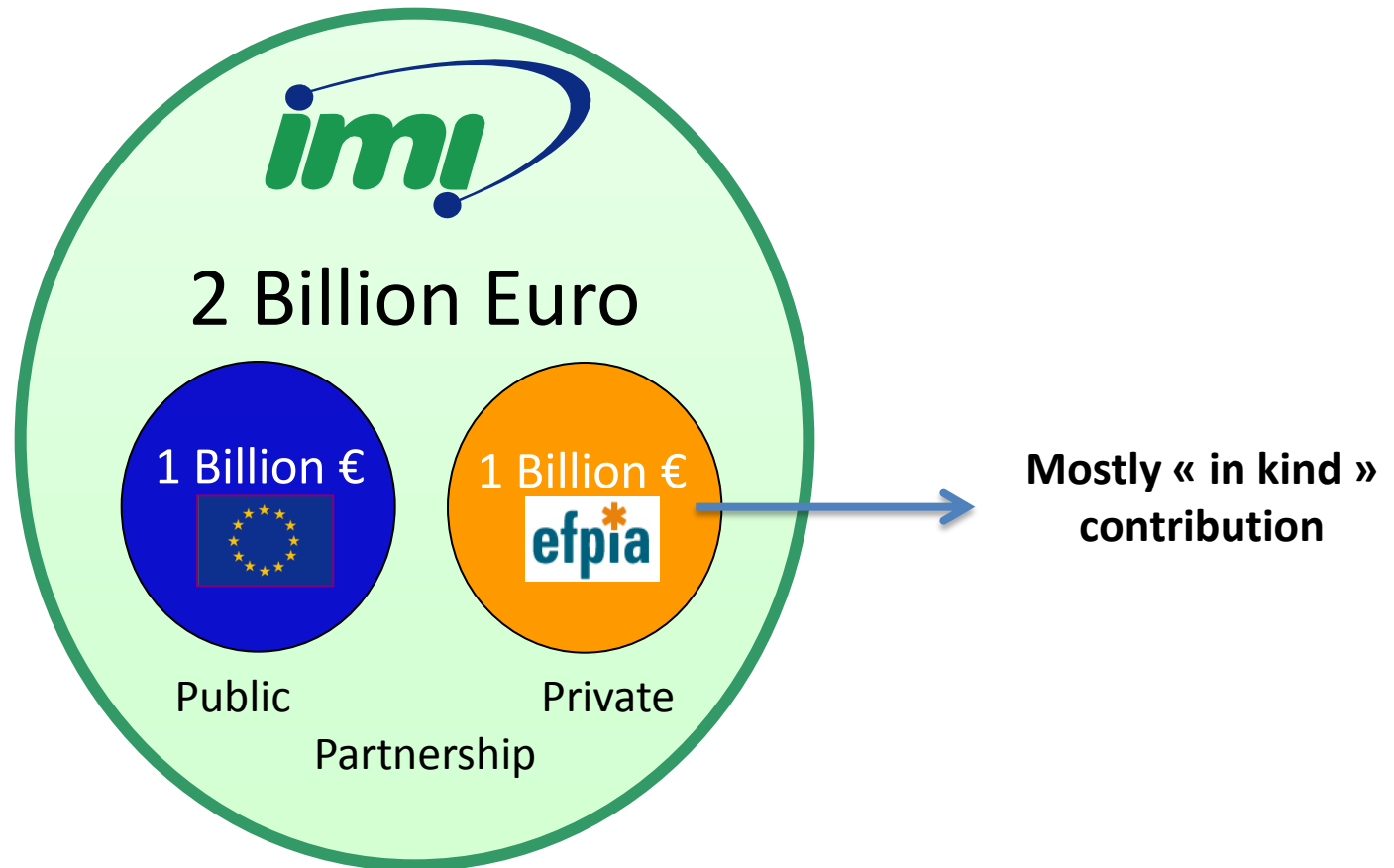
**Innovative Medicines Initiative**

A public-private partnership  
focused on needs common to  
pharmaceutical industry and patients

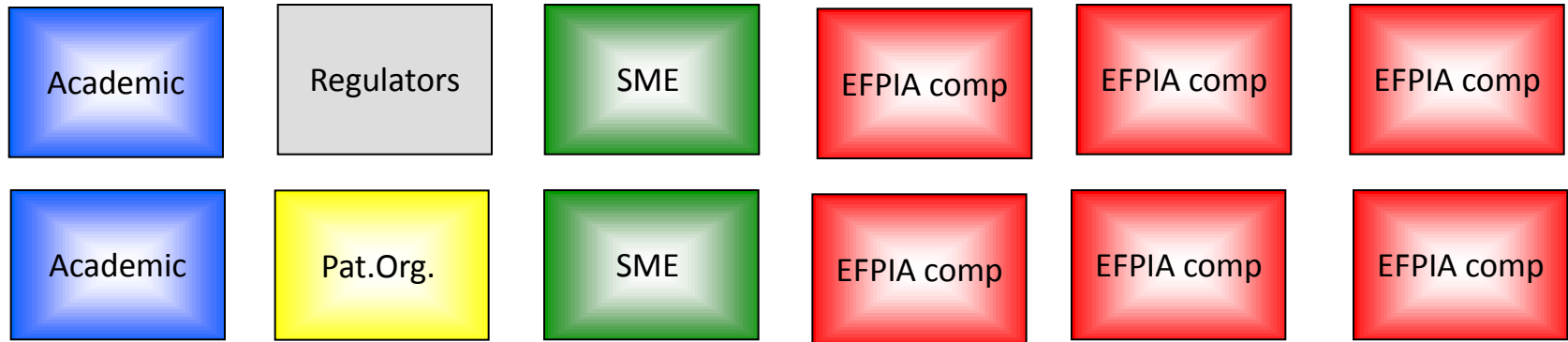


**efpia**

# Innovative Medicines Initiative: the Largest PPP in Life Sciences R&D



# Overall Structure of Research Projects



“Applicants consortium”

IMI beneficiaries



“EFPIA consortium”

EFPIA *in kind*  
contribution  
(no public funding)





**Start date: March 1<sup>st</sup> 2012; 5 years**

**Total project cost €34.9 million**

**EFPIA member companies: 9**

**Academic Partners: 27**

**SMEs: 3**

**39 partners total**



WWW.ABIRISK.EU

# The Consortium

## EFPIA MEMBER COMPANIES



GlaxoSmithKline Research & Development Limited  
United Kingdom  
[www.gsk.com](http://www.gsk.com)



Bayer Pharma AG  
Germany  
[www.bayer.com](http://www.bayer.com)



IPSEN Innovation S.A.S  
France  
[www.ipsen.com](http://www.ipsen.com)



Merck KGaA  
Germany  
[www.merckserono.com](http://www.merckserono.com)



Novartis Pharma AG  
Switzerland  
[www.novartis.com](http://www.novartis.com)



Novo Nordisk A/S  
Denmark  
[www.novonordisk.com](http://www.novonordisk.com)



Pfizer Limited  
United States  
[www.pfizer.com](http://www.pfizer.com)



Sanofi-Aventis Research and Development  
France  
[en.sanofi.com](http://en.sanofi.com)



UCB Pharma S.A.  
Belgium  
[www.ucb.com](http://www.ucb.com)

## SMEs



ALTA Ricerca e Sviluppo in Biotecnologie S.r.l.  
Italy  
[www.altaweb.eu](http://www.altaweb.eu)



Biomonitor A/S  
Denmark  
[www.biomonitor.dk](http://www.biomonitor.dk)



SciCross



Istituto Giannina Gaslini  
Italy  
[www.gaslini.org](http://www.gaslini.org)



Johann Wolfgang Goethe Universität - Klinikum und  
Fachbereich Medizin - Germany  
[www.kgu.de](http://www.kgu.de)



Karolinska Institutet  
Sweden  
[ki.se](http://ki.se)



Klinikum rechts der Isar der Technischen  
Universität München - Germany  
[www.med.tum.de](http://www.med.tum.de)



Medizinische Universität Innsbruck  
Austria  
[www.i-med.ac.at](http://www.i-med.ac.at)



Paul Ehrlich Institut, Bundesinstitut für Impfstoffe  
und biomedizinische Arzneimittel - Germany  
[www.pei.de](http://www.pei.de)



Queen Mary and Westfield - University of London  
United Kingdom  
[www.qmul.ac.uk](http://www.qmul.ac.uk)



Rambam Medical Center  
Israel  
[www.rambam.org.il](http://www.rambam.org.il)



Region Hovedstaden  
Denmark  
[www.regionh.dk](http://www.regionh.dk)



Università di Firenze  
Italy  
[www.unifi.it](http://www.unifi.it)



Universitätsklinikum Bonn  
Germany  
[www.ukb.uni-bonn.de](http://www.ukb.uni-bonn.de)



Universitätsklinikum Düsseldorf  
Germany  
[www.uniklinik-duesseldorf.de](http://www.uniklinik-duesseldorf.de)



Sheba Medical Center



University College London  
United Kingdom  
[www.ucl.ac.uk](http://www.ucl.ac.uk)



University Hospital Basel  
Switzerland  
[www.unispital-basel.ch](http://www.unispital-basel.ch)



Univerzita Karlova v Praze  
Czech Republic  
[www.cuni.cz](http://www.cuni.cz)



Institut National de la Santé et de la Recherche Médicale  
France  
[www.inserm.fr](http://www.inserm.fr)



Academisch Medisch Centrum  
the Netherlands  
[www.amc.nl](http://www.amc.nl)



Leids Universitair Medisch Centrum  
the Netherlands  
[www.lumc.nl](http://www.lumc.nl)



Centre National de la Recherche Scientifique  
France  
[www.cnrs.fr](http://www.cnrs.fr)



Commissariat à l'Energie Atomique et aux Energies  
Alternatives - France  
[www.cea.fr](http://www.cea.fr)



DRK-Blutspendedienst Baden-Württemberg - Hessen  
gemeinnützige GmbH - Germany  
[www.blutspende.de](http://www.blutspende.de)



Fondazione per l'Istituto di Ricerca in Biomedicina  
Switzerland  
[www.blutspende.de](http://www.blutspende.de)



Fundació Institut de Recerca de l'hospital Universitari  
Vall D'hebron - Spain  
[www.vhir.org](http://www.vhir.org)



Groupe d'Etudes Therapeutiques des Affections  
Inflammatoires du Tube Digestif - France  
[www.getaid.org](http://www.getaid.org)



Assistance-Publique  
Hôpitaux de Paris



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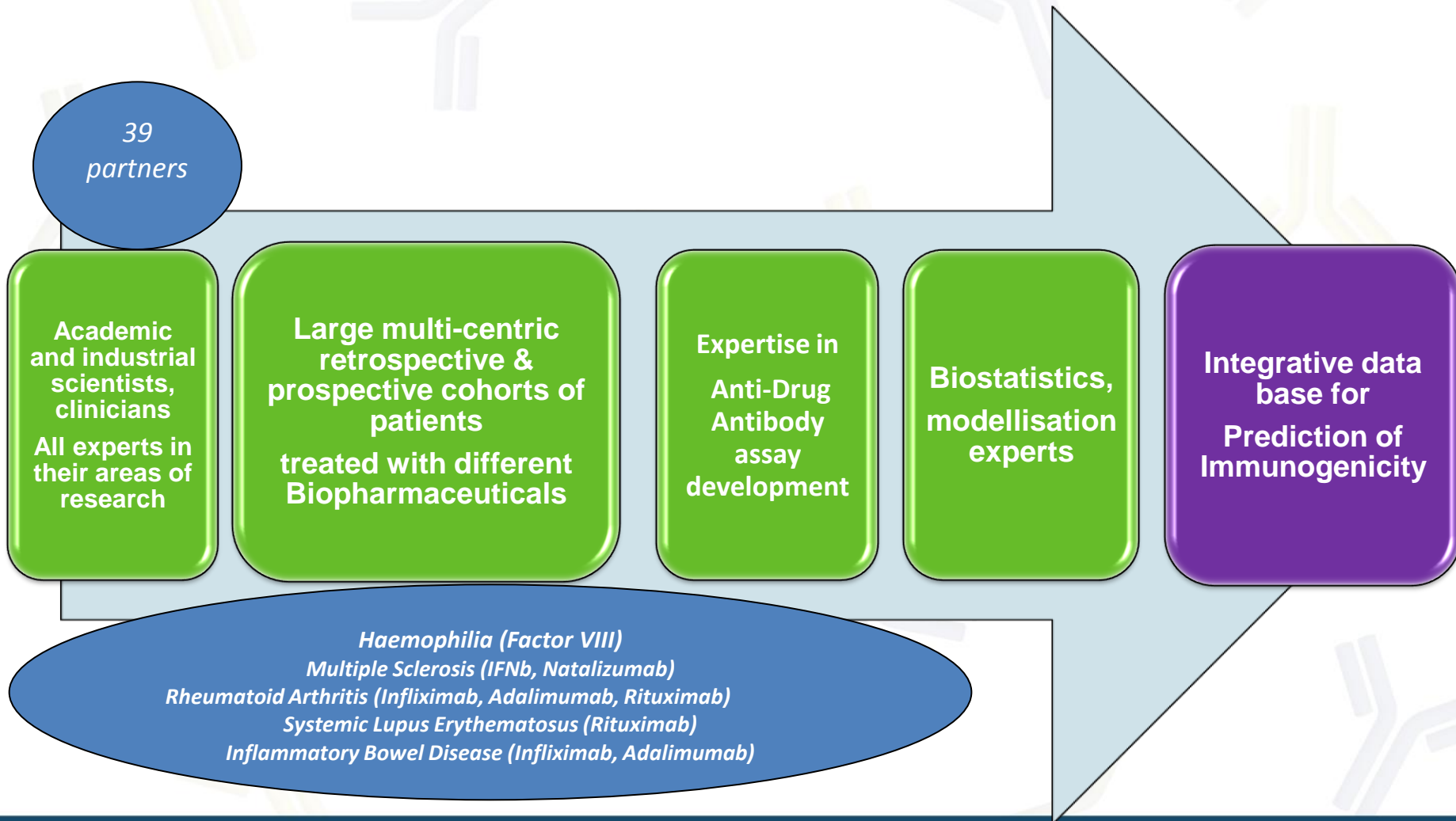
[www.imi.europa.eu](http://www.imi.europa.eu)

# Clinical Immunology/Immunogenicity

## The Challenges

- Immune responses in preclinical studies are not generally predictive of a clinical outcome
- Multiple reasons a protein can be immunogenic
- Clinical impact of an immune response can vary from “no-effect” to complete neutralization of an endogenous counterpart
- Monitoring patients for ADA/Nab is not harmonized and optimized
  - Several analytical procedures are available for the same product
  - Some assays are “proprietary”
  - Difficulties to compare results across cohorts
  - Early antibodies are often difficult to detect
- Weak effort to monitor the immune response in patients for understanding the mechanisms and for searching for predictive biomarkers
  - Mechanisms of immunogenicity in human are still poorly understood
  - Immunological mechanisms (danger signals, epitope...) ?
  - Influence of the disease ?
  - Role of concomitant treatments ?
- In case of LOR, immunogenicity and PK are not always taken into account for clinical decisions or medical treatment switching

# Objectives and driving forces (1)





# The Pillars

- **Building a unique data base** collecting data both retrospectively from patients suffering from MS, RA, IBD and HA treated with various BPs and prospectively from cohorts of patients in dedicated studies during the 5 years of the ABIRISK program.
  - **Prospective cohorts**
    - RA: 300 patients
    - IBD: 200 patients
    - Hemophilia: 100 patients
    - MS: 500 patients (IFN)
  - **Retrospective cohorts**
    - Protocols have been written for RA, in progress for MS (IFN and Natalizumab)
- **Standardization of ADA/NAB assays for the BPs assessed in ABIRISK**
  - Also provide PK assays and evaluation
- **Mechanisms of the immunological response**
  - Preliminary results are available for immunophenotyping (see Liz Jury presentation's)
- **Development and validation of innovative prediction tools for BPs immunogenicity (in silico, in vitro and in vivo)**
  - See Bernard Maillère presentation's
- **Integration of immunogenicity-related data and clinical relevance of ADA using a single immunogenicity databank.**
  - This will include the integration of various preclinical, clinical and immune monitoring factors.

# Work Packages

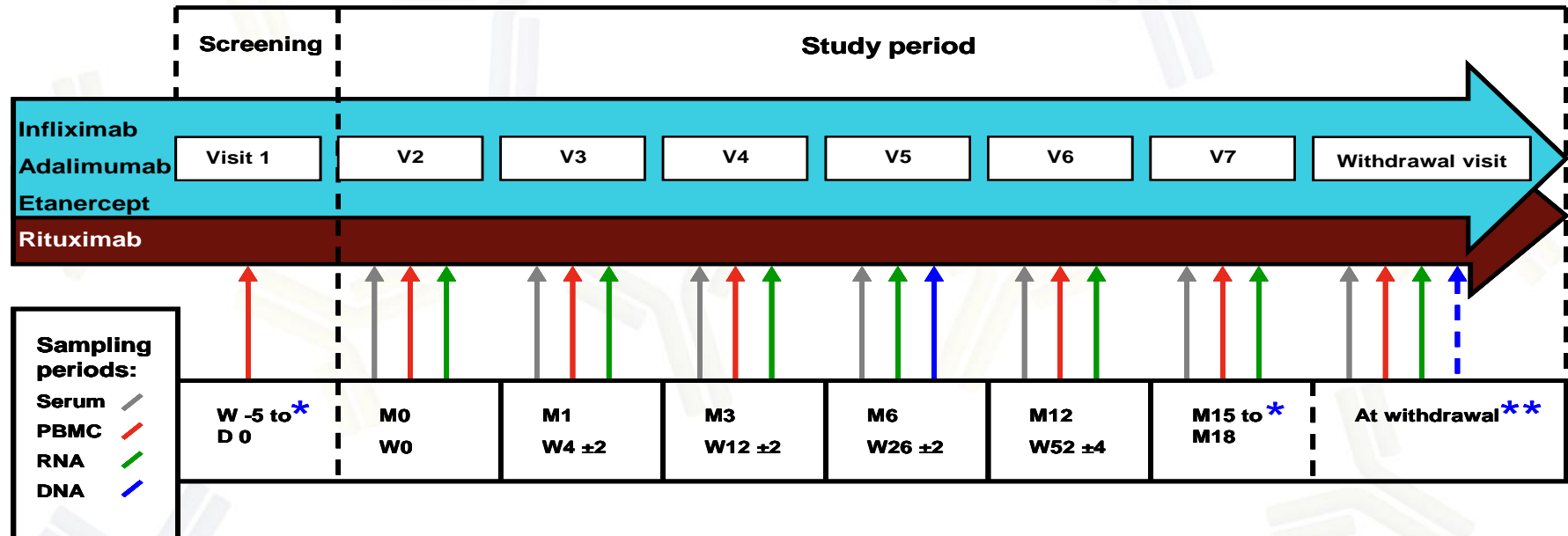
- WP1 “ADA assay development and validation and cohort management”
  - **F. Deisenhammer, Amy Loercher, Claudio Carini**
- WP2 “Cellular characterization and mechanisms of the AD immune response”
  - **C. Mauri, H. Kirby, V. Mikol**
- WP3 “Evaluation and development of technologies for predicting immunogenicity”
  - **B. Maillère , S. Spindeldreher, Ch. Ross-Pedersen**
- WP4 “Establishment of a data base, data analyses and integration”
  - **J. Davidson, Ph. Broet, A. Hincelin-Maury**
- WP5 “Project management and communication”
  - **R. Bertini, Dan Sikkema, M. Pallardy**
- Cohort management: Cohort leaders
  - **Rheumatoid Arthritis: X. Mariette, Inflammatory Bowel Disease: M. Allez; Hemophilia: J. Oldenburg; Multiple Sclerosis: A. Fogdel-Hahn**

# Patient Cohorts

- **Inflammatory diseases: Kremlin-Bicêtre (Xavier Mariette) (+ 15 French centers)**
  - University College, London (Claudia Mauri)
  - Leiden University Medical Center, Leiden (Tom Huizinga)
  - University of Amsterdam, Amsterdam (Niek de Vries)
  - Karolinska Institute (Lars Klareskog)
  - Istituto G Galini, University of Genova, paediatric patients (Nicola Ruperto)
- **Intestinal Bowel Diseases: GETAID (Mathieu Allez) (20 French, Belgium centers)**
  - RAMBA Health Care Campus, Haifa (Yehuda Chowers)
  - Chaim Sheba Medical Center (Shomron Ben Horin)
- **Hemophilia: University Clinic, Bonn (Johannes Oldenburg)**
  - Paul-Ehrlich-Institute, Langen (Rainer Seitz)
  - Goethe University, Frankfurt (Wolfhart Kreuz)
- **Multiple Sclerosis: Karolinska Institute, Stockholm (Anna Fogdell-Hahn)**
  - Innsbruck Medical University, Innsbruck (Florian Deisenhammer)
  - Heinrich Heine University, Düsseldorf (Hans-Peter Hartung)
  - Copenhagen University Hospital Rigshospitalet, Copenhagen (Per Soelberg Sorensen)
  - University Basel Hospital, Basel (Raija Lindberg)
  - General Charles University, Pragua (Eva Havrdova)
  - Hospital Univeritari Vall d'Hebron, Barcelona (Xavier Montalban)
  - Blizard Institute of Cell and Molecular Medicine, London (Gavin Giovannoni)
  - Technischen Universität, München (Bernhard Hemmer)

## Prospective cohort progress

- Scientific protocols have been established and written for each cohort
- Regulatory requirements for clinical trial application in each country have been completed and authorization obtained
- Sample management including coding and biobanking is now organized for most of the cohorts
  - Protocol number, e-CRF, laboratory manual, monitoring...
- Patient Inclusion should start between March and April



**ADAb Positive Patient:** Subject with at least 1 treatment-induced or treatment-boosted ADAb positive sample at any time during the study period.

The group of ADAb Positive Patients will be stratified in transient ADAb+ (positive at M1, M3 or M6 and negative at M12) and persistent ADAb+ (positive at M12).

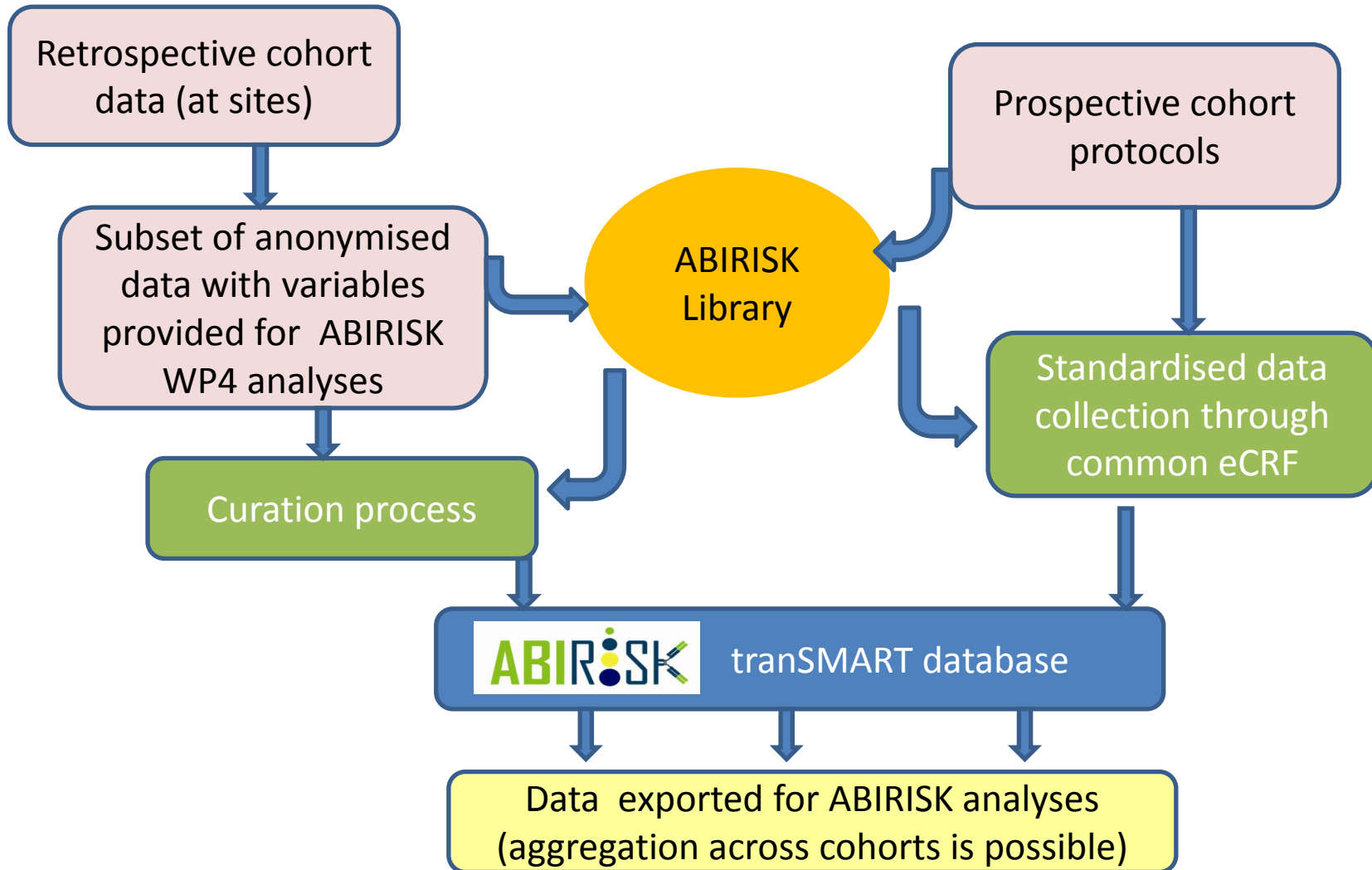
**ADAb Negative patient:** Subject without a treatment-induced or treatment-boosted ADAb positive sample during the study period.

\*\* If patient withdraws before month 18, a withdrawal visit should be planned

- Academic laboratories and SMEs have sent their updated protocols for review by EFPIA « ad-hoc » and independent committees. Goal: to meet industry standards
- Reference methods and Central labs have been selected for anti-TNF (ADA, Nab and PK)
  - Common read-out : Results will be given in titers on positive samples
- Methods and Central labs for IFNs will be selected soon
  - New ELISA bridging format for IFN beta
  - New cell-based assay for anti-IFN NAB (cut-off point method)
- Human ADA standards have been produced (A. Lanzavecchia) for IFN and Rituximab. Infliximab in progress.

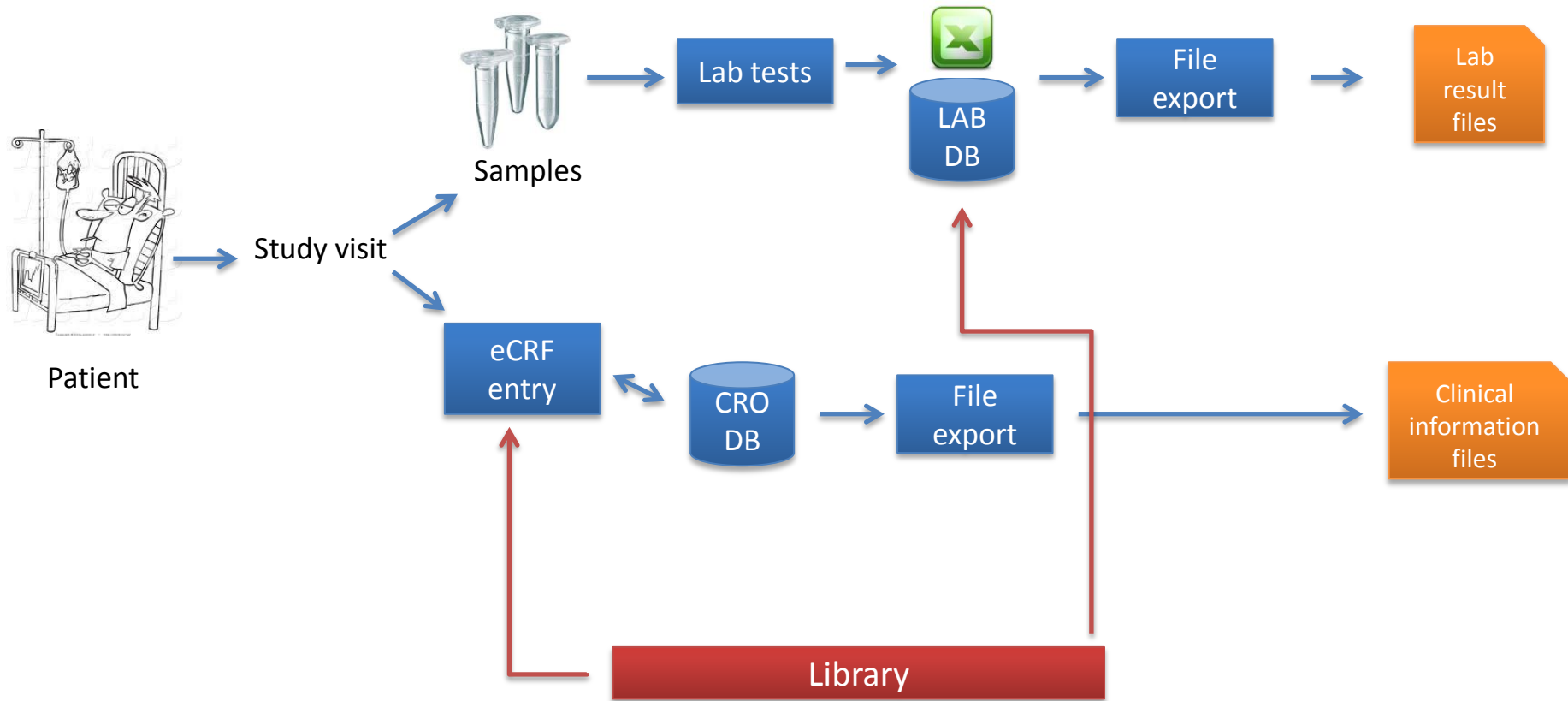
# Data Base

## Conceptual overview of the database

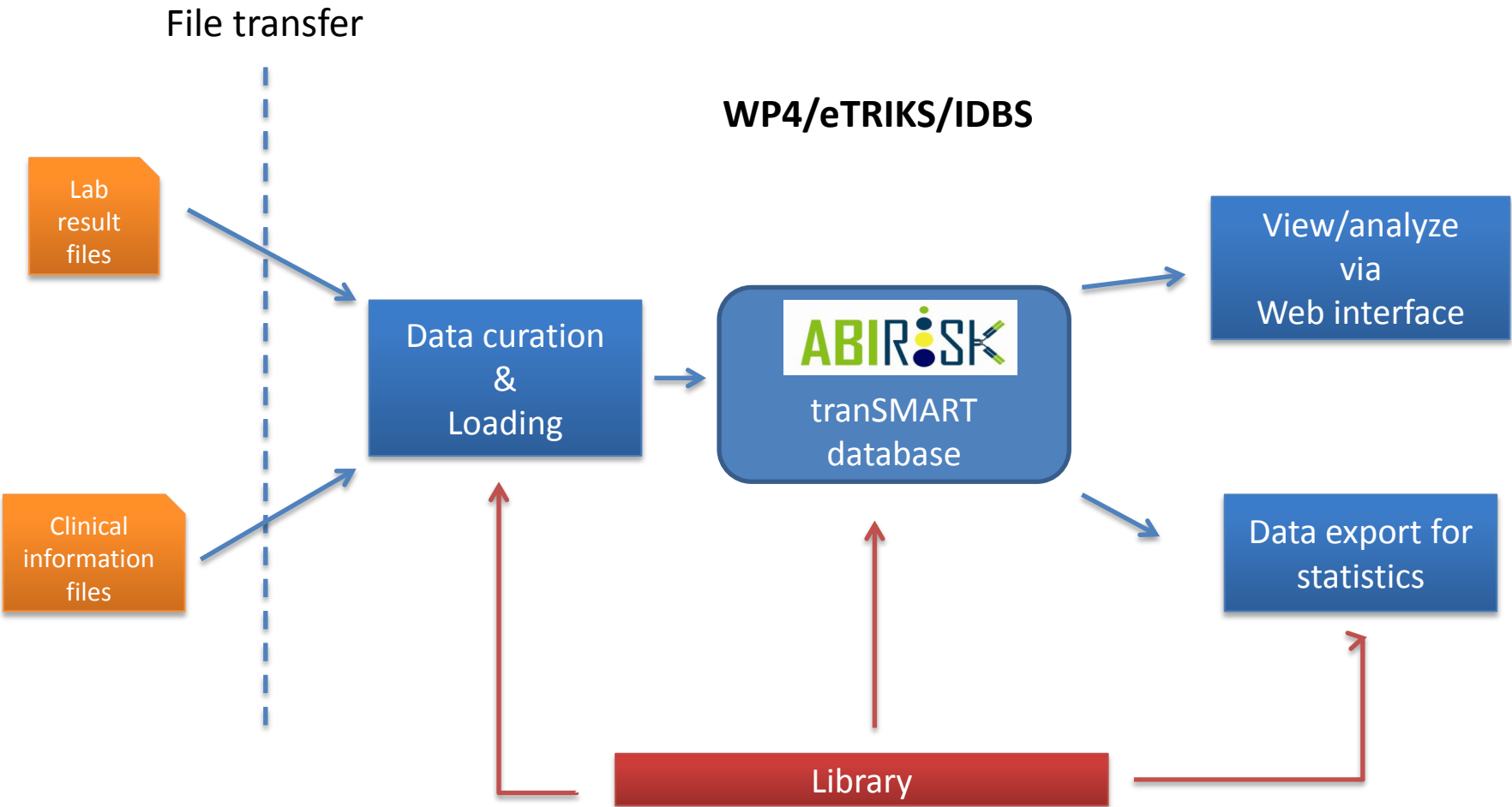




# Prospective study data flow



# Prospective study data flow



# Recent achievements

- Wave one retrospective data for MS has been achieved
- Common data base platform (TransMart) implemented (data curation etc...)
- 5 countries, 12000 patients (33000 samples)
- Data base ready for querying, analysis and storing retrodata from ABIRISK
- Example:
  - “How many patients in each country have been tested for ADA ?”

## In 2014

- Recruit patients and biobank samples from prospective cohorts
  - Start the dosing phase of ADA, NAB and PK
- Ongoing work on « cross-sectionnal » cohorts for analysis of the immune response
- Analyse first results from animal models, in silico and in vitro predictive models
- Work on retrospective cohorts data inclusion for RA and IBD; hemophilia is nearly completed
- **DO SCIENCE**

- Be an unique place providing information on BP immunogenicity
  - External Newsletter for identified stakeholders
  - Monthly Scientific Newsletter
  - Website [www.abirisk.eu](http://www.abirisk.eu)
  - LinkedIn discussion group