Inhibitor data collection systems National registries

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EUCERD core recommendations on RD registration and data collection

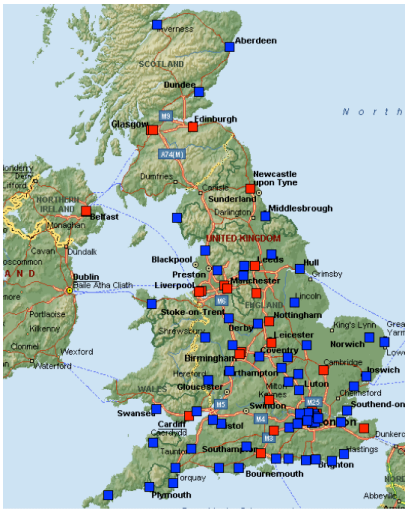
- A patient registry is an organised system that uses observational study methods
  - to collect uniform data (clinical and other)
  - to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure,
- and serves one or more predetermined scientific, clinical, or policy purposes.
- Conditions: interoperability, speed up knowledge and clinical research, support public health, adhesion to good practice guidelines, serve regulatory purposes, should be sustainable for the foreseeable timespan of the registries' utility

EUCERD: European Union Committee of Experts on Rare Diseases
EUCERD core recommendations on rare disease patient registration and data collection, 5 June 2013

- Some examples:
  - UK
  - Canada
  - France

UK National Haemophilia data base

- Created in 1968
- Nominative
- Data are collected by all haemophilia centres
- Partially public funding
- Data collection: diagnosis, genotype, family history, treatments, adverse events, mortality…
- Inhibitor risk-factors



Canadian Hemophilia Registry
& Rare Inheritied Bleeding Disorders Registry

AHCDC

A PROJECT OF THE ASSOCIATION OF HEMOPHILIA CLINIC DIRECTORS OF CANADA

- Created in 1988 by the canadian hemophilia Clinic Directors Group
- Anonymous
- Data collected: diagnosis, clinic, province, date of birth, HIV and HCV status (until 2007), treatments

The history of French registries

National Survey of Haemophilia

- Created in 1994
  - at the request of the Ministry of Health to improve the therapeutic monitoring of patients with haemophilia
- A safety guarantee given to the patients in the context of the dramatic story of HIV and HCV transmission by the blood products
- Limited to haemophilia, poor aherence, too costly…..
- Totally revised in 2000 ad replaced in 2003 by another project: FranceCoag Network

FranceCoag network

- Is a **national registry** of familial haemorrhagic diseases (except platelet disorders)
- **Anonymous**
- **Observational** study
- **An open cohort** (constantly evolving)
- Set up in 2003 (INSERM) and coordinated by the InVS (Public health surveillance institute) since 2004.
- **Exclusively public funded** (approximately 400 000 € /year)

http://www.francecoag.org

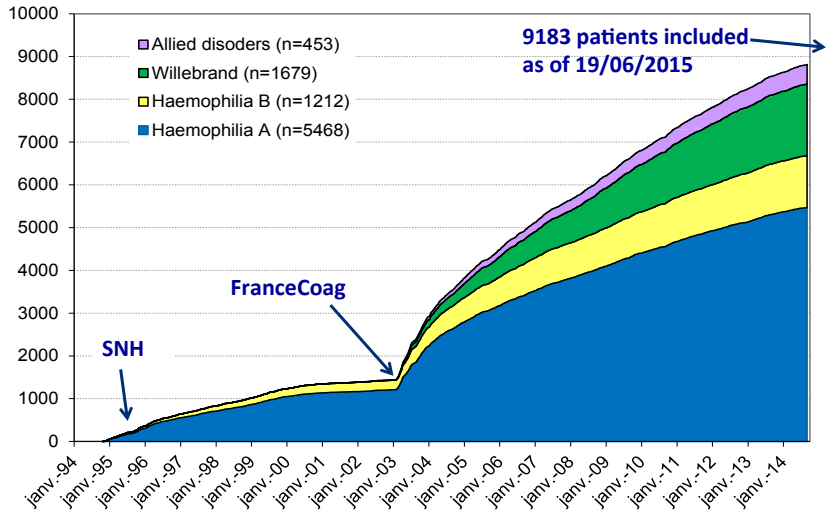
4 Main Objectives for FranceCoag

- Knowledge of the **population**
- Sanitary **surveillance**
- Knowledge on the **risk factors for inhibitor** development in children with severe haemophilia
- Assessment of the feasibility, adherence and impact of standardized **prophylaxis regimens**.

Réseau FranceCoag

http://www.francecoag.org

On going progression of the Cohort



Global results

19th June 2015

9 183 patients included

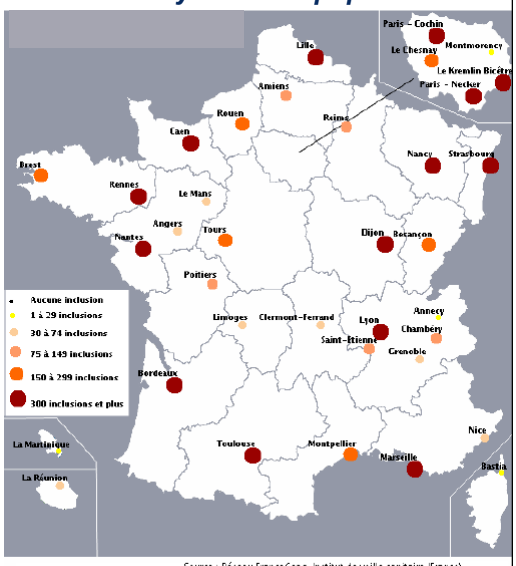
36 centres

60 037 person year cohort

8 732 patients currently followed
314 died
137 lost of FU

Réseau FranceCoag

Currently followed population



Source : Réseau FranceCoag, Institut de veille sanitaire (France)

NB : il s'agit de la répartition géographique des patients non décédés ou non perdus de vue à la date de la réactualisation des données et pour lesquels au moins un formulaire a été enregistré.

Organisation

Réseau FranceCoag

- A permanent structure (CC) based in InVs
  - (3 persons, 2 full time)
- A Steering Committee
  - (5 meetings a year)
- A working group on inhibitors
  - Clinicians, statisticians, genetician, Inserm*
  - Validation of any case of new inhibitor
  - Discussion about the results of analysis
  - 3-4 meetings per year
- On site monitoring by 3 dedicated clinical research assistants based in 3 centres (Lille, Marseille, Paris) and traveling in every participating centre.

*INSERM and UPMC Univ Paris 06 (UMR_S 1136): T Calvez, D Costagliola

The inhibitor risk in Haemophilia A

- Inhibitors : the most serious and challenging complications of replacement therapy especially in PUPs
- Development of inhibitor is a multifactorial event involving several risk cofactors that act simultaneously
- *« PUPs studies have been invaluable in determining inhibitor risk factors »* and this explains the importance of **PUPs cohorts**

Carcao M et al. Haemophilia 2015

PUPs cohorts: some examples

- The RODIN cohort

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Factor VIII Products and Inhibitor Development in Severe Hemophilia A

Samantha C. Gouw, M.D., Ph.D., Johanna G. van der Bom, M.D., Ph.D., Rolf Ljung, M.D., Ph.D., Carmen Escuriola, M.D., Ana R. Cid, M.D., Ségolène Claeyssens-Donadel, M.D., Christel van Geet, M.D., Ph.D., Gili Kenet, M.D., Anne Mäkipernaa, M.D., Ph.D., Angelo Claudio Molinari, M.D., Wolfgang Muntean, M.D., Rainer Kobelt, M.D., George Rivard, M.D., Elena Santagostino, M.D., Ph.D., Angela Thomas, M.D., Ph.D., and H. Marijke van den Berg, M.D., Ph.D., for the PedNet and RODIN Study Group*

N Engl J Med 2013;368:231-9.
DOI: 10.1056/NEJMoa1208024

CLINICAL TRIALS AND OBSERVATIONS

UK

Factor VIII brand and the incidence of factor VIII inhibitors in previously untreated UK children with severe hemophilia A, 2000-2011

Peter W. Collins,[1] Benedict P. Palmer,[2] Elizabeth A. Chalmers,[3] Daniel P. Hart,[4] Ri Liesner,[5] Savita Rangarajan,[6] Katherine Talks,[7] Michael Williams,[8] and Charles R. M. Hay,[9] on behalf of the UK Haemophilia Centre Doctors' Organization

(*Blood.* 2014;124(23):3389-3397)

CLINICAL TRIALS AND OBSERVATIONS

RFC: Reseau FranceCoag

Recombinant factor VIII products and inhibitor development in previously untreated boys with severe hemophilia A

Thierry Calvez,[1,2] Hervé Chambost,[3,4] Ségolène Claeyssens-Donadel,[5] Roseline d'Oiron,[6] Véronique Goulet,[7] Benoît Guillet,[8] Virginie Héritier,[7] Vanessa Milien,[3] Chantal Rothschild,[9] Valérie Roussel-Robert,[10] Christine Vinciguerra,[11] and Jenny Goudemand,[12] for the FranceCoag Network

(*Blood.* 2014;124(23):3398-3408)

ORIGINAL ARTICLE *Clinical haemophilia*

Canada

Incidence and risk factors for inhibitor development in previously untreated severe haemophilia A patients born between 2005 and 2010

C. VÉZINA,* M. CARCAO,† C. INFANTE-RIVARD,‡ D. LILLICRAP,§ A. M. STAIN,¶ E. PARADIS,** J. TEITEL†† and G. E. RIVARD* ON THE BEHALF OF THE ASSOCIATION OF HEMOPHILIA CLINIC DIRECTORS OF CANADA AND OF THE CANADIAN ASSOCIATION OF NURSES IN HEMOPHILIA CARE

Réseau FranceCoag

The French Cohorts

- **A general cohort:**
  - For all patients included in the registry, with the same level of informations and data
- **A Pups sub Cohort**
  - severe (<1 IU/dL) included early after diagnosis with full traceability of the first 75 EDs and closely monitored until 150 CEDs (quarterly visits recommended)
  - exhaustive: *all children born from the 1/01/2000*

Table S1: Number of live male births, number of boys with hemophilia A (HA) and estimated prevalence of HA at birth in France during the period 1991-2013.

Year	No. of live male births *	No. of boys †		Prevalence at birth (per 100 000 live male births)	
		Severe HA	All HA	Severe HA	All HA
Period 1991-2008					
1991	389 239	35	95	9,0	24,4
1992	381 744	31	82	8,1	21,5
1993	364 589	41	100	11,2	27,4
1994	364 277	35	99	9,6	27,2
1995	373 409	27	96	7,2	25,7
1996	377 003	43	101	11,4	26,8
1997	373 157	27	85	7,2	22,8
1998	378 075	27	81	7,1	21,4
1999	382 132	30	92	7,9	24,1
2000	397 352	38	91	9,6	22,9
2001	394 297	41	97	10,4	24,6
2002	389 981	37	94	9,5	24,1
2003	389 349	26	90	6,7	23,1
2004	393 477	26	80	6,6	20,3
2005	396 346	27	92	6,8	23,2
2006	407 846	41	95	10,1	23,3
2007	402 297	38	80	9,4	19,9
2008	406 784	44	74	10,8	18,2
Total	**6 961 354**	**614**	**1624**	**8.8**	**23.3**

* Source: *Institut national d'études démographique (Ined).* Births by sex. 2013.
† Boys with hemophilia A included in the FranceCoag Network as of May 19, 2014.

Prevalence of HA at birth in France: 23.3 cases per 100 000 male live births supports the exhaustiveness of the inclusion in RFC

Calvez and al. Blood 2014 Supplemental material

Réseau FranceCoag

Information collected (1)

- **For all: demographic items :**
  - Gender, date of birth, residence area, date and cause of death
- **For all : clinical and biological information:**
  - Disease, date and circumstances of diagnosis
  - Family history
  - Inhibitor history
  - History of blood borne infections (HBV, HCV, HIV)
  - Life-threatening and serious bleeds, surgical procedures
  - Highly relevant events since birth (ICH, joint prosthesis)
  - Adverse Events and comorbidities
  - Replacement therapy : type and amount of product (IU & CED), replacement regimen (prophylaxis, immune tolerance) …
  - Factor level, inhibitor screenings

Recommended periodicity : annually for severe haemophilia or every 2-3 years

Information collected (2)

- **For Pups: additional data set :**
  - **Genetics**: High risk or Low risk
  - **Ethnicity**: up to 4 ethnic origin (1 for each grand parent)
  - **Family history of inhibitor**
  - **Age at first exposure**
  - **Vaccine**
  - **Comprehensive data for 75 first ED**
  - **Comprehensive data for prophylaxis and immune tolerance**
  - Central lines
  - Haemarthrosis, target joints, clinical orthopaedic score, …

  Recommended periodicity : quarterly until 150 CEDs, then annually until 18 years of age

Réseau FranceCoag - Sous-cohorte PUPs

Collecte des premières journées d'exposition au FVIII

Version 5a - Le 24-08-2015

NB. Ce formulaire peut être imprimé soit sur 1 page (orientation portrait, réduction ≈40%), soit sur 3 pages (paysage, réduction ≈61%)

Si toute la largeur du tableau n'apparaît pas à l'écran, modifier l'affichage en réglant le Zoom

NUP (7 chiffres)

Année de naissance

En cas d'inhibiteur confirmé, date de découverte (1er titre > 0,6 UB)

Nombre d'EDs à la découverte de l'inhibiteur *

* Si une injection de FVIII a été faite à la même date, ne pas compter cet ED

Journée d'exposition			Motif(s) de l'injection (si l'injection a plusieurs motifs, préciser chacun)									Traitement				Poids
Num ED	Date	Précision de date	Saignement	Si saignement, Type	Suite de saignement	Douleur ou trauma.	Chirurgie (ou suites)	Prophy-laxie	Tolérance immune	Autre motif	Motif non disponible	Produit (FVIII)	Modalité	Si bolus, Posologie	Nb. total d'unités	
		1: Date précise et vérifiée 2: Date imprécise ou estimée	0: Non 1: Oui	1: Hémarthrose 2: Hématome 3: Sous-cutané 4: Muqueux 6: Intracrânien 7: Autre (->com.) 8: Plaie cutanée 99: Non disponible	0: Non 1: Oui	0: Non 1: Oui	0: Non 1: Oui	0: Non 1: Oui	0: Non 1: Oui	0: Non 1: Oui	0: Non 1: Oui	(cf. Codage dans les Consignes pour la collecte)	1: Bolus 2: Perfusion continue 3: Autre (->comm.) 99: Non disponible	(Nombre injections par jour)	99: Non disponible	
	(jj-mm-aaaa)															(en Kg)
1		1	0		0	0	0	0	0	0	0		1	1		
2		1	0		0	0	0	0	0	0	0		1	1		
3		1	0		0	0	0	0	0	0	0		1	1		
4		1	0		0	0	0	0	0	0	0		1	1		
5		1	0		0	0	0	0	0	0	0		1	1		

ED:
-Date
-Checked?

Clinical circumstances:
-Type of bleeding : haemarthrosis…
-Same bleeding: Y/N
-Surgery
-Prophylaxis
-ITI

Treatment:
-FVIII brand name
-Bolus, continuous infusion…
-Number of infusion/day
-Units/day

Fixed risk factors	RODIN	RFC	UK	CAN
	N: 574	N: 303	N: 407	N: 99
Date of birth	2000-2009	1991-2013	2000-2011	2005-2010
FVIII <1 IU/dL	574	303	407	91
Caucasian %	90.8	76.9	87.0	74.7
Family history of haemophilia with inhibitor (%)	14.5	11.0	10.0	ND
High risk *F8* mutation	57.7	70.6	60.0	70
Median age at 1rst exposure to FVIII (IQR) - mo	9.8 (5.4-13.5)	10.4 (5.6-14.3)	9 (5.6-14.3)	9.5

Time varying factors	RODIN	RFC	UK	CAN
Initiation of prophylaxis within first 50 EDs %	71.6	47.9		
Median EDs at start of prophylaxis	17 (7-25)	20 (11-33)		
History of peak treatment on first EDs				
> 3 consecutive days	26.0	30.0		
> 5 consecutive days	17.1	16.5	13.8	(8.1%)
History of surgery during follow up (%)	25.1	12.5		6.1

	RODIN	RFC	UK	CAN
Clinically relevant inhibitors (%)	177 (30.8%)	114 (37.6)	118 (28.9)	34 (34.3)
Cumulative incidence at 75 EDs (IQ)	32.4 (28.5-36.3)	40.2 (34.8-46.2)	*	
Median CEDs	15 (10-20)	13 (8-19)	16 (9-30)	
High titers	116	63	60	24
Cumulative incidence at 75 EDs (IQ)	22.4 (18.8-26.0)	23.9 (19.1-29.6)	*	

*Follow up : until 50 CEDs (except patients included in the Rodin cohort)

Inhibitor risk (adjusted)

	RODIN	RFC	UK	CAN
Advate	1.00	1.00	1.00	
Kogenate Bayer (Helixate Nexgen)	**1.60 (1.08-2.37)**	1.55 (0.97-2.49)	**1.75 (1.11-2.76)**	
Recombinate	0.99 (0.53-1.83)	0.97 (0.40-2.37)	1.95 (0.62-6.2)	
Refacto	1.01 (0.60-1.70)	1.2 (0.47-3.08)	0.79 (0.36-1.73)	
Refacto AF	NA	NA	**2.63 (1.26-5.47)**	

High titers (adjusted)

	RODIN	RFC	UK	CAN
Advate	1.00	1.00	1.00	
Kogenate Bayer (Helixate Nexgen)	**1.79 (1.09-2.94)**	1.56 (0.82-2.98)	**2.14 (1.12-4.1)**	
Recombinate	1.26 (0.61-2.61)	1.87 (0.59-5.89)	3.68 (0.88-15.35)	
Refacto	0.97 (0.49-1.91)	1.94 (0.54-6.91)	1.52 (0.57-4.04)	
Refacto AF	NA	NA	1.28 (0.33-5.00)	

EMA meta analysis

- Pooled data of the 3 PUPs cohorts:
  - Rodin
  - UK
  - France
- On going ….

Cohort PUPs studies from registries: the real life

- Each PUPs should be included in a registry, at least national
- Strong necessity to define a minimum common and relevant data set
- And/or to organize the conditions of interoperability between registries
- In order to collect rapidly at an international level informations on inhibitor incidence in this population
- This is an urgent task as several new innovative concentrates will soon be introduced on the market with limited informations on their long term immunogenic risk.