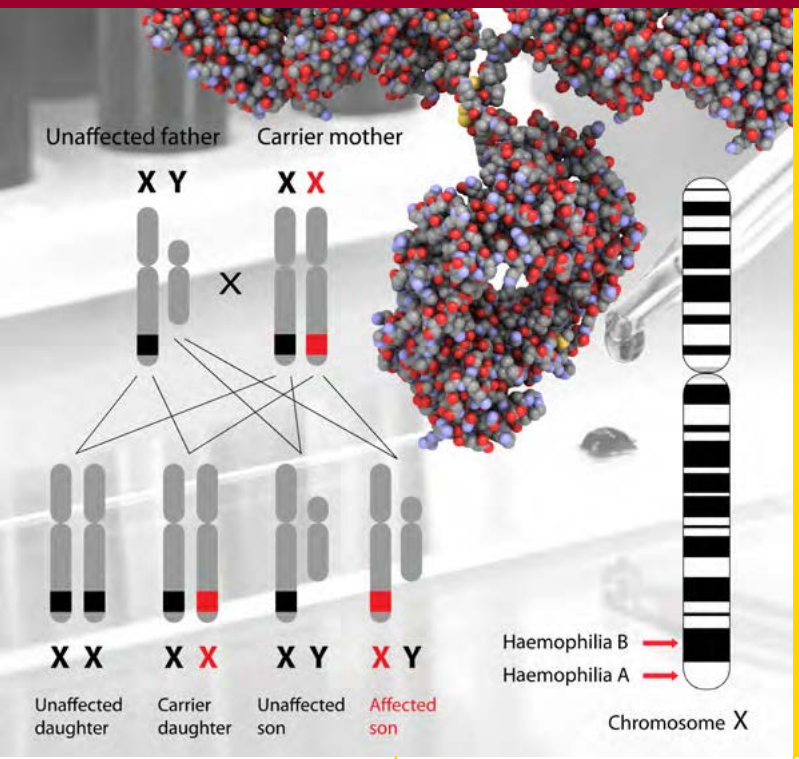
Optimal use of clotting factors and immunoglobulins



European symposium proceedings

Wildbad Kreuth
Germany

European Directorate for the Quality of Medicines & HealthCare

26-27 April 2013

LMU KLINIKUM DER UNIVERSITÄT MÜNCHEN

Paul-Ehrlich-Institut

edqm European Directorate for the Quality of Medicines & HealthCare

COUNCIL OF EUROPE
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Introduction to the 2013 Kreuth Symposium Proceedings

The symposium "Optimal use of clotting factors and immunoglobulins" was held on 26-27 April 2013 in Wildbad Kreuth (Germany) in the tradition of two previous symposia held in the same place. The first symposium in 1999, "Blood safety in the European Community: An initiative for optimal use" provided the basis for discussion. The second symposium, held in 2009, on "Optimal clinical use of blood components" took the topic further for a variety of blood components. The 2013 symposium focused on clotting factors and immunoglobulins. This latter topic had not been included in the previous symposia.

The recommendations established at the 1999 and 2009 Kreuth symposia were very well received in the field and were promoted by patient and medical organisations. They were considered useful by public health authorities in helping to pursue best practices in transfusion medicine, as well as in treatments using plasma-derived medicinal products.

Due to the ever-changing environment in the treatment of bleeding disorders arising from the introduction of novel medicinal products, a revision of the former guidelines was deemed necessary. In addition, given the wealth of new indications in the field of immunoglobulins, recommendations on best use seemed necessary in order to avoid shortages for well-established indications. Taking this into account, the organisers of the 2009 Kreuth symposium, i.e. the European Directorate for the Quality of Medicines and HealthCare (EDQM) of the Council of Europe (Strasbourg), the Ludwig Maximilians University (LMU, Munich) and the Paul-Ehrlich-Institut (PEI, Langen), agreed to organise a symposium in 2013 in the same format as the previous ones.

As before, data on clinical needs and actual use of clotting factors and immunoglobulins were collected from different European and non-European countries by means of two surveys, performed during 2012.

The National Authorities of 36 countries nominated 109 experts, who accepted an invitation to meet in Kreuth on 26-27 April 2013 in order to analyse the outcomes of the surveys and to exchange their experiences with the aim of developing an international consensus on the clinical use of:

- Clotting factors in haemophilia treatment.
- Human normal immunoglobulins in new indications.

This book represents the proceedings of the 2013 Kreuth symposium. It is based on the scientific presentations and debates held during the general sessions and workshops, their consensual conclusions and the final recommendations. The outcome is an updated appraisal of the state-of–the-art as regards optimal clinical use of clotting factors and immunoglobulins. It can be regarded as an international reference, and will be broadly distributed to relevant stakeholders, including scientific and professional societies.

These proceedings will hopefully form the basis of further discussions and recommendations at the level of the relevant National Authorities and European Institutions, and it might also be of use beyond Europe.

Prof W. Schramm	Prof R. Seitz	Dr K-H. Buchheit
(LMU)	(PEI)	(EDQM)

Contents

EUROPEAN SYMPOSIUM

Optimal use of clotting factors and immunoglobulins
26-27 April 2013, Wildbad Kreuth, Germany

Duration: 2,5 days. Working language: English

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PROGRAMME

THURSDAY 25 APRIL 2013

16:00-18:00
- Poster set-up for manufacturers
- Registration for participants
- Pre-meeting for speakers

19:00-21:30
Buffet Dinner

FRIDAY 26 APRIL 2013

8:00 Welcome
Dr Karl-Heinz Buchheit, EDQM, Council of Europe

SESSION 1: General information on the clinical use of clotting factors and immunoglobulins

Moderator: *Karl-Heinz Buchheit*
Rapporteurs: *Rainer Seitz & Harvey Klein*

8:15-8:30 **Key lecture**
Optimal clinical use of blood and plasma derivatives
Background and perspectives
Harvey Klein, National Institute of Health, Bethesda, USA

8:30-9:15 **Rationale for the meeting**
Clinical use of immunoglobulins
Hans-Hartmut Peter, *University of Freiburg, DE*

Clinical use of clotting factors (plasma-derived and recombinant)
Wolfgang Schramm, *University of Munich, DE*

Regulations for plasma-derived and recombinant medicinal products
Rainer Seitz, *Paul Ehrlich Institut, Langen, DE*

9:15-9:30 **Clinical challenges and access to clotting factor concentrates in haemophilia in Europe**
Paul Giangrande, *Churchill Hospital, Oxford, UK*

9:30-9:45 **Current data on the use of clotting factors and immunoglobulins in Europe**
Patrick Robert, *The Marketing Research Bureau, Inc, Orange, USA*

9:45-10:00 **Report on the outcome of the EDQM surveys**
Karin Berger, *University Hospital of Munich, DE*
Jacqueline Kerr, *Paul-Ehrlich-Institut, Langen, DE*

10:00-10:30 Coffee break and poster viewing

SESSION 2: Clotting Factors

Moderators & Rapporteurs: *Wolfgang Schramm & Rainer Seitz*

10:30-10:45 **Patients organisations' view - Access and unmet needs**
***Brian O'Mahony**, European Haemophilia Consortium (EHC), City, Country*

10:45-11:05 **New developments in clinical research and new treatment modalities – A clinician's perspective**
***Pier Mannucci**, IRCCS Ca' Granda Maggiore Policlinico Hospital Foundation, Milan, IT*

11:05-11:25 **Benefits and limitations with innovative clotting factor preparations**
***Flora Peyvandi**, University of Milan, IT*

11:25-11:45 **European clinical guidelines**
***Cedric Hermans**, Cliniques Universitaires Saint Luc, BE*

11:45-12:00 **European regulatory perspective**
***Anneliese Hilger**, Paul Ehrlich Institut, Langen, DE*

12:00-12:15 **Registries**
***Mike Makris**, Royal Hallamshire Hospital, Sheffield, UK*

12:15-13:30 Lunch break and poster viewing

SESSION 3: Immunoglobulins

Moderators & Rapporteurs: *Hans-Hartmut Peter, Isabella Quinti & Carrock Sewell*

13:30-13:45 **Patients Organisations' view - Access and unmet needs**
***Jose Drabwell**, International Patient Organisation for Primary Immunodeficiencies*

13:45-14:05 **Clinically established indications in primary and secondary immunodeficiencies**
***Helen Chapel**, John Radcliffe Hospital, Oxford, UK*
presented by Hans-Harmut Peter

14:05-14:25 **Immunomodulation: On-label and off-label Usage**
***Ivo Van Schaik**, University of Amsterdam, NL*

14:25-14:40 **European regulatory perspective**
***Jacqueline Kerr**, Paul Ehrlich Institut, Langen, DE*

14:40-14:55 **Demand Management Plan**
***Carrock Sewell,** Scunthorpe General Hospital, UK*

14:55-15:10 ***Innovative products and new developments*** *- cancelled*
***Lennart Hammarström**, Karolinska Institute, Stockholm, SE*

15:10-15:25 **Registries**
***Bodo Grimbacher**, University of Freiburg, DE*

15:25-16:00 Coffee break and poster viewing

SESSION 4: Working Groups Session

16:00-18:00 **Working Group 1: Clotting factors**
Moderators*: Pier Mannucci, Wolfgang Schramm*
Rapporteurs: *Pier Mannuci, Paul Giangrande, Wolfgang Schramm*

16:00-18:00 **Working Group 2: Immunoglobulins**
Moderators: *Hans-Hartmut Peter, Jacqueline Kerr*
Rapporteurs*: Hans-Hartmut Peter, Jacqueline Kerr, Isabella Quinti & Carrock Sewell*

18:00 Close of meeting

20:00 Evening Dinner

SATURDAY 27 APRIL 2013 – CLOSED MEETING

8:00-9:00 **Interim reports from Working Groups**

9:00-10:45 **Discussion in the Working Groups**

10:45-11:00 Coffee break

11:00-12:30 **Final reports from the Working Groups**
Moderators: *Rainer Seitz & Karl-Heinz Buchheit*

- **Working Group 1: Clotting factor**
- **Working Group 2: Immunoglobulins**

12:30-13:30 Lunch break

13:30-16:00 **Conclusions and Recommendations**

SCIENTIFIC PROGRAMME COMMITTEE

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Dr Marie-Emmanuelle BEHR-GROSS
Dr Karl-Heinz BUCHHEIT
Prof Dr Wolfgang SCHRAMM
Ms Karin BERGER
Dr Anneliese HILGER
Dr Jacqueline KERR
Prof Dr Hans-Hartmut PETER

Meeting Venue:see http://www.hss.de/fileadmin/media/downloads/Anfahrtsskizze_Wildbad-Kreuth.pdf http://www.hss.de/bildungszentren/wildbad-kreuth.html

List of Participants

Participant	Affiliation	Country
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Outcome of the enquiries on clinical use of coagulation factors and immunoglobulins

As part of the project entitled “Kreuth III” on optimal clinical use of coagulation factors and immunoglobulins co-sponsored by the EDQM, the LMU and PEI, the EDQM organised international surveys on clinical use: one on immunoglobulins (see PA/PH/TS (12) 46) and a second one on coagulation factors for the treatment of haemophilia (see PA/PH/TS (12) 45).

Data on the clinical need and actual consumption of plasma-derived medicinal products were collected at the global level from different European and non-European countries.

The surveys were launched in January 2013 and closed in June 2013. Thirty eight countries participated in the surveys (see Table 1).

The outcome of these surveys is compiled in this section, where overall results are shown.

The data obtained in these surveys were presented during the April 2013 meeting that was held, under the aegis of the Paul Ehrlich Institute, the Ludwig Maximilian University (LMU) of Munich and the EDQM/Council of Europe in Wildbad Kreuth (Germany), as a follow-up to the two previous meetings on optimal clinical use of blood components that were organised there in 1999 and 2009.

Table 1

	QUESTIONNAIRE			QUESTIONNAIRE	
	immunoglobulins	coagulation factors		immunoglobulins	coagulation factors
MEMBERS			OBSERVERS PARTICIPANTS PARTIES		
Austria			Armenia		
Belgium			Australia		
Bulgaria			Georgia		
Croatia			Moldova		
Czech Republic			Russian Federation		
Cyprus			USA		
Denmark			Japan		
Estonia			New Zealand		
Finland			Ukraine		
FYROM Macedonia					
France					
Germany					
Greece					
Hungary					
Ireland					
Italy					
Latvia					
Lithuania					
Luxembourg					
Malta					
Montenegro					
Netherlands					
Norway					
Poland					
Portugal					
Romania					
Serbia					
Slovak Republic					
Slovenia					
Spain					
Sweden					
Switzerland					
Turkey					
United Kingdom					

Wildbad Kreuth Meeting III (TS077) Questionnaire on clinical use of coagulation factors

1. Name

	Response Count
	35
answered question	35
skipped question	0

2. First name

	Response Count
	35
answered question	35
skipped question	0

3. Organisation/other

	Response Count
	35
answered question	35
skipped question	0

4. Professional function

		Response Percent	Response Count
Physician specialised in haemostaseology		**60.0%**	**21**
Other (please specify)		42.9%	15
		answered question	**35**
		skipped question	**0**

5. Address

	Response Count
	35
answered question	**35**
skipped question	**0**

6. Country

	Response Count
	35
answered question	**35**
skipped question	**0**

7. Telephone

	Response Count
	35
answered question	**35**
skipped question	**0**

8. E-mail

	Response Count
	35
answered question	**35**
skipped question	**0**

9. Data given are:

		Response Percent	Response Count
National data		**91.4%**	**32**
Regional data		5.7%	2
Local data		2.9%	1
	answered question		**35**
	skipped question		**0**

10. To which year do these data correspond?

		Response Percent	Response Count
2010		5.7%	2
2011		**65.7%**	**23**
Other		28.6%	10
	Other year (please specify)		10
	answered question		**35**
	skipped question		**0**

11. Country population

	Response Average	Response Total	Response Count
Population number in your country (in millions)	**27,683,129.28**	**885,860,137**	32
If data from the whole country cannot be reported indicate the size of population in the place/region in which data included in this questionnaire were collected (in absolute number)	2,646,433.33	7,939,300	3
		answered question	**35**
		skipped question	**0**

12. Which of the following products are used to treat haemophilia in your country?

	Always	Rarely	Never	Rating Count
Plasma	6.5% (2)	32.3% (10)	**61.3% (19)**	31
Cryprecipitate	3.2% (1)	25.8% (8)	**71.0% (22)**	31
Plasma derived Factor Concentrates	**67.6% (23)**	32.4% (11)	0.0% (0)	34
Recombinant Factor Concentrates	**60.0% (21)**	34.3% (12)	5.7% (2)	35
Other	14.3% (1)	14.3% (1)	**71.4% (5)**	7
			Other (please specify)	5
			answered question	**35**
			skipped question	**0**

13. Are the following haemophilia treatment modalities used in your country?

	Yes	No	Rating Count
On demand treatment	**100.0% (35)**	0.0% (0)	35
Prophylaxis	**88.6% (31)**	11.4% (4)	35
		answered question	**35**
		skipped question	**0**

14. Prophylaxis in children and adults

	None	Between 1-25%	Between 26-50%	Between 51-75%	Between 76-100%	Rating Count
Children	8.6% (3)	11.4% (4)	14.3% (5)	14.3% (5)	**51.4% (18)**	35
Adults	14.3% (5)	28.6% (10)	**37.1% (13)**	5.7% (2)	14.3% (5)	35
				answered question		**35**
				skipped question		**0**

15. What determines standards of treatment?

	Yes	No	Rating Count
European/international guidelines	**90.9% (30)**	9.1% (3)	33
National guidelines	**77.4% (24)**	22.6% (7)	31
Centre specific guidelines	**68.0% (17)**	32.0% (8)	25
Published reports	**65.2% (15)**	34.8% (8)	23
		answered question	**35**
		skipped question	**0**

16. Where are haemophilia patients generally treated?

	Less than 10%	Between 10-50%	Between 51-75%	Between 76-100%	Rating Count
CCC*	13.8% (4)	27.6% (8)	20.7% (6)	**37.9% (11)**	29
Inpatients	**69.0% (20)**	17.2% (5)	6.9% (2)	6.9% (2)	29
Outpatients	17.9% (5)	35.7% (10)	7.1% (2)	**39.3% (11)**	28
Home treatment	9.4% (3)	15.6% (5)	21.9% (7)	**53.1% (17)**	32
				answered question	**34**
				skipped question	**1**

17. Do you have a National Haemophilia Registry in your country?

		Response Percent	Response Count
Yes		**71.4%**	**25**
No		28.6%	10
		answered question	**35**
		skipped question	**0**

18. What information is covered by the National Haemophilia Registry?

	Yes	No	Rating Count
Documentation of treatment (products, modalities)	**95.7% (22)**	4.3% (1)	23
Documentation of outcomes / complications	**82.6% (19)**	17.4% (4)	23
Documentation of quality of life	40.9% (9)	**59.1% (13)**	22
Reimbursement of haemophilia treatment linked to participation	30.0% (6)	**70.0% (14)**	20
Published Reports	42.9% (9)	**57.1% (12)**	21
		answered question	**23**
		skipped question	**12**

19. Who manages the National Haemophilia Registry?

	Response Percent	Response Count
Government	16.7%	4
Academic Organisation	25.0%	6
Clinician (s)	**75.0%**	**18**
Haemophilia Patient Organisation	41.7%	10
Industry	0.0%	0
Others	12.5%	3
	Others (please specify)	7
	answered question	**24**
	skipped question	**11**

20. Is there a National Tender for the procurement of Coagulation Factor Concentrates in your country?

		Response Percent	Response Count
Yes		**54.3%**	**19**
No		45.7%	16
		answered question	**35**
		skipped question	**0**

21. Which organisation purchases Haemophilia products in your country?

		Response Percent	Response Count
Government		20.0%	7
National Health Care System		**45.7%**	**16**
Health care providers		37.1%	13
Haemophilia Patient Organisation		2.9%	1
Health insurance companies		22.9%	8
Other (please specify)		14.3%	5
		Other (please specify)	6
		answered question	**35**
		skipped question	**0**

Wildbad Kreuth Meeting III (TS077) Questionnaire on clinical use of immunoglobulins

1. Name

	Response Count
	34
answered question	34
skipped question	0

2. First name

	Response Count
	34
answered question	34
skipped question	0

3. Organisation/other

	Response Count
	34
answered question	34
skipped question	0

4. Professional function

		Response Percent	Response Count
Physician specialised in immunodeficiency treatment		41.2%	14
Other (please specify)		**58.8%**	**20**
		answered question	**34**
		skipped question	**0**

5. Address

	Response Count
	34
answered question	**34**
skipped question	**0**

6. Country

	Response Count
	34
answered question	**34**
skipped question	**0**

7. Telephone

	Response Count
	34
answered question	**34**
skipped question	**0**

8. E-mail

	Response Count
	34
answered question	**34**
skipped question	**0**

9. Data given are:

		Response Percent	Response Count
National data		**85.3%**	**29**
Regional data		5.9%	2
Local data		8.8%	3
	answered question		**34**
	skipped question		**0**

10. To which year do these data correspond?

		Response Percent	Response Count
2010		5.9%	2
2011		**61.8%**	**21**
Other (please specify)		32.4%	11
	answered question		**34**
	skipped question		**0**

11. Country population

	Response Average	Response Total	Response Count
Population number in your country (in millions)	**28,252,340.60**	**847,570,218**	30
If data from the whole country cannot be reported indicate the size of population in the place/region in which data included in this questionnaire were collected (in absolute number)	3,894,900.00	15,579,600	4
		answered question	**34**
		skipped question	**0**

12. Which immunoglobulin (IG) products are available in your country for primary and secondary immunodeficiency (ID) indications (intravenous (i.v.), subcutaneous (s.c.) and/or intramuscular (i.m)) and established immune modulatory indications (Guillain-Barré Syndrome, Idiopathic thrombocytopenic purpura and Kawasaki disease – i.v.) (Non-ID)? Product - Company - Route are indicated in the left column.

	ID	Non ID	Rating Count
KIOVIG - Baxter - i.v.	**100.0% (22)**	90.9% (20)	22
Gammagard S/D - Baxter - i.v.	**100.0% (16)**	68.8% (11)	16
Subcuvia - Baxter - s.c., i.m.	**100.0% (16)**	37.5% (6)	16
Intratect - Biotest - i.v.	**100.0% (10)**	90.0% (9)	10
Sandoglobulin - CSL Behring - i.v.	**100.0% (11)**	63.6% (7)	11
Beriglobin - CSLB - s.c.,i.m.	**100.0% (5)**	20.0% (1)	5
Vivaglobin - CSLB - s.c.	**100.0% (10)**	20.0% (2)	10
Hizentra - CSLB - s.c.	**100.0% (15)**	26.7% (4)	15
Privigen - CSLB - i.v.	**100.0% (17)**	82.4% (14)	17
Flebogamma 5% - Grifols - i.v.	**100.0% (11)**	72.7% (8)	11
Flebogamma DIF - Grifols - i.v.	**100.0% (8)**	87.5% (7)	8
Gamunex - Grifols - i.v.	**100.0% (6)**	83.3% (5)	6
Ig Vena - Kedrion - i.v.	**100.0% (9)**	77.8% (7)	9
Gammanorm - Octapharma - s.c., i.m.	**100.0% (15)**	40.0% (6)	15
Octagam 5% - Octapharma - i.v.	**100.0% (22)**	77.3% (17)	22
Octagam 10% - Octapharma - i.v.	**100.0% (22)**	81.8% (18)	22
Nanogam - Sanquin - i.v.	**100.0% (4)**	75.0% (3)	4
Other	**100.0% (11)**	63.6% (7)	11
		Other (please specify)	16
		answered question	**33**
		skipped question	**1**

13. For which other indications are IG preparations used in your country (besides primary/ secondary ID and established immune modulatory indications)?

	Licensed	Off label	Rating Count
Alzheimer's disease	0.0% (0)	**100.0% (5)**	5
Autoimmune haemolytic anemia	15.8% (3)	**84.2% (16)**	19
Chronic inflammatory demyelinating polyneuropathy (CIDP)*	39.1% (9)	**60.9% (14)**	23
Dermatomyositis/polymyositis	26.7% (4)	**73.3% (11)**	15
Multifocal motor neuropathy (MMN) **	37.5% (6)	**62.5% (10)**	16
Multiple sclerosis in pregnant women	8.3% (1)	**91.7% (11)**	12
Myasthenia gravis/ Lambert Eaton syndrome	15.8% (3)	**84.2% (16)**	19
Pure red cell aplasia	0.0% (0)	**100.0% (12)**	12
Septicemia and septic shock	29.2% (7)	**70.8% (17)**	24
Systemic lupus erythematosus (SLE)	0.0% (0)	**100.0% (14)**	14
Systemic vasculitis	17.6% (3)	**82.4% (14)**	17
Toxic epidermal necrolysis	0.0% (0)	**100.0% (14)**	14
Other	42.9% (6)	**57.1% (8)**	14
		Other (please specify)	12
		answered question	**33**
		skipped question	**1**

14. Are off label IG uses reimbursed in your country?

		Response Percent	Response Count
Yes		**58.8%**	**20**
No		41.2%	14
		answered question	**34**
		skipped question	**0**

15. If so, for which indications?

	Response Count
	17
	answered question **17**
	skipped question **17**

16. Is the following immunoglobulin treatment modality used in your country?

	Yes	No	Rating Count
Prophylactic passive immunisation (e.g. before travelling to developing countries)	42.4% (14)	**57.6% (19)**	33
		answered question	**33**
		skipped question	**1**

17. What determines standards of treatment?

	Yes	No	Rating Count
European/international guidelines	**86.2% (25)**	13.8% (4)	29
National guidelines	**77.3% (17)**	22.7% (5)	22
Centre specific guidelines	**68.4% (13)**	31.6% (6)	19
Published Reports	**84.2% (16)**	15.8% (3)	19
		answered question	**34**
		skipped question	**0**

18. Where are primary ID patients treated?

	Less than 10%	10-50%	51-75%	76-100%	Rating Count
Comprehensive care centers	10.0% (2)	25.0% (5)	30.0% (6)	**35.0% (7)**	20
Inpatients	**52.2% (12)**	13.0% (3)	13.0% (3)	21.7% (5)	23
Outpatients	27.3% (6)	**36.4% (8)**	9.1% (2)	27.3% (6)	22
Home treatment	**31.6% (6)**	**31.6% (6)**	21.1% (4)	15.8% (3)	19
				answered question	**31**
				skipped question	**3**

19. Is there an ID registry in your country?

		Response Percent	Response Count
Yes		**50.0%**	**17**
No		**50.0%**	**17**
		answered question	**34**
		skipped question	**0**

20. Which ID registries are in use in your country?

	Response Percent	Response Count
National	68.8%	11
ESID*	**81.3%**	**13**
Other (please specify)		5
answered question		**16**
skipped question		**18**

21. Which information is inluded in your national ID registry

	Response Percent	Response Count
Documentation of treatment (products, modalities)	**100.0%**	**14**
Documentation of outcomes / complications	71.4%	10
Documentation of quality of life	42.9%	6
Published Reports	21.4%	3
answered question		**14**
skipped question		**20**

22. Which organisation manages your national ID registry ?

		Response Percent	Response Count
Government		26.7%	4
Academic organisation		20.0%	3
Clinician		**60.0%**	**9**
Patient Organisation		13.3%	2
Industry		0.0%	0
Other (please specify)		20.0%	3
		answered question	**15**
		skipped question	**19**

23. Is there a national tender for the procurement of immunoglobulins in your country?

		Response Percent	Response Count
Yes		36.4%	12
No		**63.6%**	**21**
		answered question	**33**
		skipped question	**1**

24. Which organisation purchases immunoglobulin products in your country?

		Response Percent	Response Count
National tender / price negotiations		36.4%	12
Comprehensive immunodeficiency centres		15.2%	5
Health care providers		**54.5%**	**18**
Insurances		9.1%	3
Other (please specify)		27.3%	9
		answered question	**33**
		skipped question	**1**

Presentations

Optimal Use of Clotting Factors and Immunoglobulins

Wildbad Kreuth, 26-27 April 2013

Welcome Address

Karl-Heinz Buchheit,
EDQM Council of Europe

Organising Institutions

- European Directorate for the Quality of Medicines & HealthCare (EDQM), Council of Europe
- Ludwig-Maximilian-University (LMU), Klinikum, Munich (Germany)
- Paul-Ehrlich-Institut (PEI), Langen (Germany)

Scientific Programme Committee

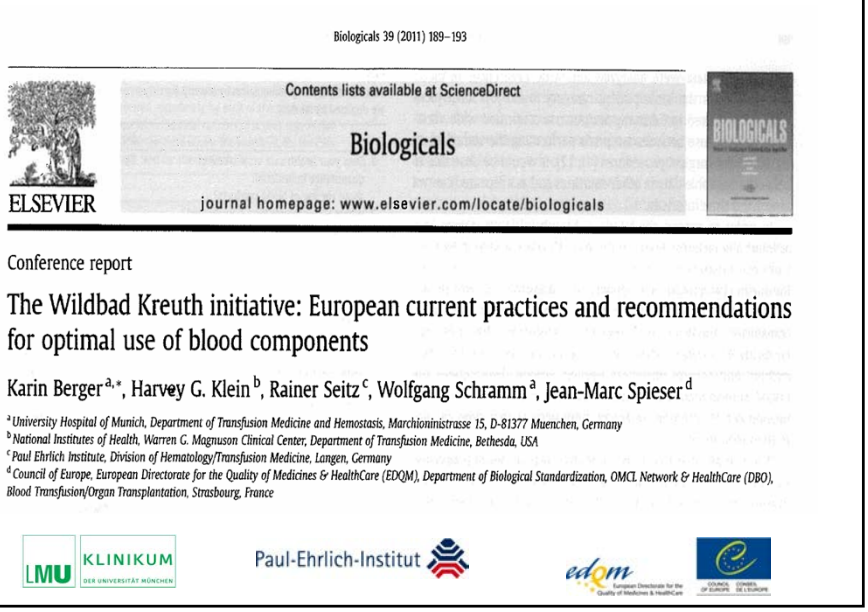
LMU	PEI	EDQM
Prof. W. Schramm	Prof. R. Seitz	Dr. M.E. Behr-Gross
Dr. K. Berger	Dr. A. Hilger	Dr. K.H. Buchheit
	Dr. J. Kerr	

Prof. H.H. Peter, University of Freiburg (Germany)

Technical Organisation

Ms. F. Baumgarthen, Ms. E. Zachari (EDQM)

Kreuth 2



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journal homepage: www.elsevier.com/locate/biologicals

ELSEVIER

Conference report

The Wildbad Kreuth initiative: European current practices and recommendations for optimal use of blood components

Karin Berger[a,*], Harvey G. Klein[b], Rainer Seitz[c], Wolfgang Schramm[a], Jean-Marc Spieser[d]

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[b] National Institutes of Health, Warren G. Magnuson Clinical Center, Department of Transfusion Medicine, Bethesda, USA
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[d] Council of Europe, European Directorate for the Quality of Medicines & HealthCare (EDQM), Department of Biological Standardization, OMCL Network & HealthCare (DBO), Blood Transfusion/Organ Transplantation, Strasbourg, France

Jean-Marc Spieser (1949-2013)

LMU KLINIKUM DER UNIVERSITÄT MÜNCHEN

Paul-Ehrlich-Institut

edqm European Directorate for the Quality of Medicines & HealthCare

COUNCIL OF EUROPE CONSEIL DE L'EUROPE

U.S. Department of Health and Human Services

National Institutes of Health

Department of Transfusion Medicine

Optimal Clinical Use of Blood and Plasma Derivatives

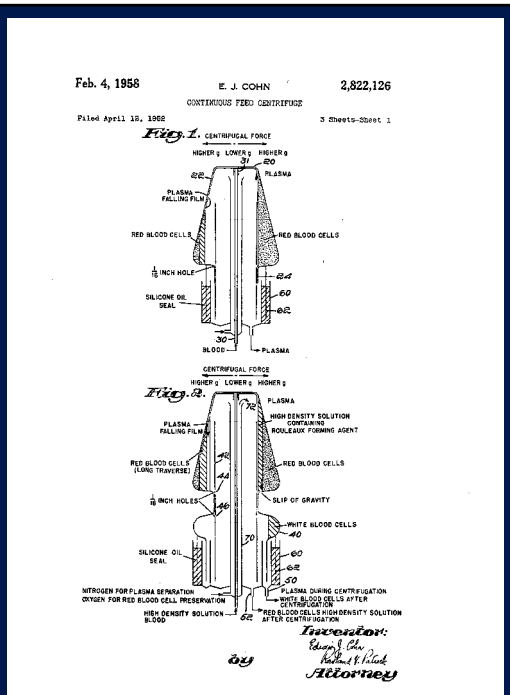
Background and Perspectives

Harvey G. Klein, MD
Department of Transfusion Medicine
Clinical Center
National Institutes of Health

Origins of Protein Fraction Therapy

Confluence of Need, Biology, and Technology

- 1940 -"Plasma for Britain" and Cohn Laboratory purification of proteins (Cohn et al. J Am Chem Soc 1940)
- 1944 – Cohn-Oncly (Cold ethanol) Fractionation (J Am Chem Soc 1940)
- 1947 Description of VI major fractions (Ann. Int. Med. 26: 341)
- 1949 - Cohn Fractionator (Science 1950; 112:12)
- 1955 - ADL Cohn Blood Fractionator (Tullis et al.Science 1956)
- 1975 – Kohler and Milstein Monoclonal Antibodies
- 1977 – Genentech clones Somatostatin



Feb. 4, 1958 E. J. COHN 2,822,126

CONTINUOUS FEED CENTRIFUGE

Filed April 18, 1952 3 Sheets-Sheet 1

Fig. 1. CENTRIFUGAL FORCE

HIGHER g LOWER g HIGHER g

PLASMA

PLASMA FALLING FILM

RED BLOOD CELLS

RED BLOOD CELLS

1/8 INCH HOLE

SILICONE OIL SEAL

BLOOD

PLASMA

Fig. 2.

CENTRIFUGAL FORCE

HIGHER g LOWER g HIGHER g

PLASMA

HIGH DENSITY SOLUTION CONTAINING ROULEAUX FORMING AGENT

PLASMA FALLING FILM

RED BLOOD CELLS (LONG TRAVERSE)

RED BLOOD CELLS

1/8 INCH HOLES

SLIP OF GRAVITY

WHITE BLOOD CELLS

SILICONE OIL SEAL

NITROGEN FOR PLASMA SEPARATION
OXYGEN FOR RED BLOOD CELL PRESERVATION

HIGH DENSITY SOLUTION

PLASMA DURING CENTRIFUGATION

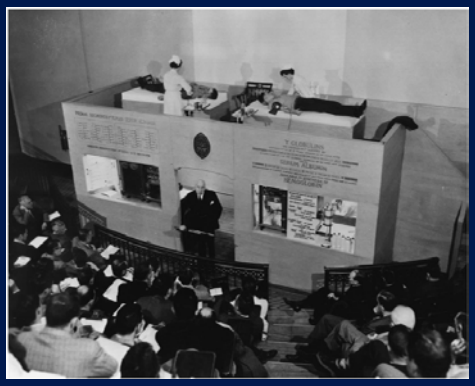
WHITE BLOOD CELLS AFTER CENTRIFUGATION

RED BLOOD CELLS HIGH DENSITY SOLUTION AFTER CENTRIFUGATION

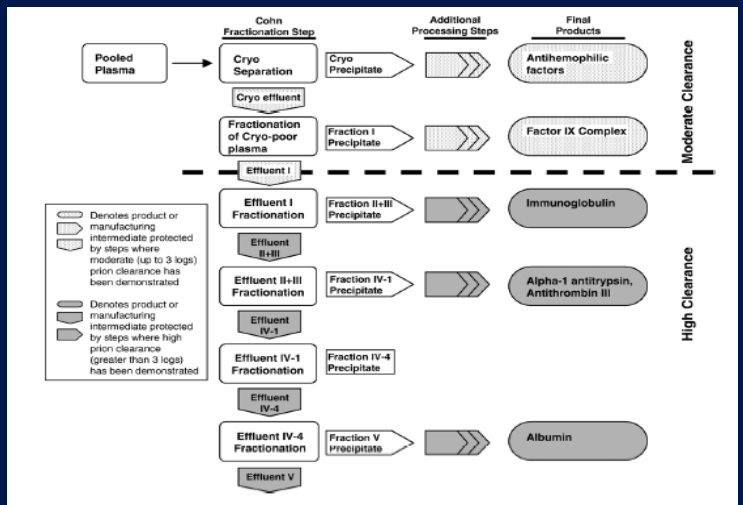
Inventor:

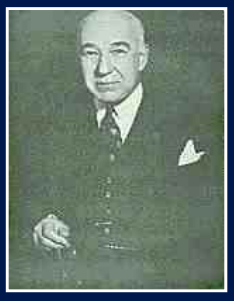
by

Attorney



Cold Ethanol Fractionation





Albumin Preparations

- Hyperoncotic - 25 %
- Hemorrhagic shock, burns
- Does not contain agglutinins

  Can be carried in backpack
- Not to exceed 250 g/48 hr
  - Responsible for 80% of intravascular colloid oncotic pressure

Selected Protein Fraction Concentrates

Product	Daltons	mg/L	Indication
Albumin	66,500	40,000	Volume replacement
Immunoglobulin (IgG)	150,000	12,500	Replacement; immune modulation
Coagulation/Anticoagulation			
Fibrinogen (Factor I)	300,000	3,000	Replacement
Prothrombin (Factor II)**	72,000	150	Replacement
Factor V*	286,000	7	Replacement
Factor VII**	50,000	0.5	Replacement
Factor VIII	330,000	0.3	Haemophilia A
Factor IX**	57,000	5	Haemophilia B
Factor X**	59,000	10	Replacement
Factor XI	80,000	5	Haemophilia C
Factor XII*	76,000	40	None
Factor XIII	320,000	10	Replacement
Protein C	57,000	4	Replacement
Protein S*	69,000	9	
Von Willebrand Factor	220,000	10	Von Willebrand Disease
Protease			
ADAMTS 13***	190,000	1	TTP
Protease Inhibitors			
Alpha 1 antitrypsin	52,000	1,500	Replacement
C1-esterase Inhibitor	104,000	170	Hereditary Angioedema
Antithrombin	58,000	100	Replacement

*No commercial concentrate **Prothrombin complex ***In development

Short History of Clotting Factor Therapy

1950	Whole blood
1950-70	FFP and Cryoprecipitate
1970's	Commercial Plasma derived Concentrates
1981	First reported AIDS cases in Hemophilia
1983	Heat-treated FVIII
1985	All Commercial concentrates heat-treated
1987	Monoclonal Factor concentrates
1992	Recombinant FVIII
1994	Recombinant IX – Albumin free
2001	2nd Generation recombinant FVIII
2003	3rd Generation recombinant FVIII

Clotting Factors

Disease Severity (genetic variant)
Prophylactic vs. Therapeutic
Nature of hemorrhage / Procedure
Factor level (therapeutic or prophylactic)
Length of treatment (prophylactic or therapeutic)
Concentrate Purity (Plasma derived vs recombinant)
and which recombinant

Immunoglobulins

Plasma Replacement therapy

IM Injection (subcut.) – specific (Tetanus, rabies, RhD, etc)

1980's IVIg (subcutaneous) replacement in Immunodef.
- Primary (Bruton, SCID, CVID, WAS, etc.)
- Secondary (Lymphoma, Myeloma, Transplant, etc.)

1980's – Immune modulation
- ITP, PTP, GBS, Kawasaki, Infalammatory neuropathies. MS, MGS

2000 - Subcutaneous Ig

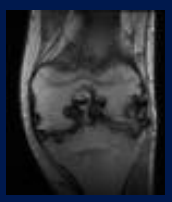
Indications for Use

Licensed Indications
Level of Evidence
Off-label use
Rare disease - no approved medicine is available

Patients' Rights

The transfusion of whole plasma is often unnecessary and usually inefficient

- Access to Safe, Effective Medicines
- Right Product
- Right Dose
- Right Time
- Right Indication
- Right Patient



Clinical Endpoints – Laboratory Monitoring

Parachutes reduce the risk of injury
after gravitational challenge

but their effectiveness has not been proved
with randomized controlled trials

What will be the Projected Demand?

You have to skate to where the puck is going, not to where it has been

Wayne Gretsky

Clinical use of immunoglobulins

HH Peter
Centre of Chronic Immunodeficiency (CCI), Freiburg

Continous increase of indications for IVIG use*

1973
Replacement therapy in patients with hypo- or agammglobulinemia

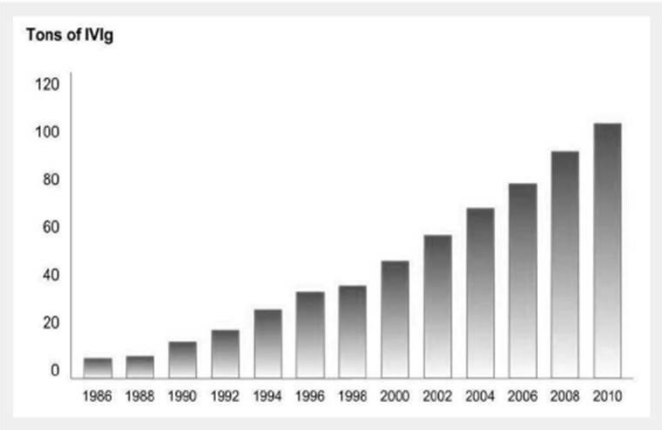
1981
Immunomodulatory therapy of ITP

2013	n
High priority use	12
Medium priority use	18
Low priority use	27
Not recommended use	16

Among all therapeutic blood products IVIG is today the main driving force for an increasing demand of human plasma.

*Demand management plan for immunoglobulin use, 2012. Department of Health PO Box 777, London SE1 6XH, UK

The total world consumption of IVIG*



*Int Blood Plasma News IBPN; Imbach P, 2012; Swiss Medical Weekly 142: w13593

Demand management plan for IVIG use 2012

(Dept. Health London)

Evidence 1A-2A | Evidence 2B-C | No evidence

Red – Priority - High

Condition	Short Term	Long Term
Alloimmune thrombocytopenia (foeto-maternal/neonatal)*		
Chronic inflammatory demyelinating polyradiculoneuropathy		
Guillain-Barré syndrome		
Haemolytic disease of the newborn		
HSCT in primary immunodeficiencies		
Immune thrombocytopenic purpura (acute and persistent, excluding chronic*)		
Kawasaki disease		
Paraprotein-associated demyelinating neuropathy (IgM, IgG or IgA)		
Primary immunodeficiencies		
Specific antibody deficiency		
Thymoma with immunodeficiency		
Toxic epidermal necrolysis, Stevens Johnson syndrome		

* Updated May 2012

Blue – Priority - Medium

Condition	Short Term	Long Term
Acquired red cell aplasia		
Autoimmune congenital heart block		
Autoimmune haemolytic anaemia		
Autoimmune uveitis		
Coagulation factor inhibitors (alloantibodies and autoantibodies)		
Haemophagocytic syndrome		
Immunobullous diseases		
Inflammatory myopathies		
Multifocal motor neuropathy		
Myasthenia gravis (including Lambert-Eaton myasthenic syndrome)		
Necrotising (PVL-associated) staphylococcal sepsis		
Post-transfusion purpura		
Rasmussen syndrome		
Secondary antibody deficiency (any cause)		
Severe or recurrent Clostridium difficile colitis		
Staphylococcal or streptococcal toxic shock syndrome		
Stiff person syndrome		
Transplantation (solid organ)		

Grey – Priority - Low

Immune-mediated disorders with limited evidence of immunoglobulin efficacy	Presumed immune-mediated disorders with little or no evidence of efficacy
Acute disseminated encephalomyelitis (if high-dose steroids have failed)	Acquired red cell aplasia NOT due to parvovirus B19
Autoimmune encephalitis (including NMDA and VGKC antibodies, among others)	Acute idiopathic dysautonomia
Catastrophic antiphospholipid syndrome	Aplastic anaemia/pancytopenia
Cerebral infarction with antiphospholipid antibodies	Atopic dermatitis/eczema
Chronic ITP	Autoimmune neutropenia
CNS vasculitis	Chronic facial pain
Complex regional pain syndrome	Diabetic proximal neuropathy
Neuromyotonia	Haemolytic uraemic syndrome
Intractable childhood epilepsy	PANDAS
Neuromyotonia	Paraneoplastic disorders that are known not to be B- or T-cell mediated
Opsoclonus Myoclonus	POEMS
Post-exposure prophylaxis for viral or pathogenic infection if intramuscular injection is contraindicated, or treatment when hyper-immune immunoglobulins are unavailable	SLE without secondary immunocytopenias (including juvenile)
Pyoderma gangrenosum	
Systemic juvenile idiopathic arthritis	
Systemic vasculitides and ANCA disorders	
Urticaria (severe, intractable)	

Black

Immunodeficiency secondary to paediatric HIV infection
Autologous BMT
Adrenoleukodystrophy
Alzheimer's disease
Amyotrophic lateral sclerosis
Chronic fatigue syndrome
Critical illness neuropathy
Multiple sclerosis
Rheumatoid arthritis
Neonatal sepsis (prevention or treatment)
Sepsis in the intensive care unit not related to specific toxins or C. difficile
Asthma
Graves' ophthalmopathy
IVF failure
Recurrent spontaneous pregnancy loss

Established indications for Ig treatment (Wimperis et al 2011, Deforge et al 2011)				
Recommended duration of treatment (short ≤ 3 months, long ≥ 3 months)			short	long
Immunology		Primary immunodeficiency	selected	yes
	*	Kawasaki disease	yes	no
Hematology		Fetal/neonatal Alloimmune thrombocytopenia (FNAIT)	yes	no
	*	Immunthrombocyopenia (ITP)	selected	no
		Erythroblastopenia due to Parvo B19	selected	no
		Posttransfusion purpura	yes	no
	*	Coagulation factor inhibitors (allo- and autoantibodies)	selected	no
		Post-HSCT in PID	selected	selected
Hemato-Oncology		Chronic lymphocytic leukemia (CLL)	selected	selected
		Multiple myloma	selected	selected
		Symptomatic hypogamma due NHL leukemia or post HSCT	selected	Selected
Neurology	*	Guillain-Barré syndrome	selected	no
	*	Chronic inflammatory demyelinating polyneuropathy (CIDP)	selected	selected
	*	Multifocal motor neuroparthy (MMN)	selected	selected
	*	Myasthenia gravis/ Lambert-Eaton syndrome	selected	selected
	*	Multiple sclerosis during pregnancy	selected	no
Rheumatology	*	Dermatomyositis (childhood)	selected	selected
Dermatology	*	Toxic epidermal necrolysis/Stevens Johnson syndrome	selected	no

Some emerging conditions for IVIg

(still beyond evidence 2A)*

- Systemic autoimmune diseases
  - Dermato-/Polymyositis in adults
  - SLE, catastrophic anti-phospholipid syndrome, CHB
  - Evans syndrome
  - Epidermolysis bullosa/ Steven-Johnson syndrome
  - Acquired hemophilia
  - Pure red cell aplasia
- Kidney transplantation (to reduce alloantibodies)
- Septicemia
- Acute disseminated encephalomyelitis (ADEM)
- Alzheimer‘s disease
- Stiff person syndrome
- Pemphigus vulgaris

* Orange et al 2006, Deforge et al 2011, Criteria for clinical use of IVIg in Australia 2012

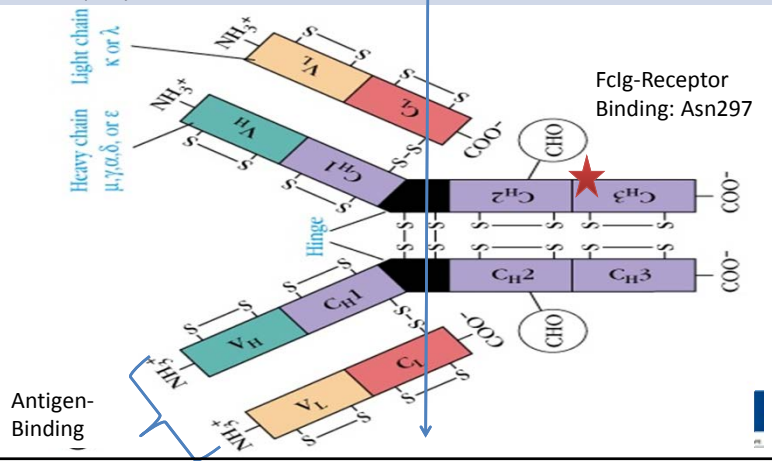
Mechanisms underlying immunomodulatory effects of IVIg in autoimmune disease

	Immunomodulatory mechanisms
1	Neutralisation of auto-antibodies (anti-idiotypes)
2	Suppression/neutralisation of pathogenic cytokines
3	Neutralisation of super-antigens
4	Down-regulation of T and B cell function, upregulation of Treg
6	Inhibitory effects of IVIg mediated via FcRIIb binding
5	Enhanced clearance of pathogenic autoantibodies via saturation of the FcRn with normal IVIg
7	Immunomodulation via IgG4
8	Blockade of CD95

Immunomodulatory effects of FcR

Dual function of IgG

A. Ig replacement therapy	*B. Immunmodulatory therapy*
a. Replacement of insufficient antibody repertoire in immunodeficiency b. Neutralisation of autoantibodies (Anti-idiotypic antibodies) or cytokines	Activating or inhibiting functions of immune cells mediated via FcIg-Rezeptor binding

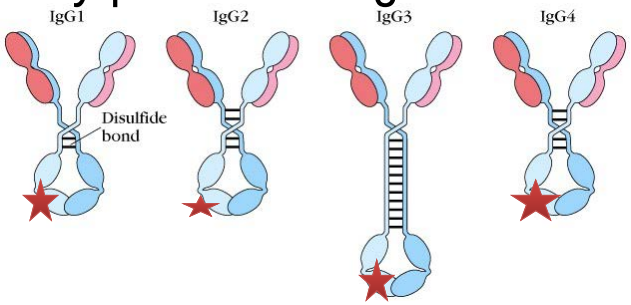


Established conditions for IVIG therapy (1A-2A)

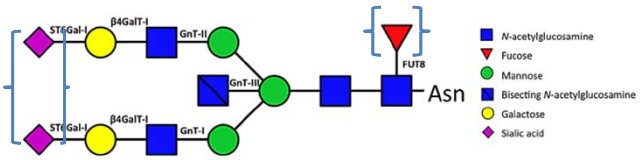
A. Ig replacement therapy	*B. Immunmodulation therapy*
Primary Immundeficiency (PID) Absolute: XLA, CVID, HIM, Relative: Subclass-deficiency, SAD, THI	Neuroimmunological diseases: GBS, CIDP, MMN, MGS/LES, SPS, MS in pregnancy
Secondary Immundeficiency (SID) CLL, NHL, MM, other related conditions Post stem cell transplantation	Hematological diseases: ITP, neonatal hemochromatosis, FNAIT Kawasaki Syndrome Inflammatory myopathies in children
Dosage: - PID: 0,4g/kg every 3-4 Wo (25 g/ Monat). continued and regular -SID: 0.4g/kg every 3-4 Wo (25g/Monat) until cure of underlying disease	Dosage: - Neurology: 0,2 - 2g/kg 2-5 days once or at irregular intervals -Hematology and others: 1-2g/kg 3-5 Tage once or at irregular intervals

Peter HH, Salama A: Human Immunglobulins Cross-sectional guidelines for therapy with blood components and plasma derivatives **Transfus Med Hemoth**, 2009; 36: 449-459;
Criteria for the clinical use of ivIg in Australia 2nd Edition 2012, Natl. Blood Authority, Australia

Inhibitory potential of IgG subclasses

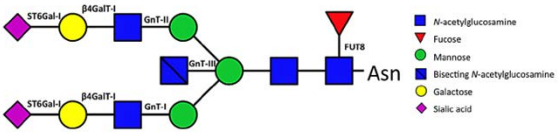


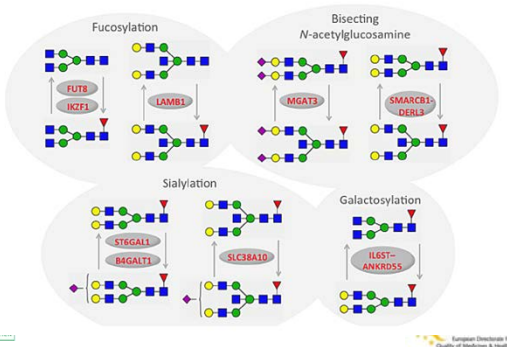
Sialic acid (SA) residue at position Asn297 of Fc-Ig promotes anti-inflammatory activity. 7-10% of IgG share the SA residue.



A summary of changes to IgG N-glycan structures that were associated with 16 loci identified through GWA study.

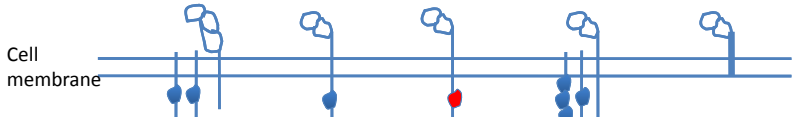
Lauc G et al Plos Genetic 2013 doi:10.1371/journal.pgen.1003225.g002





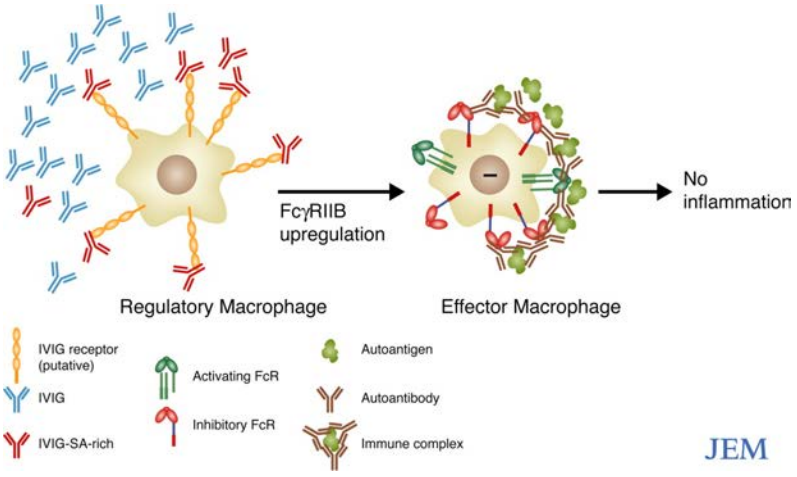
Immunmodulation through IVIg/SCIg Therapy critically depends on FcR Polymorphismen

FcγR -Typ	FcγR I CD64	FcγRIIa CD32a	FcγRIIb CD32b	FcγRIIIa CD16a	FcγRIIIb CD16b
Affinität	high	low	low	low	low
Isotyp Restriction	IgG1	broad	broad	broad	broad
Vorkommen	Mac PMN Eos	Mac PMN Eos Thrombo	B cells Mac	NK cells Eos Mac Mast cells	PMN
ITAM-Motife	++	++		++	
ITIM Motife			++		

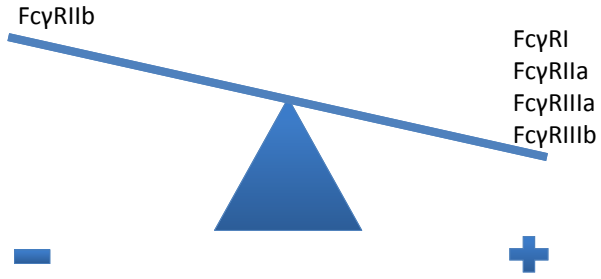


Nimmerjahn, F. et al. J. Exp. Med. 2007;204:11-15

Figure 2. Two-cell model for the mechanism of IVIG activity



Hypothesis on Immunmodulation through Fcγ-Rezeptoren (T. Kuijpers 2010)

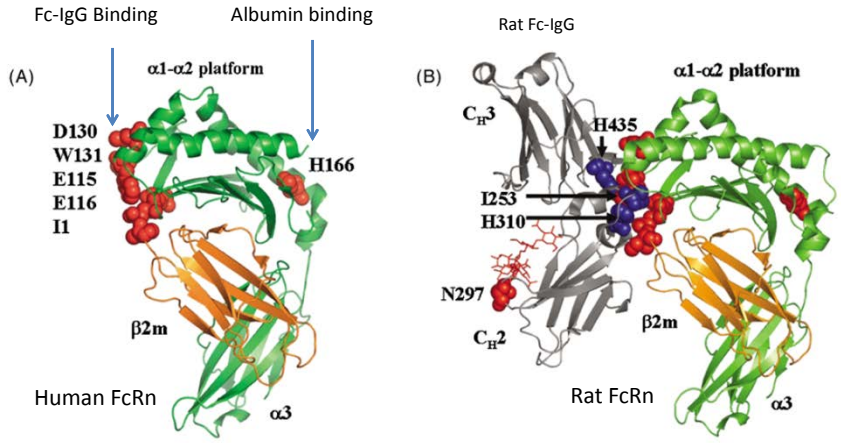


IgG-mediated cellular functions are critically dependent on cell type and the ballance between expressed inhibitory and activating FcRs.

Enhanced clearance of pathogenic autoantibodies via saturation of the FcRn with normal IVIg

Structure and binding sites of FcRn in man and rat

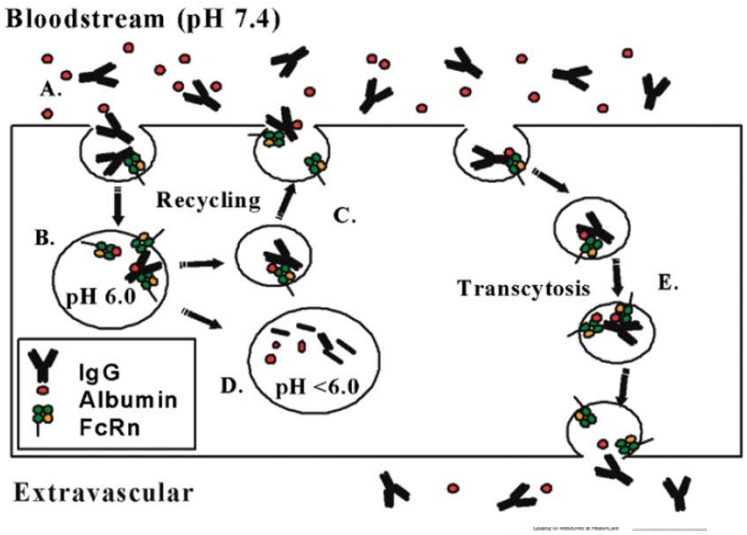
(Andersen JT, Dandlie I. Drug Metab. Pharmacokinet. 24 (4): 318–332 (2009).



FcRn is a MHC I related molecule with a 30-40% sequence homology in the α-chain of MHC class I .

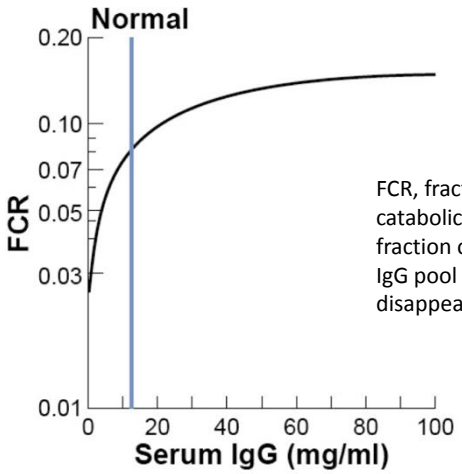
Function of FcRn: Recycling & trancytosis of IgG and Albumin

(Andersen JT, Dandlie I. Drug Metab. Pharmacokinet. 24 (4): 318–332(2009).



Relationship of serum IgG concentrations to clearance

Waldmann TA, Strober W. Metabolism of immunoglobulins. Prog Allergy. 1969; 13:1–110



FCR, fractional catabolic rate; the fraction of the serum IgG pool that disappears per day.

Conclusions

- IVIg is effectiv in an ever increasing number of diseases
- Besides PID and hematological conditions, autoimmune diseases represent the third group of indications for IVIg.
- Some mechanisms underlying the efficacy of IVIg in autoimmune diseases are:
  - Neutralisation of autoantibody u. cytokines,
  - Increased degradation of pathogenic antibody via saturation of FCRn with IVIg
  - Inhibitory effects of IVIg on immune cells via FcϒRIIb ligation
  - Immunomodulation via IgG4

EUROPEAN SYMPOSIUM

Optimal use of clotting factors and immunoglobulins

26-27 April 2013, Wildbad Kreuth, Germany

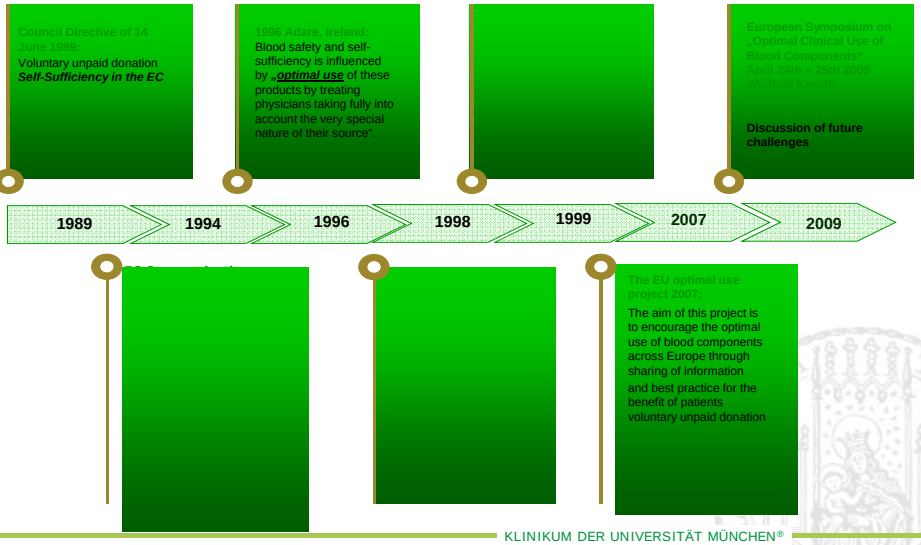
Rationale for the meeting

Clinical use of clotting factor concentrates (plasma-derived and recombinant)

Wolfgang Schramm

Ludwig-Maximilians University (LMU)
Rudolf Marx Stiftung
Munich, Germany

From Self- Sufficiency to Optimal Use of Blood and Blood Products in Europe – Initiatives from 1989 until 2009



From Self- Sufficiency to Optimal Use of Blood and Blood Products in Europe - Rationale for Wildbad Kreuth Initiative III (2013)

INCREASING DIVERSITY OF FACTOR CONCENTRATES – HOW ABOUT CLINICAL USE, ACCESS FOR PROVIDER AND PATIENTS?

- A series of plasma derived and recombinant factor concentrates are licensed.
- Several innovative clotting factor concentrates are under development and clinical research. Their market licensing can be expected in the near future.

MEINUNGSSEITE

Mittwoch, 20. Februar 1991

Immer unterwegs zu neuen Ufern: Dr. Johann Eibl (65)

Zeichnung: D. Hautzsch

Blick in die Presse

Letzte Chance

Mit Gorbatschows Friedensplan zur Beendigung des Golfkriegs beschäftigen sich die meisten Tageszeitungen.

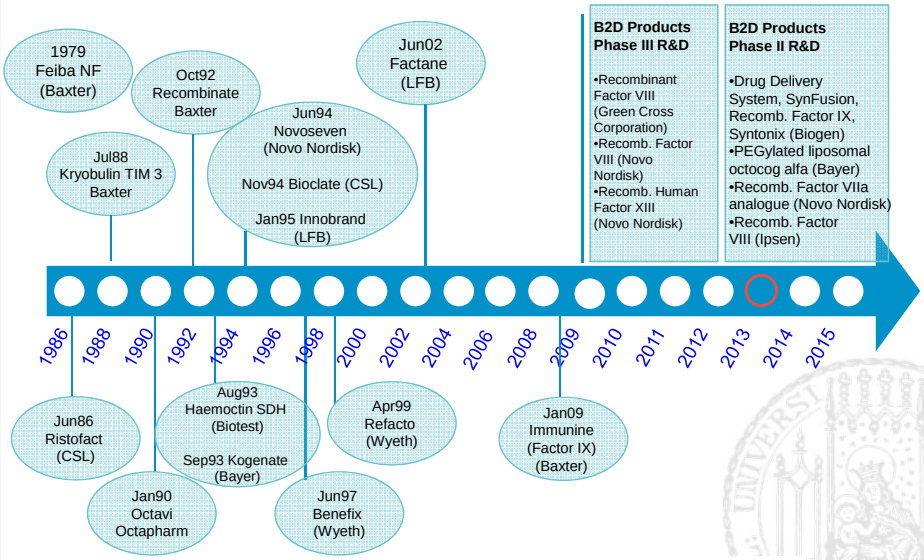
EL PAÍS (Madrid):

„Noch sind nicht viele Karten dieser komplizierten, diplomatischen Verhandlungen in Moskau, Teheran und anderen Hauptstädten aufgedeckt worden, aber daraus kann eine Beschleunigung des Kriegsendes entstehen. Offensichtlich hatte Gorbatschow aufgrund des Drucks im Innern . . . und des Wunsches, sich eine wichtige Rolle bei der künftigen Neuordnung der Region, die der UdSSR so nahe ist, zu sichern, ein besonderes Interesse daran, diese letzte Anstrengung zu unternehmen. Aber er agiert nicht allein . . . Auf jeden Fall scheint sich in diesem Krieg eine Wende abzuzeichnen. Was gestern unvorstellbar schien, nämlich daß Saddam Hussein schließlich den Rückzug aus Kuwait akzeptiert, ist eine Möglichkeit, die nicht ausgeschlossen werden kann. Angesichts dieser Entwicklung müssen . . . die alliierten Streitkräfte die Bodenoffensive aufschieben, deren Beginn bevorsteht, zumindest solange, bis klar ist, ob sich der Irak den Entscheidungen der UNO unterwirft."

LA REPUBBLICA (Rom):

„Nach den Informationen, die bisher

BLOOD COAGULATION PRODUCT LAUNCHES AND R&D PIPELINE TRIGGERS THE REQUEST FOR ECONOMIC DATA



Blood Safety in the European Community: Wildbad Kreuth initiative I (1999): recommendations and conclusions

How to define optimal use?

OPTIMAL USE IS TO AVOID[1] …

- Overuse
- Underuse
- Inappropriate use

Optimal use in haemophilia care requires[2] ...

... administering the <u>right quantity</u> of the <u>right blood product</u> in the right way at the right time to the <u>right patient</u>, and <u>appropriate documentation</u> of both the process and the outcome.

1:Advisory Council on the Assessment of Developments in the Health Care System: Report Appropriateness and Efficiency 2000/2001, Addendum
2: Wildbad Kreuth Initiative: Conclusions and Recommendations No 71

Blood Safety in the European Community: Wildbad Kreuth Initiative I (1999): recommendations and conclusions

recombinant* - *plasma-derived

- The merits of recombinant coagulation factor concentrates over conventional plasma-derived products remain controversial.
- With regard to the *transmission of human pathogens*, it was agreed that recombinant products offer an *increased margin of safety* over plasma-derived products.
- Incidence of inhibitors
- Costs

Blood Safety in the European Community: Wildbad Kreuth Initiative I (1999): recommendations and conclusions

Prophylactic Therapy

- preventing spontaneous bleeding episodes
- reducing long-term joint damage

- *further issues:*
  - >>> time when prophylaxis should start
  - >>> age at which prophylaxis should be suspended
  - >>> dosage and frequency of injections

Wildbad Kreuth Initiative 1999
Recommendations and their Translation into clinical practice

Wildbad Kreuth Initiative

- 125…registers of patients with haemophilia and related disorders should be established and maintained ...
- 126…to gather information on such patient complications as inhibitor development, allergic reactions, viral transmission and other miscellaneous adverse events.
- 127 A network of Comprehensive Care Centres (CCC) should be established in accordance with common criteria, which would provide 24-hour clinical and laboratory service and be accessible to all patients.
- 131 As a general rule, prophylactic treatment for children with severe haemophilia is recommended.
- 133 The outcome of treatment, including parameters related to quality of life and economic aspects, still needs to be assessed, and further studies, which will require funding, should be initiated.

Translation into practice

- Local and European registries have been successful established e.g:
  - EUHANET
  - UKHCDO
  - DHR
- Establishment of hemovigilance registers
  - EUHASS
- Comprehensive care centres are quite well linked
- Studies with high evidence leves have proven the outcome of prophylactic treatment in children and subsequently it is now acceptes as a general rule.
- The number of studies refering on hard outcome data and health economic aspects data is still limited

LMU Ludwig Maximilians Universität München

European Symposium on "Optimal Clinical Use of Blood Components" April 24th-25th 2009, Wildbad Kreuth, Germany

10 years after Wildbad Kreuth 1999

Since that time a tremendous number of new publications, new trends in treatment patterns, and a growing focus on economic issues have changed the environment as compared to 1999.

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Blood Safety in the European Community: Wildbad Kreuth Initiative II, (2009): recommendations and conclusions

Modified Recommendations on clotting factor concentrates:

(125) Registers of patients with haemophilia and related disorders should be established and maintained in each country.

(126) Gathering **pharmacovigilance** information on such complications as inhibitor development, allergic reactions, viral transmission and other miscellaneousadverse events is mandatory. An **European initiative (EUHASS)** has recently been launched and it is hoped that this will be financed beyond the initial three year term.

(127) A network of **Comprehensive Care Centres** should be established in each country and should provide a seven days a week 24 hour clinical and laboratory service and be accessible to all patients. In order to be so designated, **such a centre** should normally provide treatment for **at least 40 patients** with severe haemophilia in order to maintain the expertise required

Blood Safety in the European Community: Wildbad Kreuth Initiative II, (2009): recommendations and conclusions

Modified Recommendations on clotting factor concentrates:

(128) Adequate amounts of coagulation factor concentrates for the treatment of patients with hemophilia and related disorders should be available in each country. There is a continuing need for both plasma-derived and recombinant products. **At national level, the minimum acceptable level of factor concentrate use should be 2 units per capita.** Coagulation factor concentrates are now included in the WHO list of essential medications and cryoprecipitate should no longer be used for the treatment of haemophilia

(130) **The various guidelines** from medical bodies in different countries **should be harmonized and expanded to include advice on dosages for the treatment of common bleeding problems. These should include details of the level of evidence and grade of recommendations.**

Blood Safety in the European Community: Wildbad Kreuth Initiative II, (2009): recommendations and conclusions

Modified Recommendations on clotting factor concentrates:

(131) As a general rule, prophylactic treatment for children with severe haemophilia is recommended. **Ongoing prophylaxis in adults may also be considered.**

(132) Immune tolerance should be offered to all patients with haemophilia who develop clinically-significant inhibitory antibodies.

(133) Data on outcome of treatment should be collected, including clinical data such as frequency of bleedings and **assessment of joint function** as well as **quality of life and economic information.**

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Blood Safety in the European Community: Wildbad Kreuth Initiative II, (2009): recommendations and conclusions

New recommendations on clotting factor concentrates:

(New) In order to foster the cooperation of patient organizations and physicians, it is recommended that a formal mechanism be established in each country to develop best practice in hemophilia care.

(New) Home treatment with coagulation factor concentrate should be encouraged in patients with severe haemophilia.

(New) Family trees for patients with haemophilia and other inherited bleeding disorders should be drawn up and genetic counselling offered.

LMU

Blood Safety in the European Community: Wildbad Kreuth Initiative II, (2009): recommendations and conclusions

New recommendations on clotting factor concentrates:

(New) Awareness should be drawn to rarer bleeding disorders which affect both men and women. Data on these patients should also be included in the national registers.

(New) Patients with rare bleeding disorders should be treated with specific coagulation factor concentrates wherever possible. The development of "orphan drugs" for the treatment of such patients should be encouraged. If fresh frozen plasma is used, it should be subjected to viral inactivation/removal treatment. Prophylaxis in patients with a severe phenotype should be considered.

(New) The European Union should foster the development of **equitable care in all member states.**

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Blood Safety in the European Community: Wildbad Kreuth Initiative II, (2009): recommendations and conclusions

New recommendations should be added:

- **Outcomes need to be defined and benchmarked for disease/condition specific groups, but also relevant demographic groups within populations (eg elderly, IHD)**
- **Outcomes need to be measured at relevant time points, including short and long-term**
- **Observational studies are needed to focus prospective studies on the outcome of transfusion therapy**
- **When evaluating plasma derived products for treating coagulation disorders, the issue of alternative strategies and their clinical relevance should be taken into consideration**
- **This is true for clinical outcomes as well as for cost-effectiveness issues**
- **The effectiveness and safety of plasma derived and recombinant products for treating coagulation disorders needs to be assessed.**
- **This is relevant in view of the different costs of treatments with plasma derived products as compared to recombinant products**
- **Research funding should be committed to generate adequately powered in clinical trials.**

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Actual trend in pricing and reimbursement: Value Based Pricing
1st step benefit assessment, 2nd step cost assessment

AMNOG
Main decision criteria for price and reimbursement: Incremental patient relevant benefits compared to standard therapy (IQWIG benefit assments, G-BA final decision)

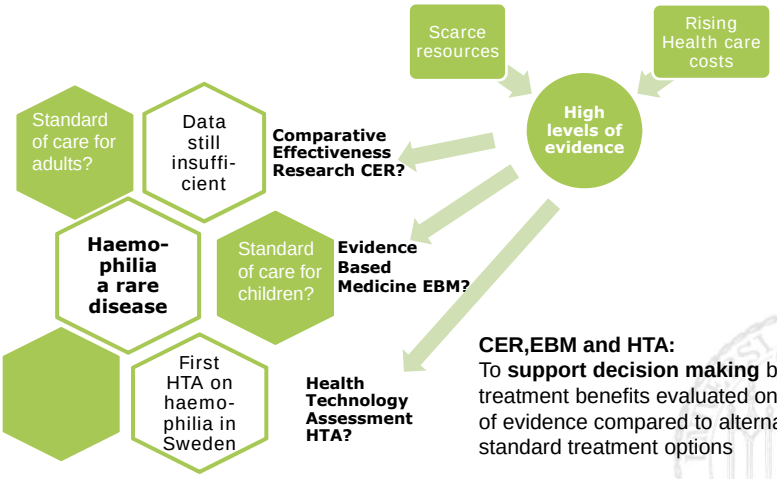
NICE
„… the National Institute for Health and Clinical Excellence … will solely give advice on the effectiveness of treatments. The move is part of the government's previously announced plan to overhaul drug funding in the UK“

US Comparative Effectiveness Research (CER)
„CER is the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat and monitor a clinical condition or to improve the delivery of care … to assist consumers, clinicians and policy makers to make informed decisions that will imporve health care noth at the individual and population level“

Clear evidence on outcomes / effectiveness (comparative effectiveness reserach) is a key element for access to and reimbursement of factor concentrates

17

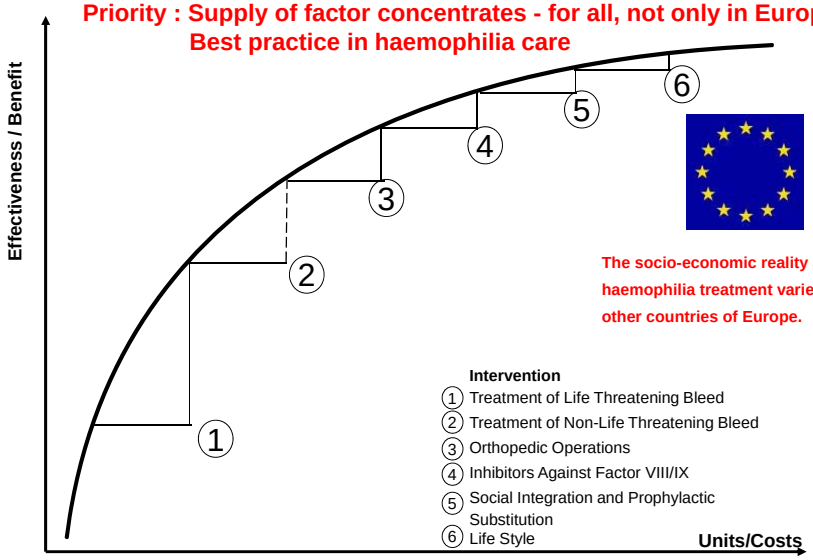
RESEARCH REQUIREMENTS TO MEET PAYERS‘ REQUESTS FOR REIMBURSEMENT OF INNOVATIVE CLOTTING FACTOR CONCENTRATES



CER,EBM and HTA:
To **support decision making** based on treatment benefits evaluated on high level of evidence compared to alternative or standard treatment options

Haemophilia Care in Europe

Priority : Supply of factor concentrates - for all, not only in Europe – Best practice in haemophilia care



The socio-economic reality and haemophilia treatment varies in the EU & other countries of Europe.

Intervention

1. Treatment of Life Threatening Bleed
2. Treatment of Non-Life Threatening Bleed
3. Orthopedic Operations
4. Inhibitors Against Factor VIII/IX
5. Social Integration and Prophylactic Substitution
6. Life Style

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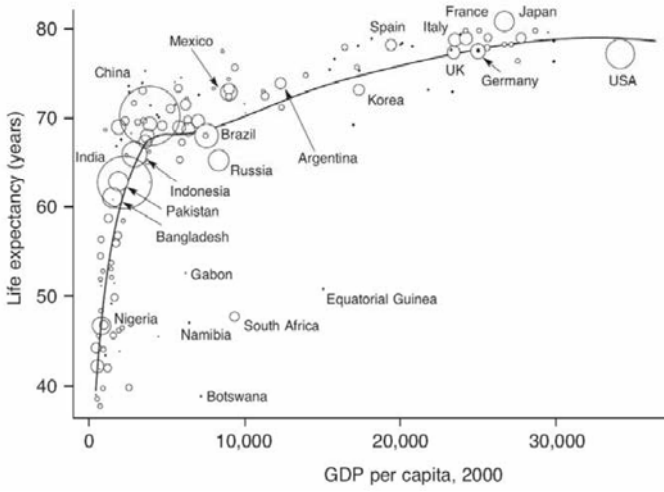
Preston Curve in 2000



(Deaton, 2004)

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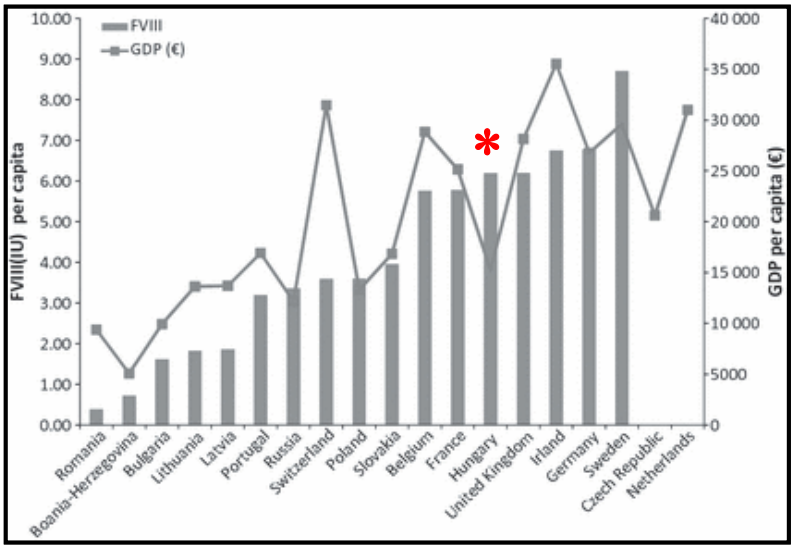
WHO Commission on Social Determinants of Health
August 28 2008

Comparison of GDP per capita (€) and FVIII per capita use.
Haemophilia care in Europe: a survey of 19 countries



(B. O'Mahony et al: Haemophilia, 17, 35-40, 2010)

TOPICS TO BE DISCUSSED AT THE WILDBAD KREUTH III MEETING

1. Expected additional clinical and patient relevant benefit associated with innovative clotting factor concentrates and innovative therapeutical approaches compared to standard haemophilia treatment
2. Research in haemophilia: difference between clinical trials for market authorization, investigator initiated trials and registries
3. Status quo of new therapies (patient tailored, low dose prophylaxis, gene therapy)
4. Access and requirements for reimbursement of clotting factor concentrates at present and in the future in Europe

WORKSHOP DISCUSSIONS SHOULD LEAD TO...

- Critical appraisal of status quo and identification of gaps in clinical and outcomes research in haemophilia
- Identification of future needs and to dos in haemophilia treatment and research
- Equity of haemophilia care in Europe?

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RUDOLF-MARX-STIFTUNG AND DEPARTMENT OF TRANSFUSION MEDICINE, CELL THERAPEUTICS AND HAEMOSTASIS

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Paul-Ehrlich-Institut

edqm

Rationale for the meeting:

Regulations for plasma-derived and recombinant medicinal products

Rainer Seitz, MD
Paul-Ehrlich-Institut

EUROPEAN SYMPOSIUM

Optimal use of clotting factors and immunoglobulins
26-27 April 2013, Wildbad Kreuth, Germany

DISCLAIMER
Any opinions/recommendations presented are my own and
do not necessarily reflect those of any official body

European Regulators

- Marketing authorisation
  - CP (EMA), DCP, MRP (NRA of member states)
- Blood Product Working Party (BPWP)
  - Guidelines for clinical studies, core SmPC
- Paediatric Committee (PDCO)
  - Paediatric investigation plan (PIP), input to guidelines
- Pharmacovigilance Risk Assessment Committee (PRAC)
  - Risk management plan (RMP), periodic safety update report (PSUR), post-authorisation safety studies (PASS)

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Marketing Authorisation - Immunoglobulins

- Variety of safe and efficacious products authorised
- BPWP guidelines and core SmPC available (Rapporteur: J. Kerr)
- **Issues**
  - **Off-label use**
  - **New indications**
  - **Supply**

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Marketing Authorisation - Haemophilia

- Variety of safe and efficacious plasma derived and recombinant products authorised
- BPWP guidelines and core SmPC available (Rapporteur: A. Hilger)
- **Issues**
  - Therapy modalities (e.g. continuous infusion, ITI)
  - **Novel products with e.g. prolonged half life**
    - Clinical trials according GCP
    - Safety, particularly immunogenicity?

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FVIII Potency Assay

- Assessment report for **Refacto AF**; Procedure No. EMEA/H/C/II/59-68
  - The labelled potency of ReFacto AF is based on the European Pharmacopoeial chromogenic substrate assay, in which the manufacturing potency standard has been calibrated to the WHO International Standard using the chromogenic substrate assay. Another moroctocog alfa product approved for use outside Europe has a different potency assigned using a manufacturing potency standard that has been calibrated to the WHO International Standard using a one-stage clotting assay; this product is identified by the tradename XYNTHA. **Due to the difference in methods used to assign product potency of XYNTHA and ReFacto AF, 1 IU of the XYNTHA product (one-stage assay calibrated) is approximately equivalent to 1.38 IU of the ReFacto AF product (chromogenic assay calibrated)**.

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Recommendations on the potency labelling of factor VIII and factor IX concentrates

OFFICIAL COMMUNICATION OF THE SSC

A R HUBBARD[1], J DODT[2], T LEE[3], K MERTENS[4], R SEITZ[2], A SRIVASTAVA[5], M WEINSTEIN[3] ON BEHALF OF THE FACTOR VIII AND FACTOR IX SUBCOMMITTEE OF THE SCIENTIFIC AND STANDARDISATION COMMITTEE OF THE INTERNATIONAL SOCIETY ON THROMBOSIS AND HAEMOSTASIS

doi: 10.1111/jth.12167

This paper addresses:

1. Manufacturer's characterisation of new product potency
2. Calibration of manufacturer's product reference
3. Manufacturer's pharmacokinetic studies
4. Post-infusion testing in clinical laboratories

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Orphan Medicinal Products

- Criteria for designating a medicinal product as an orphan medicinal product if:
  - (a) condition affecting not more than five in 10 thousand persons in the Community,
    or
    without incentives it is unlikely that the marketing in the Community would generate sufficient return to justify the necessary investment;
    and
  - (b) there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition.

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Orphan Medicinal Products

- Incentives
  - Member States shall not, **for a period of 10 years, accept another application** for a marketing authorisation, or grant a marketing authorisation or accept an application to extend an existing marketing authorisation, for the same therapeutic indication, in respect of a **similar medicinal product**.
  - Protocol assistance
  - Options for reduced fees, research grants

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10 Designated Orphan MP for treatment of haemophilia A

Product	Sponsor	Date of Designation
Pegylated rh FVIIa	Novo Nordisc	4 June 2008
Liposomal rh FVIII	Bayer Pharma AG	24 July 2009
Sequence-modified rhFVIIa	Bayer Pharma AG	9 October 2009
Recombinant porcine factor VIII (B domain deleted)	Inspiration Biopharmaceuticals	20 September 2010
Recombinant fusion protein FVIII attached to Fc of IgG1	Biogen Idec	20 September 2010
Pegylated rh BDD sequence-modified FVIII	Bayer Pharma AG	23 February 2011
Recombinant fusion protein FVIIa with albumin	CSL Behring	15 April 2011
Pegylated rH FVIII	Novo Nordisk	26 April 2012
Vatreptacog alfa (activated)	Novo Nordisk	9 August 2012
Hum. moAb TFPI	Novo Nordisk	10 October 2012

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COMMUNICATION FROM THE COMMISSION

Guideline on aspects of the application of Article 8(1) and (3) of Regulation (EC) No 141/2000: Assessing similarity of medicinal products versus authorised orphan medicinal products benefiting from market exclusivity and applying derogations from that market exclusivity

The **mechanism of action** of an active substance is the functional description of the interaction of the substance with a pharmacological **target** that elicits a pharmacodynamic **effect**. In case the mechanism of action is not fully known, it will be for the applicant to demonstrate that the two active substances do not act via the same mechanisms.

Two active substances may only be considered to have the **same mechanism of action,** provided that *both* share the same pharmacological target and pharmacodynamic effect.

Factors not relevant to the mechanism of action are differences between two substances in terms of:

- Mode of administration;
- Pharmacokinetic properties;
- Potency; or
- Tissue distribution of the target.

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Concerns

WFH 50 YEARS OF ADVANCING TREATMENT FOR ALL
WORLD FEDERATION OF HEMOPHILIA
Fédération mondiale de l'hémophilie
Federación Mundial de Hemofilia

The WFH recommends that Orphan Drug designation should not be used to hinder, for the same condition or indication, the development, licensing and marketing of other products which have demonstrably different protein modification or enhancement. We see a danger that market exclusivity could create a monopoly rather than allowing for competition that will ensure the widest possible access at the most affordable prices to products which are actually different on the molecular level. Furthermore, the product with the orphan marketing authorization may not have the best efficacy or safety profile of the possible products. We urge regulators to consider these issues when deciding questions of market exclusivity for various products for the treatment of hemophilia.

This statement was approved by the WFH Blood Products Safety, Supply and Availability Committee on June 13, 2012, and adopted by the WFH Executive Committee on July 8, 2012.

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EMA Response

- Market exclusivity applies only to similar MP
- CHMP decides about similarity of products
- Similar MP could still be licensed
  - with consent of MAH of original orphan
  - when MAH of original orphan is unable to produce sufficient quantities
  - when it can be established that the similar MP is safer, more effective or otherwise clinically superior
- Orphan designation is based on voluntary applications; concerns should be addressed to the applicants

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Health Technology Assessment (HTA)

- Classical criteria for MA are quality, efficacy and safety of new MP
- In recent years, health care providers increasingly ask for the incremental value of a new MP for public health and individual patients
- While MA confirms that a new MP is safe and “works” as claimed, HTA takes into account medical, economic, social and ethical implications

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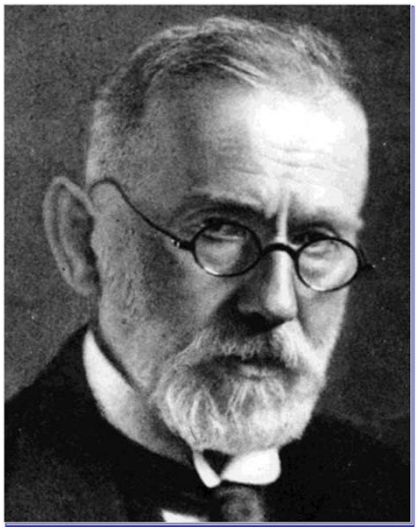
Health Technology Assessment (HTA)

- In Germany, the Federal Joint Committee (G-BA) is the highest decision-making body of the joint self-government of physicians, dentists, hospitals and health insurance funds
- One of its tasks is the benefit assessment of pharmaceuticals in accordance with the Act on the Reform of the Market for Medicinal Products (AMNOG)
- In this task, the G-BA is assisted by the Institute for Quality and Efficiency in Health Care (IQWIG), which performs analyses of the available scientific evidence
- The reimbursement of new MP is connected to the incremental benefit the applicant can document in a dossier on the basis of clinical data

Paul-Ehrlich-Institut

Thank you for your attention !



Paul Ehrlich

UNIVERSITY OF OXFORD

Oxford University Hospitals NHS
NHS Trust

Clinical challenges in haemophilia and access to concentrates in Europe

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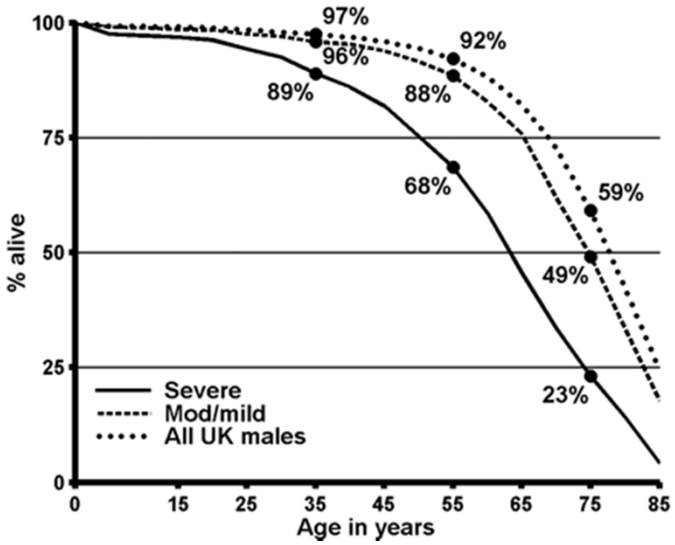
Our strengths in Europe:

- Several major pharmaceutical companies and production facilities based in our continent
- Treatment usually provided free to patients (or at least at highly subsidized prices)
- Strong professional and scientific interest in haemophilia among health care professionals
  - EAHAD held first conference in 2008
- Strong and influential patient organizations (EHC)
- Widespread availability of safe treatment has improved life expectancy and quality of life

Life expectancy and haemophilia:

Darby SC et al. Blood 110: 815-825 (2007)



Haemophilia

Haemophilia (2012), **18**, 729–737

DOI: 10.1111/j.1365-2516.2012.02847.x

ORIGINAL ARTICLE *Clinical haemophilia*

Haemophilia Care in Europe: the ESCHQoL study

W. SCHRAMM,* A. GRINGERI,† R. LJUNG,‡ K. BERGER,*§ A. CRISPIN,* M. BULLINGER,¶ P. L. F. GIANGRANDE,** S. VON MACKENSEN,¶ L. G. MANTOVANI,†† L. NEMES,‡‡ and M. SERBAN§§ FOR THE ESCHQOL STUDY GROUP[1]

**Department of Transfusion Medicine and Haemostasis, University Hospital of Munich, Munich, Germany; †Department of Internal Medicine, IRCCS Fondazione Ca' Granda Ospedale Maggiore and University of Milan, Milan, Italy; ‡Department of Paediatrics, Lund University, Skåne University Hospital, Malmö, Sweden; §Medical Economics Research Group (MERG), Munich; ¶Institute and Policlinics of Medical Psychology, Centre of Psychosocial Medicine, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany; **Churchill Hospital, Oxford University Hospitals NHS Trust, Oxford, UK; ††University of Milan, Centre of Pharmacoeconomics, Milan, Italy; ‡‡National Haemophilia Centre and Haemostasis Department, State Health Centre, Budapest, Hungary; and §§3rd Paediatric Clinic, University of Medicine & Pharmacy 'Victor Babes', Timisoara, Romania*

Summary. The aim of this study was to determine the clinical conditions of patients with haemophilia within Europe as recommended by the European Commission. In this multicentre, cross-sectional, ambispective study, conducted within 21 European countries patients' clinical data were collected, amongst others haemophilia type, severity, treatment pattern, use of factor products, bleeding, orthopaedic joint scores and infections. A total of 1400 patients, 84.3% with haemophilia A and 15.7% with haemophilia B were enrolled by 42 centres between 2004 and 2006. Thereof, 417 were children (30.0%) and 983 were adults (70.0%). About 70% of patients had severe factor deficiency (<1%). More than half of the adults were carriers of chronic infections (12.6% HIV, 55.8% HCV), compared to only 3.8% children (no HIV, 2.9% HCV). Patients were grouped according to per capita amount of clotting factor used in patients' region of residence in 2005: region 1: >5 IU; region 2: 2–5 IU; region 3: <2 IU. Paediatric and adult patients in region 3 had median numbers of three and eight joint bleeds, respectively, with worse joint scores compared to region 1 with zero and one bleed. Prophylactic therapy was used in only 31.3% children and 8.9% adults with severe haemophilia in region 3 compared to 93.7% and 54.1%, respectively, in region 1. Statistical analysis revealed that residence in areas with low factor consumption/availability is the most prominent risk factor for joint disease. Access of European patients with haemophilia to optimal care with safe factor VIII concentrates is limited and depends on the region of residence.

Keywords: arthropathy, clinical outcomes, European countries, factor consumption, haemophilia, severity, treatment

Haemophilia The Official Journal of the World Federation of Hemophilia, European Association for Haemophilia and Allied Disorders and the Hemostasis & Thrombosis Research Society

Haemophilia (2013), 1–9 DOI: 10.1111/hae.12125

ORIGINAL ARTICLE

Haemophilia care in Europe – a survey of 35 countries

B. O'MAHONY,* D. NOONE,* P. L. F. GIANGRANDE† and L. PRIHODOVA‡
Irish Haemophilia Society, Dublin, Ireland; †Oxford Comprehensive Haemophilia Centre, Oxford, UK; and ‡Graduate School, Kosice Institute for Society and Health, Medical Faculty, PJ Safarik University, Kosice, Slovak Republic

Summary. A questionnaire was circulated in 2012 to national haemophilia patient organizations in Europe affiliated to the European Haemophilia Consortium (EHC) and the World Federation of Hemophilia (WFH) to seek information about the organization of haemophilia care and treatment available at a national level. The 35 responses received highlighted major differences in the availability of treatment and care. There was a wide range in factor VIII consumption with usage ranging from 0.20 IU per capita in Armenia to 8.56 IU per capita in Sweden (median: IU per capita). The decrease in health budgets in many countries was not matched by decreases in use of FVIII per capita. In the 19 countries that responded to the previous survey, there was a significant improvement in access to prophylaxis and home treatment.

Keywords: Organisation, Specialist Care, Treatment

Haemophilia care in Europe:

- Survey of 35 countries conducted in 2012
  - Sequel to similar survey of 19 countries in 2009
- Wide range in factor VIII consumption:
  - 0.2 IU/capita (Armenia) → 8.56 (Sweden)
  - 2 IU/capita was minimum recommended national consumption at Wildbad Kreuth 2009 meeting
  - Consumption still below this in 12/35 countries
  - Consumption has risen in 15/19 surveyed in 2009

ESCHQoL study:

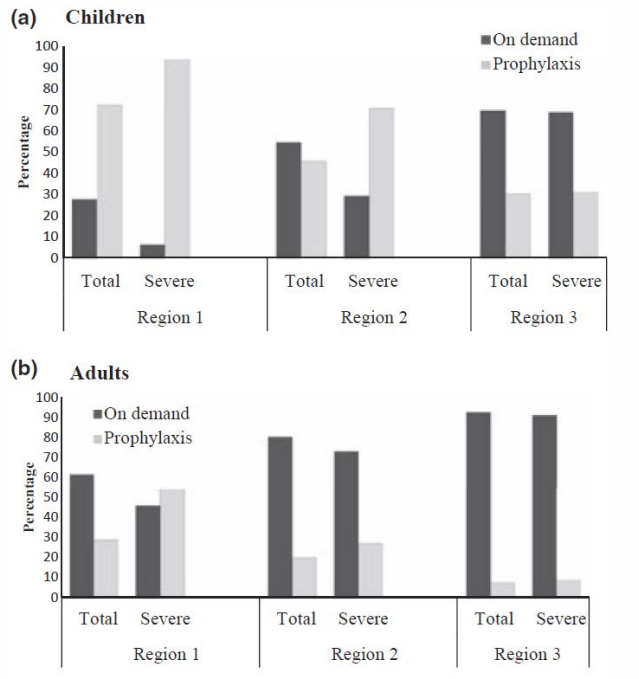
Schramm W et al. Haemophilia 18: 729-737 (2012)

- Region 1: prophylaxis used in 93.7% of children with severe haemophilia and 54.1% of adults
- Region 2: prophylaxis used in 70.6% of children with severe haemophilia and 27.0% of adults
- Region 3: prophylaxis used in 31.7% of children with severe haemophilia and 8.9% of adults

ESCHQoL study:

Schramm W et al. Haemophilia 18: 729-737 (2012)

- Data from 1400 patients in 21 European countries collected in period 2004-2006
  - 417 children (30%) and 983 adults (70%)
  - 964 (70%) had severe haemophilia (<1%)
  - 1180 (84.3%) had haemophilia A
- Patients grouped according to per capita factor consumption in country of residence:
  - Region 1: > 5 IU (A,D,DK,F,GB,S)
  - Region 2: 2-5 IU (B,FIN,GR,H,I,P,SK,SLO,S,CH)
  - Region 3: <2 IU (CZ,LT,PL,RO,TR)



EAHAD Principles of Care:

Haemophilia 14: 361-374 (2008)

- Network of designated treatment centres
- Specialist services and emergency care
- National registries
- Central organisation with local groups
- Partnership in delivery of care
- Safe and effective treatment
- Home treatment and delivery
- Prophylaxis
- Immune tolerance for inhibitors
- Education and research

www.euhanet.org

Organization of haemophilia care:

- "There are 409 known treatment centres in Europe. The size and services offered vary enormously"
- Need to define criteria for designation of haemophilia treatment centres and set standards of care throughout Europe
- Wide consultation among physicians and organizations in Europe
- Aim is to define and then designate two tiers of treatment centres in Europe (EHCCC/EHTC):
  - Patient numbers will be an important criterion: 40 patients with severe haemophilia or type 3 VWD for designation as EHCC and 10 for EHTC
  - Based on self-assessment for initial 3 year period: system of external audit inspections may be established in due course

What is our goal?

Skinner M. Haemophilia 18 (Suppl. 4): 1-12 (2012)

- FVIII level of 1% “wholly insufficient”
- Trough level of 15% “ideal” but “unattainable in short term due to cost”
- “Improving patient quality of life should drive treatment decisions, not economics”
- “Moving forward incrementally to higher baseline levels of 3 or 5% would be a step in the right direction”
- Novel products with prolonged half-lives will facilitate this

Novel products (1):

- Clinical trials well under way and more to start soon
- Development wholly based on recombinant technology
- Products under development include:
  - Biosimilars
  - Long-acting factor VIII
  - Long-acting factor IX
  - Porcine factor VIII
  - Activated factor VII analogues
  - Anti-TFPI antibodies
  - Transgenic factor VIII & IX manufactured using animals

Novel products (2):

- I am confident that at least some of these products will be available within 5 years
- Potential to change clinical practice radically
- Success not guaranteed: several failures/problems encountered already
  - FVIII and pegylated liposomes (Bayer)
  - TFPI inhibitor (Baxter)
  - Recombinant FIX (Ipsen/Inspiration)
  - Long-acting factor VII & vatreptacog (NovoNordisk)
- Need for vigilance for unexpected problems

Enhanced pharmacokinetic properties of a glycoPEGylated recombinant factor IX: a first human dose trial in patients with hemophilia B

Claude Negrier,[1] Karin Knobe,[2] Andreas Tiede,[3] Paul Giangrande,[4] and Judi Møss[5]

[1]Hôpital Edouard Herriot, Centre Régional de Traitement de l'Hémophilie, Université Claude Bernard Lyon 1, Lyon, France; [2]Malmö Centre for Thrombosis and Haemostasis, Lund University, Malmö, Sweden; [3]Hematology, Hemostasis, Oncology and Stem Cell Transplantation, Hannover Medical School, Hannover, Germany; [4]Oxford Haemophilia & Thrombosis Centre, Churchill Hospital, Oxford, United Kingdom; and [5]Department for Medical and Science, Haemophilia, Novo Nordisk A/S, Søborg, Denmark

Replacement therapy with factor IX (FIX) concentrates is the recommended treatment for patients with hemophilia B, an X-linked bleeding disorder occurring in 1:25 000 male births. N9-GP is a recombinant FIX molecule with a prolonged half-life which is obtained by site-directed glycoPEGylation where a 40-kDa polyethylene glycol molecule is attached to the activation peptide of FIX. This first human dose trial in patients with hemophilia B investigated the safety and pharmacokinetic properties of a single IV dose of N9-GP. Sixteen previously treated patients received one dose of their previous FIX product followed by one dose of N9-GP at the same dose level (25, 50, or 100 U/kg). None of the patients developed inhibitors. One patient developed transient hypersensitivity symptoms during administration of N9-GP and was excluded from pharmacokinetic analyses. In the remaining 15 patients, N9-GP was well-tolerated. The half-life was 93 hours, which was 5 times higher than the patient's previous product. The incremental recovery of N9-GP was 94% and 20% higher compared with recombinant and plasma-derived products, respectively. These results indicate that N9-GP has the potential to reduce dosing frequency while providing effective treatment of bleeding episodes with a single dose. The trial was registered at www.clinicaltrials.gov as NCT00956345. (*Blood.* 2011;118(10): 2695-2701)

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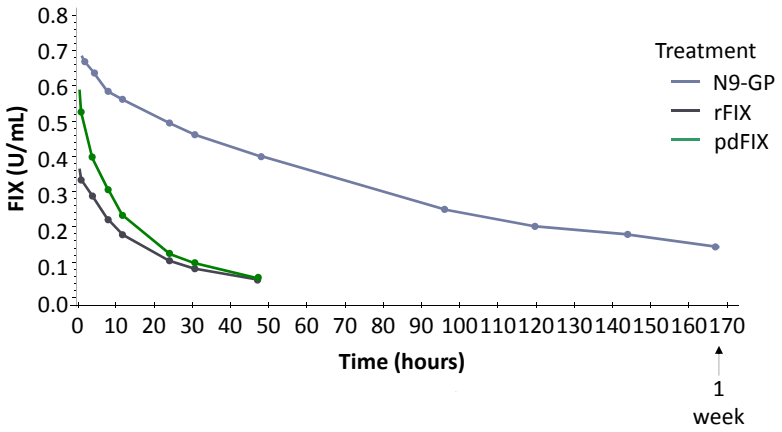
Summary profiles comparing N9-GP to previous FIX – normalised to 50 U/kg



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Comparison of derived PK parameters between N9-GP and previous FIX:

PK Parameters	N9-GP Mean (N=15)	rFIX Mean (N=7)	pdFIX Mean (N=8)	Ratio N9-GP/FIX
$t_{1/2}$ (hours)	92.7	19.3	17.8	5.00
Incremental Recovery (U/dL per U/kg)	1.33	0.69	1.12	1.53 (1.94 ; 1.20)
CL (mL/hour/kg)	0.70	6.99	5.48	0.11
Vz (mL/kg)	94.2	195	141	0.57
Time to 1% activity (days)	22.5	4.5	4.0	
Time to 3% activity (days)	16.2	2.8	2.7	

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My predictions for the future:

- Much greater emphasis on cost effectiveness of therapy:
  - Novel products will not necessarily be adopted for routine use
  - Collection of much more outcome data (e.g. quality of life; trough levels, joint scores) will be routine
  - Much closer monitoring of factor usage by individual patients
  - Greater involvement by commercial companies in direct patient care through establishment of home care companies:
    - Offer 24-hour telephone advisory service and nurse visits
- Fewer but larger dedicated treatment centres:
  - Better distribution according to patient density
  - Significant internal migration of patients within EU to countries where better treatment is available
  - Merged adult and paediatric treatment centres

Current Data and Trends on the Use of Clotting Factors and Immunoglobulins in Europe

Patrick Robert
The Marketing Research Bureau, Inc.

EUROPEAN SYMPOSIUM
OPTIMAL USE OF CLOTTING FACTORS AND IMMUNOGLOBULINS IN EUROPE
April 26-27, 2013
Kreuth, Germany

METHODOLOGY & COPYRIGHT

The data used to develop the charts and tables shown in this presentation have been compiled from surveys conducted by the Marketing Research Bureau in some fifty countries, and published in various syndicated reports.

All the data and information come from sources generally available to the public. Their accuracy is not guaranteed, and the Marketing Research Bureau assumes no liability for their use.

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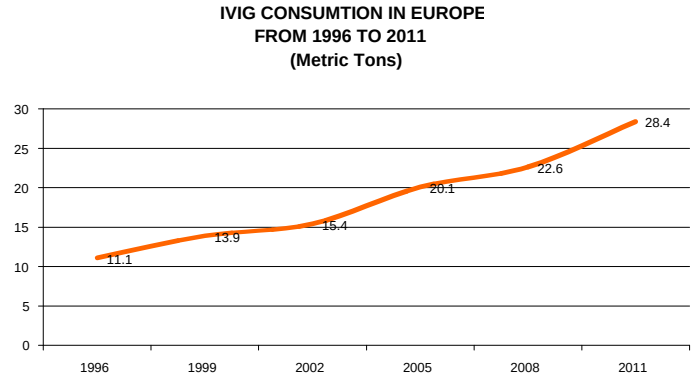
- **Introduction: IVIG & Factor VIII Demand**
- **Use of IVIG and Factor VIII by Country**
- **Self-Sufficiency Ratio by Country**

Note: more extensive data will be presented at the meeting

Table of Contents

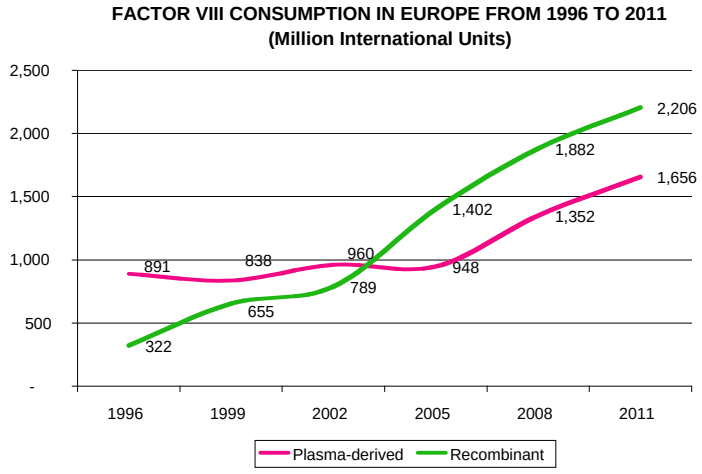
- **Introduction: IVIG & Factor VIII Demand**
- **Use of IVIG and Factor VIII by Country**
- **Self-Sufficiency Ratio by Country**

The demand for intravenous/subcutaneous immune globulin (IVIG/SCIG) has been multiplied by 2.5 between 1996 and 2011 in Europe.



IVIG drives the market in Europe and America, albumin in most Asian countries, and coagulation factors in the developing countries

Between 1996 and 2011, the factor VIII demand has been multiplied by 3.1 in Europe.



Total factor VIII in 2011: 3,862 Million International Units

The demand for IVIG and Factor VIII is driven by:

1. Health services improvement,
2. Demographics (population aging, weight gains)
3. Funding,
4. Lobbying by patient groups,
5. Medical Indications,
6. Treatment practices,
7. Product availability,
8. Product awareness and promotion to physicians, patients and the general public

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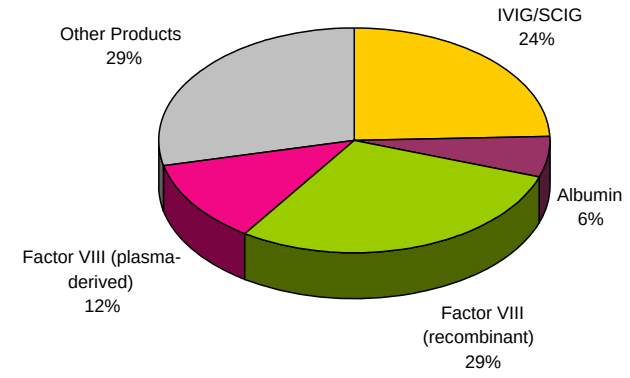
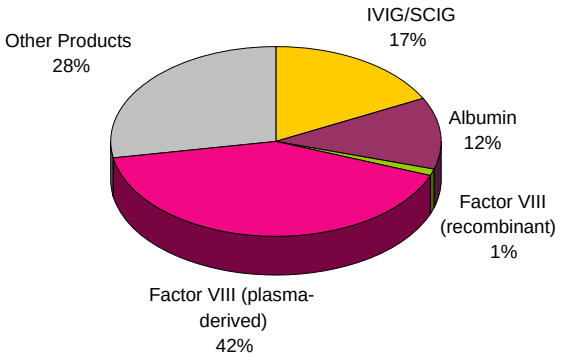
THE PLASMA AND RECOMBINANT PROTEINS MARKET IN EUROPE 2011



Total Market: $7.4 billion

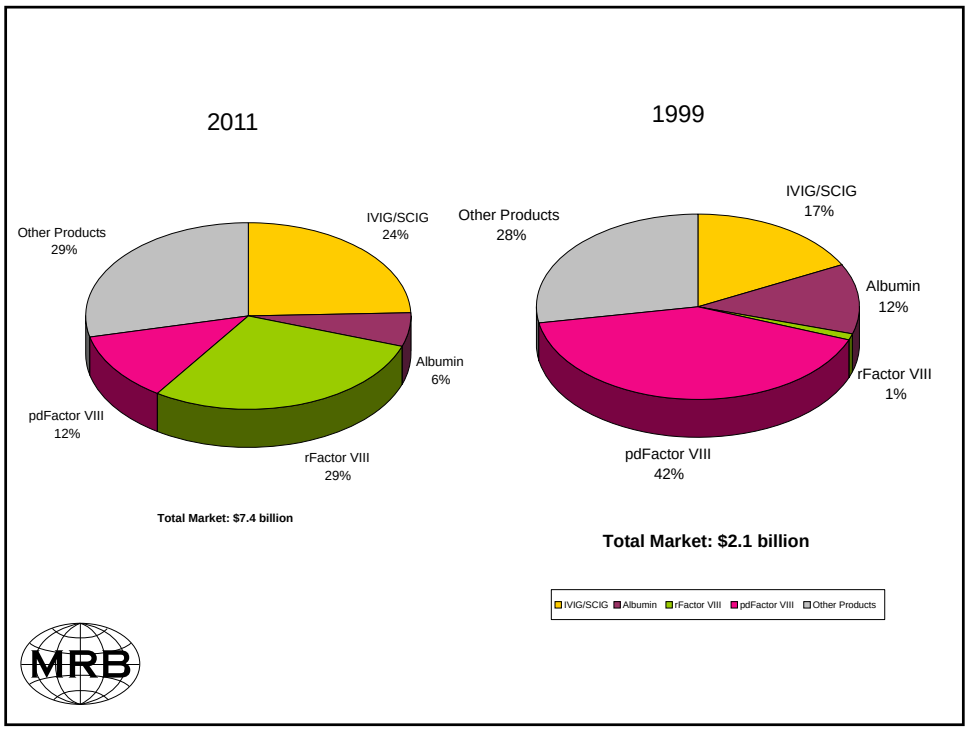
IVIG/SCIG
Albumin
Factor VIII (recombinant)
Factor VIII (plasma-derived)
Other Products

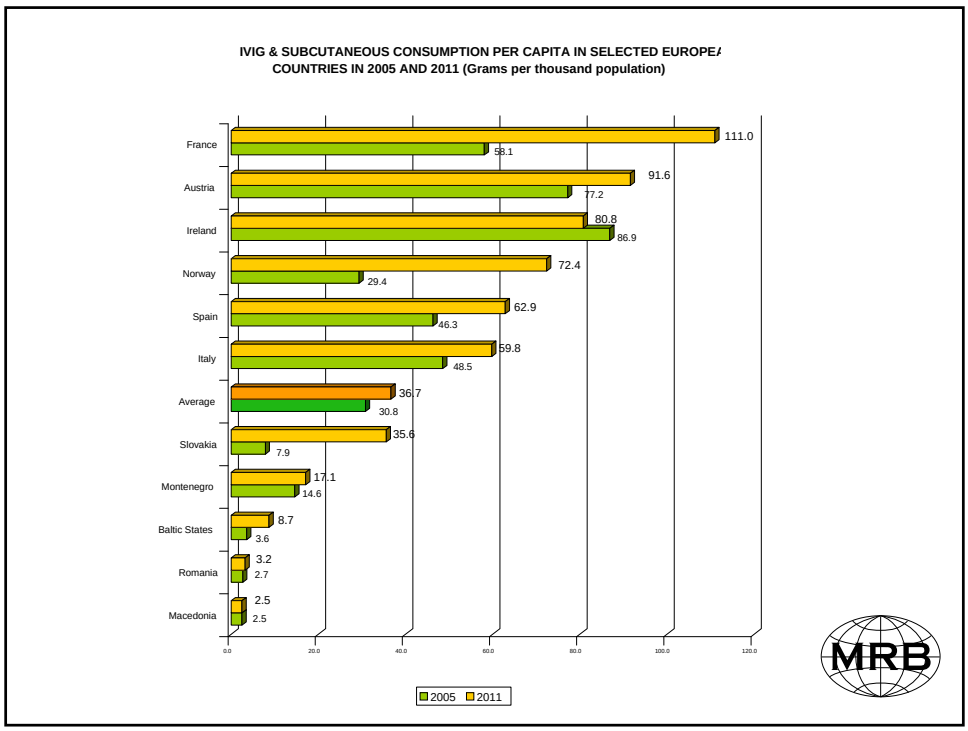
THE PLASMA AND RECOMBINANT PROTEINS MARKET IN EUROPE 1999



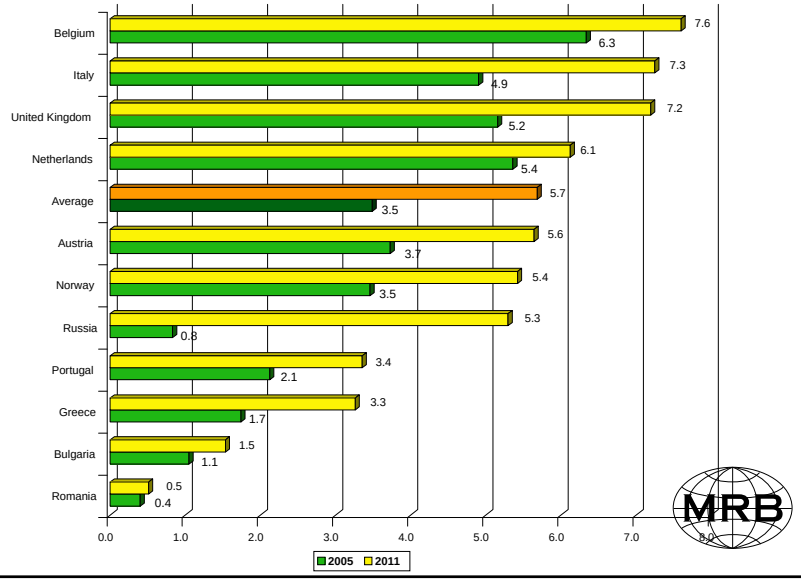
Total Market: $2.1 billion

IVIG/SCIG
Albumin
Factor VIII (recombinant)
Factor VIII (plasma-derived)
Other Products


2011
1999
Other Products
29%
IVIG/SCIG
24%
Albumin
6%
pdFactor VIII
12%
rFactor VIII
29%
Total Market: $7.4 billion
Other Products
28%
IVIG/SCIG
17%
Albumin
12%
rFactor VIII
1%
pdFactor VIII
42%
Total Market: $2.1 billion
IVIG/SCIG
Albumin
rFactor VIII
pdFactor VIII
Other Products
MRB


IVIG & SUBCUTANEOUS CONSUMPTION PER CAPITA IN SELECTED EUROPEA
COUNTRIES IN 2005 AND 2011 (Grams per thousand population)
France
111.0
58.1
Austria
91.6
77.2
Ireland
80.8
86.9
Norway
72.4
29.4
Spain
62.9
46.3
Italy
59.8
48.5
Average
36.7
30.8
Slovakia
35.6
7.9
Montenegro
17.1
14.6
Baltic States
8.7
3.6
Romania
3.2
2.7
Macedonia
2.5
2.5
0.0
20.0
40.0
60.0
80.0
100.0
120.0
2005
2011
MRB

FACTOR VIII PER CAPITA IN SELECTED EUROPEAN COUNTRIES IN 2005 AND 2011
(International Units/Inhabitant)



MRB

Table of Contents

- Introduction: IVIG & Factor VIII Demand
- Use of IVIG and Factor VIII by Country
- Self-Sufficiency Ratio by Country

MRB

Countries that are Self-sufficient with plasma products procurements have either:

- **Low consumption level of plasma products or**
- **Large collection volumes of plasma, mostly for export.**

Strict self-sufficiency may reduce access to therapy

SELF SUFFICIENCY BY COUNTRY - 2011

Country	Population (million)	Plasma for Fractionation Liters (000)	Kilograms IVIG/Subcu. (Mkt Data)	IVIG/Subcu. Kilograms per million Inhabitants	Plasma Volume required Liters (000) 4.5 gr./Liter	Degree of Self-sufficiency (Percent)
Austria	8.429	460	655	77.7	146	316%
Baltic States	6.867	30	122	17.8	27	111%
Belgium	10.431	150	1,200	115.0	267	56%
Croatia	4.483	23	75	16.7	17	138%
Czech Republic	10.190	550	320	31.4	71	773%
France	63.296	784	7,045	111.3	1,566	50%
Germany	81.230	3,000	4,450	54.8	989	303%
Greece	10.760	-	410	38.1	91	0%
Hungary	9.950	108	84	8.4	19	579%
Italy	61.016	660	3,650	59.8	811	81%
Norway	4.920	53	360	73.2	80	66%
Poland	38.317	280	582	15.2	129	216%
Russia	142.703	500	580	4.1	129	388%
Spain	46.754	400	2,930	62.7	651	61%
Sweden	9.221	145	1,019	110.5	226	64%
Switzerland	7.850	72	577	73.5	128	56%
United Kingdom	62.700	-	3,360	53.6	747	0%
Total	579.117	7,215	27,419	47.3	6,093	
United States	306.700	22,500	45,000	146.7	10,000	225%

CONCLUSIONS

- **The industry consolidation has contributed to improving product availability, safety and quality, thus fueling the demand,**
- **In the future, new indications for IVIG/SCIG will contribute to the demand growth,**
- **Consequently, higher volumes of plasma will be required, challenging self-sufficiency policies.**
- **Recombinant factor VIII products will continue to cannibalize the plasma-derived products**

MRB

Thank you!

MRB

EUROPEAN SYMPOSIUM

OPTIMAL USE OF CLOTTING FACTORS AND IMMUNOGLOBULINS

26-27 APRIL 2013, WILDBAD KREUTH, GERMANY

SUMMARY OF THE EDQM SURVEY
CLOTTING FACTOR CONCENTRATES

KARIN BERGER, LMU
ANNELIESE HILGER, PEI

SURVEY EUROPEAN SYMPOSIUM „OPTIMAL USE OF CLOTTING FACTORS AND IMMUNOGLOBULINS

Responders	N = 32 Luxembourg, The Netherlands, Finland, Russia, Spain, Portugal, Malta, Czech Republic, Belgium, Italy, USA, Switzerland, Greece, Denmark, Ireland, Hungary, Austria, Macedonia, Romania, Lithuania, Estonia, Moldova, Ukraine, Georgia, Serbia, Poland, Bulgaria, Croatia, Armenia, Slovakia, Turkey, Slovenia
Area	93,8% national data
Time frame	6,3 % refer on 2010 data, 62,5 % refer on 2011 data, 31,3% refer on 2012 data

CLOTTING FACTOR USAGE IN EUROPEAN COUNTRIES

5. Which of the following products are used to treat haemophilia in your country?

	Always	Rarely	Never	Rating Count
Plasma	7.1% (2)	28.6% (8)	**64.3% (18)**	**28**
Cryoprecipitate	3.6% (1)	28.6% (8)	**67.9% (19)**	**28**
Plasma-derived Factor Concentrates	**71.0% (22)**	29.0% (9)	0.0% (0)	**31**
Recombinant Factor Concentrates	**59.4% (19)**	37.5% (12)	3.1% (1)	**32**
Other	14.3% (1)	14.3% (1)	**71.4% (5)**	**7**

PROHYLACTIC AND ON DEMAND TREATMENT

6. Are the following haemophilia treatment modalities used in your country?

	Yes	No	Rating Count
On demand treatment	**100.0% (32)**	0.0% (0)	32
Prophylaxis	**87.5% (28)**	12.5% (4)	32

7. Prophylaxis in children and adults

	None	Between 1-25%	Between 26-50%	Between 51-75%	Between 76-100%	Rating Count
Children	9.4%(3)	12.5% (4)	15.6% (5)	15.6% (5)	**46.9% (15)**	32
Adults	15.6% (5)	31.3% (10)	**37.5% (12)**	6.3% (2)	9.4% (3)	32

TREATMENT STANDARDS?

8. What determines standards of treatment?

	Yes	No	Rating Count
European/International guidelines	**93.3% (28)**	6.7% (2)	30
National guidelines	**75.0% (21)**	25.0% (7)	28
Centre specific guidelines	**63.6% (14)**	36.4% (8)	22
Published reports	**70.0% (14)**	30.0% (6)	20

TREATMENT SETTINGS?

9. Where are haemophilia patients generally treated?

	Less than 10%	Between 10-50%	Between 51-75%	Between 76-100%	Rating Count
CCC*	15.4% (4)	30.8% (8)	15.4% (4)	**38.5% (10)**	26
Inpatients	**65.4% (17)**	19.2% (5)	7.7% (2)	7.7% (2)	26
Outpatients	20.0% (5)	40.0% (10)	8.0% (2)	32.0% (8)	25
Home treatment	10.3% (3)	17.2% (5)	24.1% (7)	**48.3% (14)**	29

*Comprehensive Care Center

NATIONAL HAEMOPHILIA REGISTRIES

10. Do you have a National Haemophilia Registry in your country?

		Response count
Yes	68.8%	**22**
No	31.3%	10

11. What information is covered by the National Haemophilia Registry?

	Yes	No	Rating count
Documentation of treatment (products, modalities)	**95.0% (19)**	5.0% (1)	20
Documentation of outcomes / complications	**80.0% (16)**	20.0% (4)	20
Documentation of quality of life	42.1% (8)	**57.9% (11)**	19
Reimbursement of haemophilia treatment linked to participation	29.4% (5)	**70.6% (12)**	17
Published Reports	38.9% (7)	**61.1% (11)**	18

MANAGEMENT OF HAEMOPHILIA REGISTRY?

12. Who manages the National Haemophilia Registry?

		Response Percent	Response count
Government		14.3%	3
Academic Organisation		23.8%	5
Clinician(s)		**76.2%**	**16**
Haemophilia Patient Organisation		42.9%	9
Industry		0.0%	0
Others		14.3%	3

PURCHASING CLOTTING FACTOR CONCENTRATES?

13. Is there a National Tender for the procurement of Coagulation Factor Concentrates in your country?

	Response count	
Yes	56.3%	**18**
No	43.8%	14

14. Which organsation purchases Haemophilia products in your country?

	Response Percent	Response count
Government	21.9%	7
National Health care System	**50.0%**	**16**
Health care providers	31.3%	10
Hamophilia Patient Organisation	3.1%	1
Health Insurance companies	25.0%	8
Other	12.5%	4

KLINIKUM DER UNIVERSITÄT MÜNCHEN®
RUDOLF-MARX-STIFTUNG AND DEPARTMENT OF TRANSFUSION MEDICINE, CELL THERAPEUTICS AND HAEMOSTASIS

Wildbad Kreuth III
Summary of Immunoglobulin Survey

General (34/34)

- 34/43 Countries: Europe, USA, New Zealand and Japan
- Time frame: 94% data from 2011 – 2013
- Area: 85% national data
  6% regional data
  9% local data
- Specialisation: 40 % Immunodeficiency
  60 % Transfusion/haemovigilance
- Organisation : 18 university hospitals or medical institutes
  10 transfusion/blood supply centres
  4 Ministries of Health (ES, GR, LI, SER)
  2 agencies (USA, BE)
- Standard of treatment: ~85% European/International GL + publ. reports
  77% Nat. GL
  68% Centre GL

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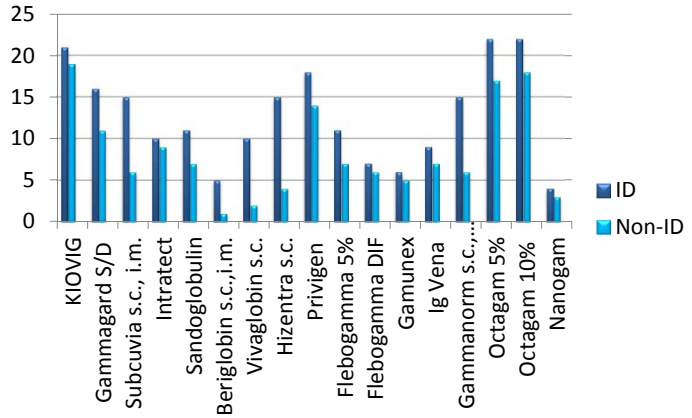
2

Ig Use in Countries (33/34)



- **All listed brands were 100% available for ID**
- All listed brands were 20-90% available for established non-ID
- 16 „other" brands, (3/16 other national names)

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3

Purchasing Ig (32/34)

- National tender ? 37.5% yes
  62.5% no

- Which organisation?
  53% Health care providers
  28% Other (mainly hospitals)
  16% Immunodeficiency centres
  9% Insurances

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4

PID

- Where? 30/34

  13/19 – (68%) > 51% care centres
  12/22 – (55%) < 10% inpatients
  8/21 – (38%) > 51% outpatients
  7/18 – (39%) > 51% home treatment

- ID registry? 33/34 — 48.5% yes (11/15 nat., 12/15 ESID, 5 „other“)
  51.5% no

- Nat. Registry
  - Which info? 13/34
    100% treatment modalities
    77% outcomes/complications
    46% QOL
    23% published reports
  - Management 14/34
    57% clinician
    29% government
    21% academic organisation
    14% patient organistion

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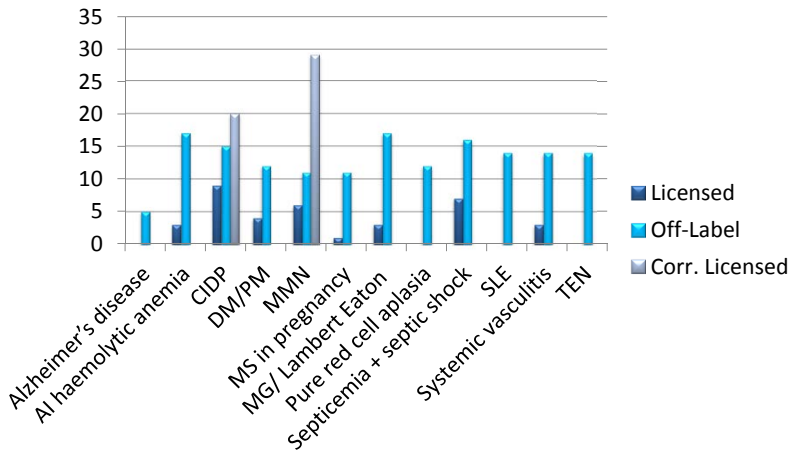
Licensed vs. off-label (33/34)



Off-label reimbursed ? 19 yes (16/19 most indications, with restrictions)
14 no

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Patient Access Issues and Unmet Needs

Brian O'Mahony
President, EHC
EDQM Meeting, Munich, April 2013

European Principles of care

1. Establishment of a central haemophilia organisation in each country with supporting local group
2. National Haemophilia patient registries
3. A network of multidisciplinary comprehensive care centres and complementary haemophilia treatment centres
4. Partnership of health care professionals and patients in the delivery of haemophilia care
5. Safe and effective concentrates at optimum treatment levels
6. Home treatment and delivery
7. Prophylaxis
8. Specialist services and emergency care
9. Management of inhibitors
10. Encouragement of education and research

EDQM Optimal use recommendations, April 2009

- Recommended minimum use of 2 IU per capita for FVIII
- Prophylaxis for adults should also be considered


edqm

24-25 April 2009

Optimal Clinical Use of Blood Components

PROCEEDINGS

International Symposium co-organised by the EDQM & HealthCare/DBO - Transfusion Medicine, Council of Europe
PEI, the German Official National Agency for Biologicals
The Transfusionsmedizin und Haemostaseologie, Klinikum der Universitaet Muenchen

Wildbad Kreuth, Bavaria, Germany

LMU KLINIKUM

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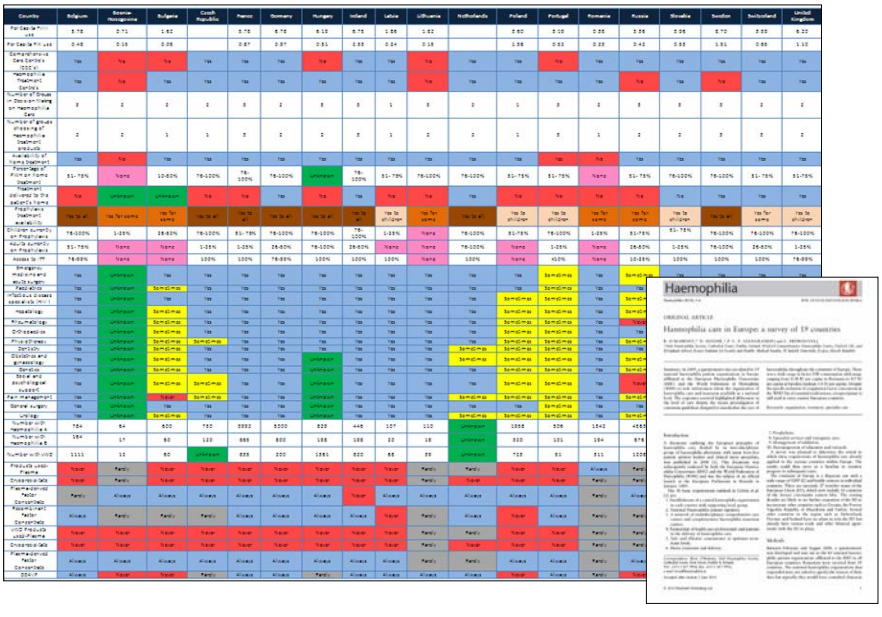
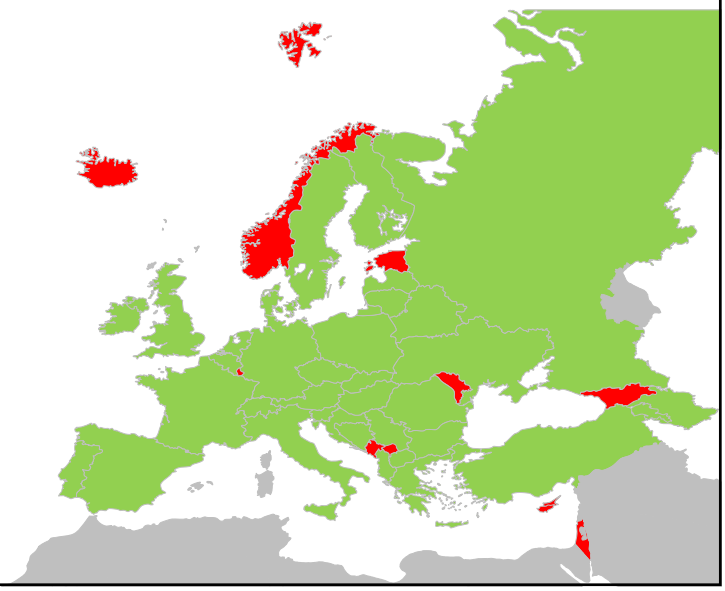
2009 Survey of 19 Countries


Haemophilia

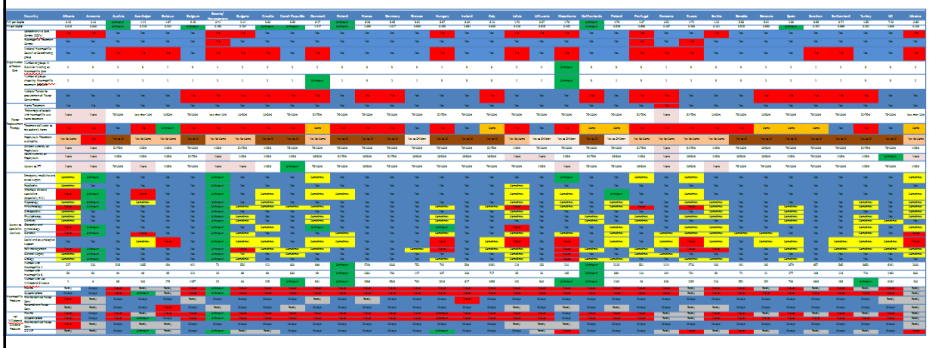
Haemophilia care in Europe a survey of 19 countries

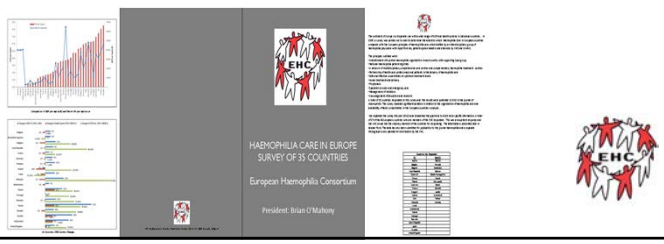
2012 Survey Response – 35 Countries

- Responded (35)
- Did Not Respond (8)
  - •Cyprus
  - •Georgia
  - •Estonia
  - •Iceland
  - •Luxembourg
  - •Israel
  - •Moldova
  - •Norway



Haemophilia Care in Europe 2012



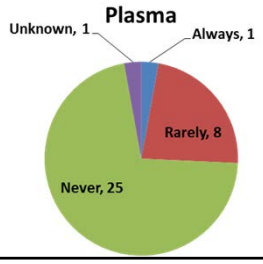


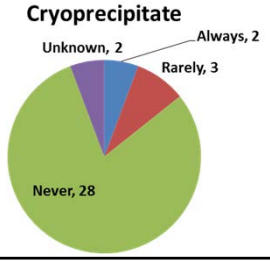
" Safe and Effective Concentrates at Optimum treatment levels"

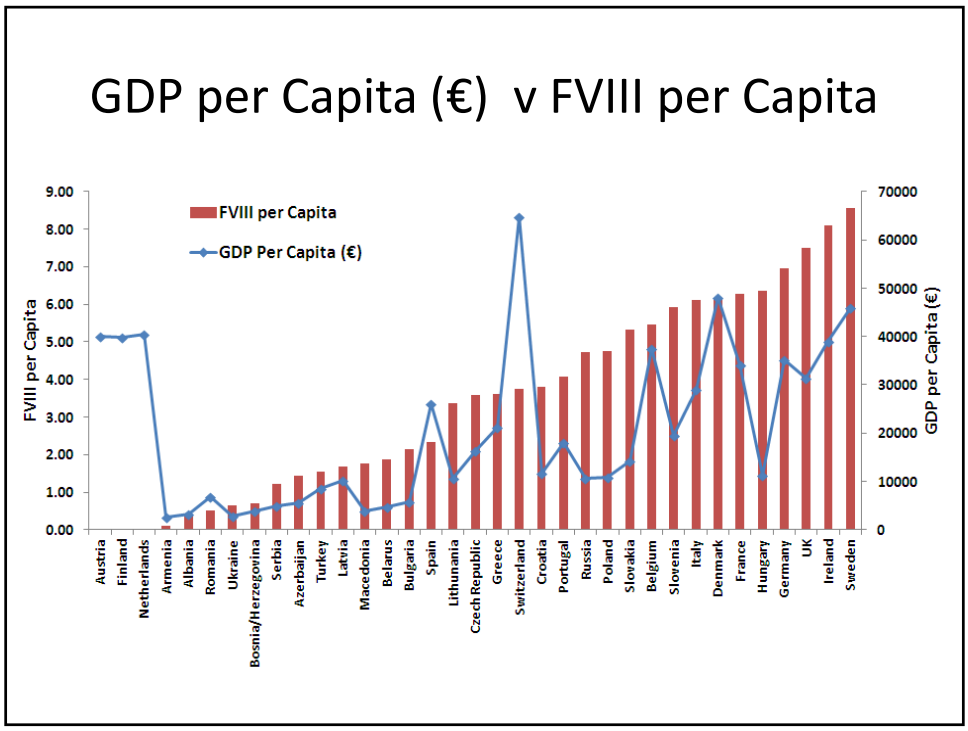
- Despite previous EDQM recommendations - 2 IU per capita minimum… 12/35 European countries remain below this.
- 5/35 remain below 1 IU per capita
- Trends in 2009-2012 in 19 countries encouraging. Most increased use of FVIII but some such countries as Latvia decreased.

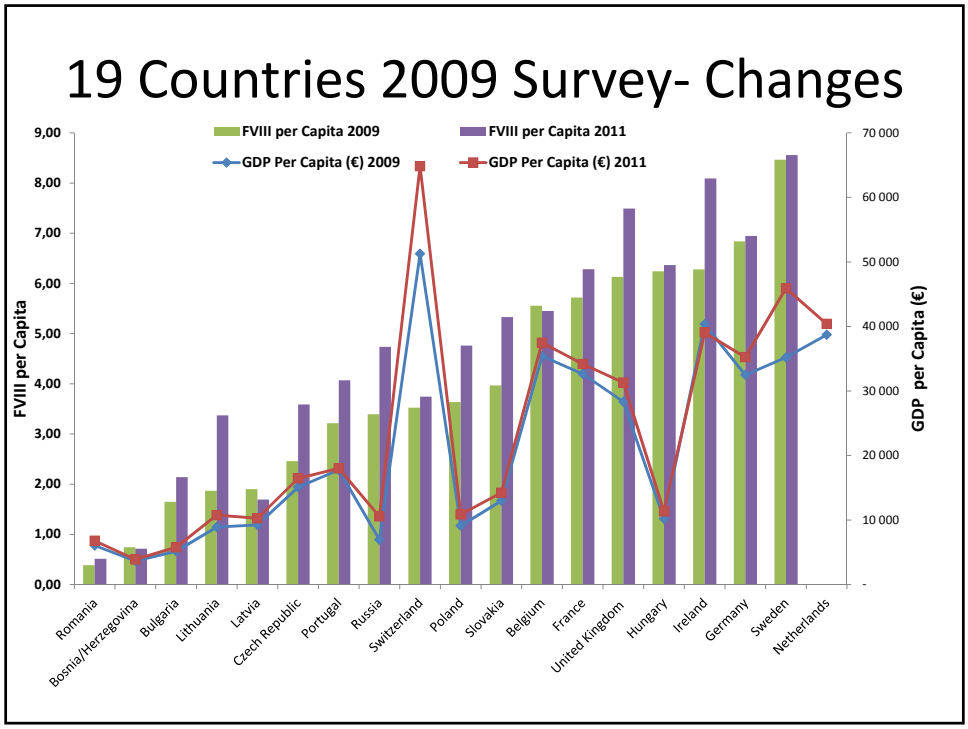
" Safe and Effective Concentrates at Optimum treatment levels"

- 1 Country- Armenia- continues to use Plasma as main source of replacement therapy
- 2 countries- Albania, Armenia- continue to use cryoprecipitate as main source of therapy

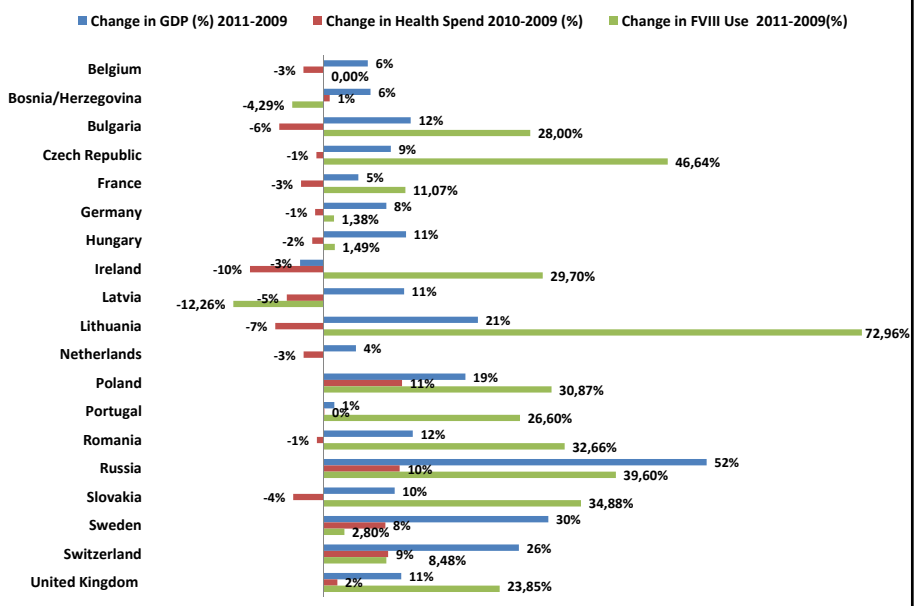





GDP per Capita (€) v FVIII per Capita
FVIII per Capita
GDP Per Capita (€)
FVIII per Capita
GDP per Capita (€)
9.00
8.00
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.00
70000
60000
50000
40000
30000
20000
10000
0
Austria
Finland
Netherlands
Armenia
Albania
Romania
Ukraine
Bosnia/Herzegovina
Serbia
Azerbaijan
Turkey
Latvia
Macedonia
Belarus
Bulgaria
Spain
Lithunania
Czech Republic
Greece
Switzerland
Croatia
Portugal
Russia
Poland
Slovakia
Belgium
Slovenia
Italy
Denmark
France
Hungary
Germany
UK
Ireland
Sweden


19 Countries 2009 Survey- Changes
FVIII per Capita 2009
FVIII per Capita 2011
GDP Per Capita (€) 2009
GDP Per Capita (€) 2011
FVIII per Capita
GDP per Capita (€)
9,00
8,00
7,00
6,00
5,00
4,00
3,00
2,00
1,00
0,00
70 000
60 000
50 000
40 000
30 000
20 000
10 000
-
Romania
Bosnia/Herzegovina
Bulgaria
Lithuania
Latvia
Czech Republic
Portugal
Russia
Switzerland
Poland
Slovakia
Belgium
France
United Kingdom
Hungary
Ireland
Germany
Sweden
Netherlands

19 Countries 2009 Survey- Changes



Factor Replacement 2009-2012

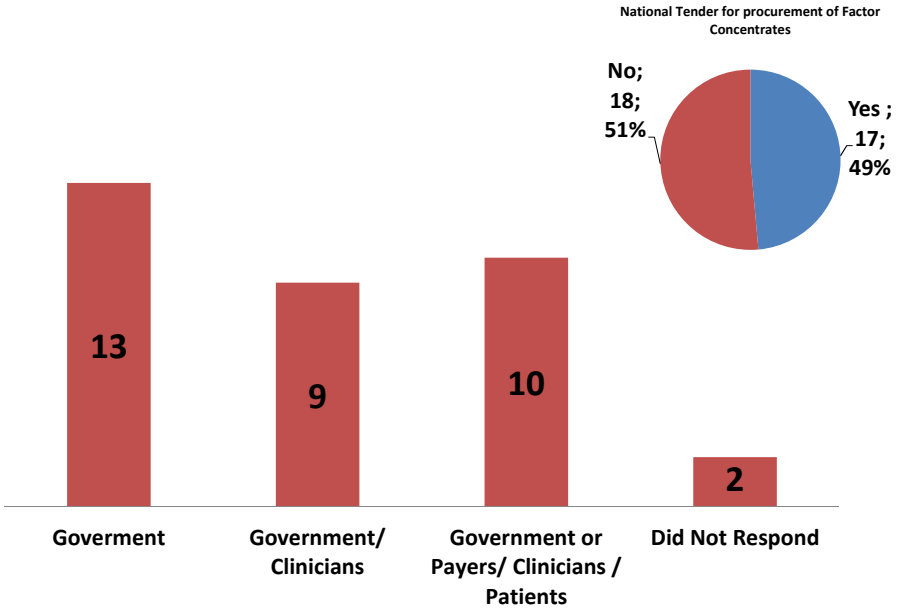
- **13/19 Countries had increased FVIII per capita**
- 8 of these 13 had decreased health spending while increasing FVIII use:
- Bulgaria (28.0%) Czech Republic (46.6%)
- Hungary (1.5%) Ireland (29.7%)
- France (11.1%) Germany (1,4%)
- Lithuania (73.0%) Slovakia (34.9%)

- 4/8 had a National Tender
- Hungary, Ireland, Lithuania, Slovakia – 3 of these 4 had greatest increase in FVIII per capita use.

Factor Replacement

- **CASE STUDIES-** Ireland / Latvia … both countries have economic problems. Irish FVIII use up by 30% / Latvia down by 12%
- **DIFFERENCE**- National Tender Process. Irish process includes haemophilia clinicians and patients – has led to significant savings each tender over the past 10 years (now 60% below total cost per unit in 2003 for r FVIII).
- Latvia - Tender Commission – No knowledge of products … No haemophilia clinicians or patients on commission
- Later this year - EHC Survey of procurement models and systems in Europe

Procurement of Factor Concentrates

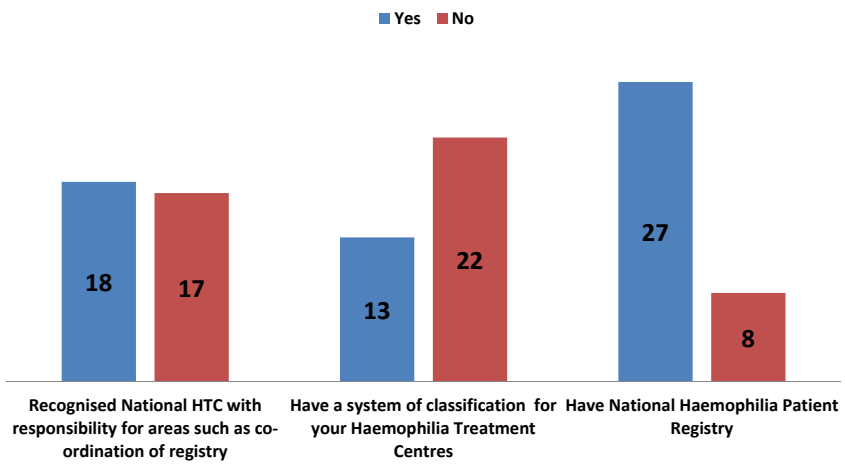


"Partnership of health care professionals and patients in the delivery of haemophilia care"

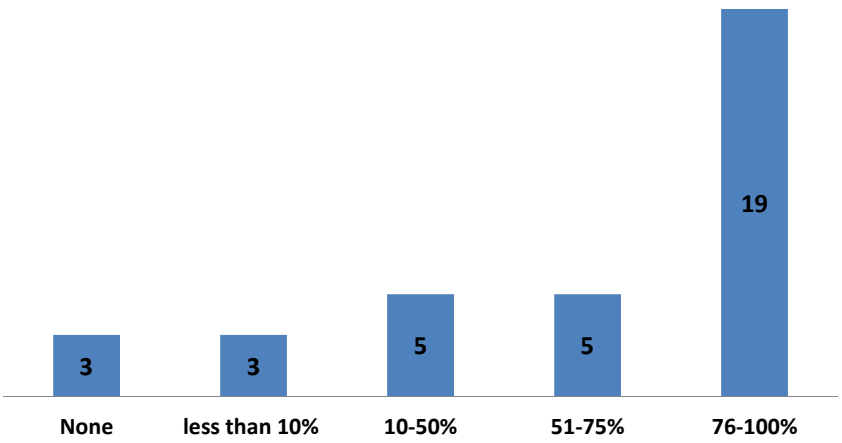
- 10/35 Countries involve patients/ organisation in national factor tender
- 19/35 countries have a council or co-ordinating group including patients
- Only 13/19 have a formal role
- Statutory role only in Ireland- National Haemophilia Council

Principle honoured more in the breach than in the implementation

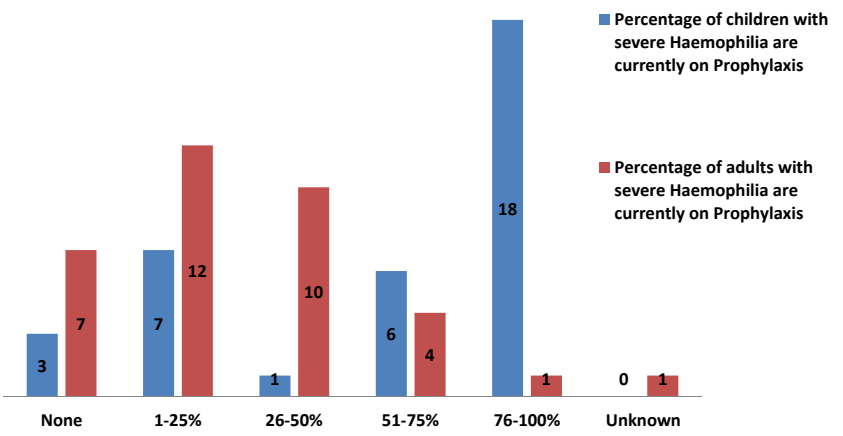
National Registries – 27/35



Availability of Home Treatment



EDQM: *"Prophylaxis for Adults should also be considered"*

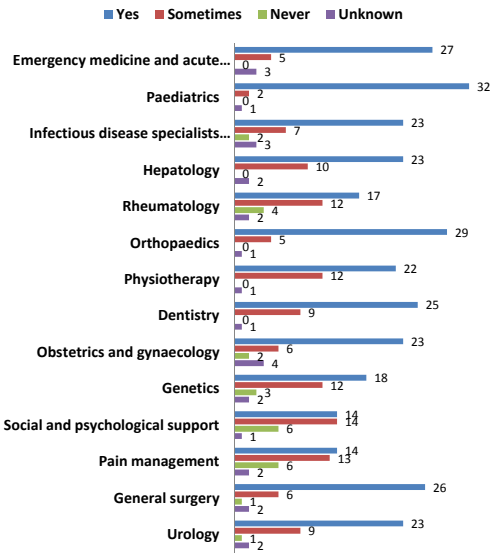


Availability of Comprehensive Care

Least Availability

Most Availability

- Social and psychological support
- Pain management
- Rheumatology
- Genetics
- Physiotherapy
- Urology
- Hepatology
- Dentistry
- Infectious disease specialists (especially HIV)
- Obstetrics and gynaecology
- General surgery
- Emergency medicine and acute surgery
- Orthopaedics
- Paediatrics



Improved Access to Comprehensive Care : 2009-2012

- Poland - Physiotherapy, Dental services, Pain management
- Portugal - Genetics, Psychological support
- Czech Republic - Physiotherapy, Psychological support
- UK -Dental services, Genetics
- Slovakia- Pain management
- Sweden- Genetics

Deficiencies in Comprehensive Care

Sometimes or Never available :

- Social and Psychological support- 20 countries
- Pain management – 19 countries
- Rheumatology – 16 countries
- Genetics – 15 countries
- Physiotherapy – 12 countries

Unmet Needs

- Lack of resources for comprehensive care centres and HTC's

  - Government should allocate proportion of Haemophilia budget for centre infrastructure/ staffing requirements

  - proportion of any savings made in tender should remain with centres

- Alternative is pharmaceutical funding or grants linked to higher prices paid by HTC's

Future Opportunity

- Next generation of longer acting products may transform treatment
- Individualised treatment regimes based on pharmacokinetics
- If prices “realistic” – may be cost effective using HTA process and reimbursed
- May lead to lower prices for current recombinant
- Use of IVIG for Alzheimers may lead to greater availability of plasma derived factor at lower prices
- Prospect of increased access to treatment

Current Challenges to Maintain Future Opportunity

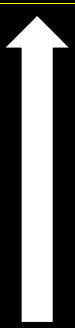
- EMA Clinical Trial Guidelines may delay access in Europe by 2/3 years
- Products licensed first and market prices set by USA –higher prices
- Need to seek derogation from EMA Guidelines for Haemophilia products
- Proactive dialogue with industry to set price expectations at a realistic level

NEW DEVELOPMENTS IN CLINICAL RESEARCH AND NEW TREATMENT MODALITIES

P.M. Mannucci

Scientific Direction, IRCCS Ca' Granda Foundation Maggiore Hospital, Milan, Italy

LIFE EXPECTANCY FOR FREQUENT MONOGENIC DISEASES



- **Hemophilia** ~ 75 years
- **Cystic fibrosis** ~ 37 years
- **Thalassemia major** ~ 30 years
- **Muscular dystrophy** ~ 10-20 years

FUTURE HEMOPHILIA THERAPY IN THE THIRD MILLENNIUM:

building on strength!

BUILDING ON STRENGTH: THE GOALS

- **Greater and wider coagulation factor availability**
- **Less alloantibodies (inhibitors) in previously untreated patients (PUPs)**
- **Longer-acting engineered factor VIII, factor IX and factor VIIa**
- **Towards cure: gene transfer**

GREATER AND WIDER FACTOR AVAILABILITY:

no treatment available for at least two thirds of 472.150 persons with hemophilia in the world!

LONGER ACTING PRODUCTS

WHY DO WE NEED LONGER ACTING PRODUCTS?

- FVIII products have an approximate plasma half-life of 10 to 12 hours (longer for FIX)
- Potential benefits of long-acting factors:
  - Extended protection from bleeding
  - Reduced infusion frequency
  - May avoid central catheter implantation for venous access

CHALLENGES FOR NEW COAGULATION FACTORS

- Cost
- Potential for neo-antigenicity
- Very demanding clinical trial protocols required by regulatory agencies

Haemophilia (2012), 1–5 DOI: 10.1111/hae.12041

REVIEW ARTICLE

Evolution of the European guidelines for the clinical development of factor VIII products: little progress towards improved patient management

P. M. MANNUCCI
Scientific Direction, IRCCS Ca' Granda Maggiore Policlinico Hospital Foundation, Milan, Italy

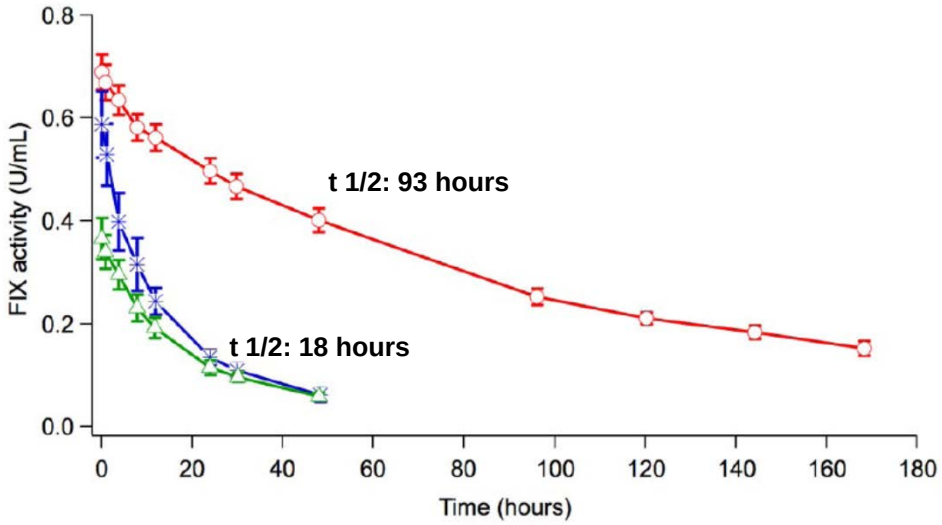
- **Longer-acting recombinant factor VIII, factor IX and factor VIIa**

FACTOR IX

Enhanced pharmacokinetic properties of a glycoPEGylated recombinant factor IX: a first human dose trial in patients with hemophilia B

Claude Negrier,[1] Karin Knobe,[2] Andreas Tiede,[3] Paul Giangrande,[4] and Judi Møss[5]

Replacement therapy with factor IX (FIX) concentrates is the recommended treatment for patients with hemophilia B, an X-linked bleeding disorder occurring in 1:25 000 male births. N9-GP is a recombinant FIX molecule with a prolonged half-life which is obtained by site-directed glycoPEGylation where a 40-kDa polyethylene glycol molecule is attached to the activation peptide of FIX. This first human dose trial in patients with hemophilia B investigated the safety and pharmacokinetic properties of a single IV dose of N9-GP. Sixteen previously treated patients received one dose of their previous FIX product followed by one dose of N9-GP at the same dose level (25, 50, or 100 U/kg). None of the patients developed inhibitors. One patient developed transient hypersensitivity symptoms during administration of N9-GP and was excluded from pharmacokinetic analyses. In the remaining 15 patients, N9-GP was well-tolerated. The half-life was 93 hours, which was 5 times higher than the patient's previous product. The incremental recovery of N9-GP was 94% and 20% higher compared with recombinant and plasma-derived products, respectively. These results indicate that N9-GP has the potential to reduce dosing frequency while providing effective treatment of bleeding episodes with a single dose. The trial was registered at www.clinicaltrials.gov as NCT00956345. (*Blood*. 2011;118(10): 2695-2701)

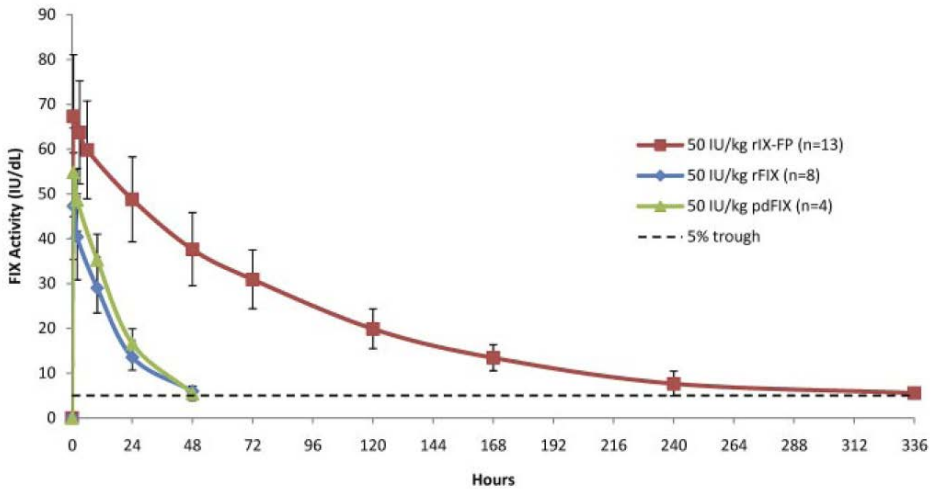


Safety and pharmacokinetics of a novel recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP) in hemophilia B patients

Elena Santagostino,[1] Claude Negrier,[2] Robert Klamroth,[3] Andreas Tiede,[4] Ingrid Pabinger-Fasching,[5] Christine Voigt,[6] Iris Jacobs,[6] and Massimo Morfini[7]

A recombinant fusion protein linking coagulation factor IX (FIX) with human albumin (rIX-FP) has been developed to facilitate hemophilia B treatment by less frequent FIX dosing. This first-in-human dose-escalation trial in 25 previously treated subjects with hemophilia B (FIX ≤ 2 IU/dL) examined the safety and pharmacokinetics of 25, 50, and 75 IU/kg rIX-FP. Patients in the 50-IU/kg cohort underwent a comparative pharmacokinetics assessment with their previous FIX product (plasma-derived or recombinant). No allergic reactions or inhibitors were observed. Four mild, possibly treatment-related adverse events were reported. In the 50-IU/kg cohort (13 subjects), the mean half-life of rIX-FP was 92 hours, more than 5 times longer than the subjects' previous FIX product. After 25 or 50 IU/kg rIX-FP administration, the baseline-corrected mean FIX activity remained elevated at day 7 (7.4 IU/dL and 13.4 IU/dL, respectively) and day 14 (2.5 IU/dL and 5.5 IU/dL, respectively). The incremental recovery of rIX-FP was higher than both recombinant and plasma-derived FIX (1.4 vs 0.95 and 1.1 IU/dL per IU/kg, respectively). These results demonstrated both the safety and improved pharmacokinetics of rIX-FP, thus indicating this new product with extended half-life as possibly able to control and prevent bleeding with less frequent injection. The trial was registered at www.clinicaltrials.gov as no. NCT01233440. (*Blood*. 2012;120(12):2405-2411)

14



Recombinant factor IX-Fc fusion protein (rFIXFc) demonstrates safety and prolonged activity in a phase 1/2a study in hemophilia B patients

Amy D. Shapiro,[1] Margaret V. Ragni,[2] Leonard A. Valentino,[3] Nigel S. Key,[4] Neil C. Josephson,[5] Jerry S. Powell,[6] Gregory Cheng,[7] Arthur R. Thompson,[5] Jaya Goyal,[8] Karen L. Tubridy,[9] Robert T. Peters,[9] Jennifer A. Dumont,[9] Donald Euwart,[8] Lian Li,[9] Bengt Hallén[10], Peter Gozzi,[10] Alan J. Bitonti,[9] Haiyan Jiang,[9] Alvin Luk,[9] and Glenn F. Pierce[9]

Current factor IX (FIX) products display a half-life ($t_{1/2}$) of ~ 18 hours, requiring frequent intravenous infusions for prophylaxis and treatment in patients with hemophilia B. This open-label, dose-escalation trial in previously treated adult subjects with hemophilia B examined the safety and pharmacokinetics of rFIXFc. rFIXFc is a recombinant fusion protein composed of FIX and the Fc domain of human IgG_1, to extend circulating time. Fourteen subjects received a single dose of rFIXFc; 1 subject each received 1, 5, 12.5, or 25 IU/kg, and 5 subjects each received 50 or 100 IU/kg. rFIXFc was well tolerated, and most adverse events were mild or moderate in intensity. No inhibitors were detected in any subject. Dose-proportional increases in rFIXFc activity and Ag exposure were observed. With baseline subtraction, mean activity terminal $t_{1/2}$ and mean residence time for rFIXFc were 56.7 and 71.8 hours, respectively. This is ~ 3-fold longer than that reported for current rFIX products. The incremental recovery of rFIXFc was 0.93 IU/dL per IU/kg, similar to plasma-derived FIX. These results show that rFIXFc may offer a viable therapeutic approach to achieve prolonged hemostatic protection and less frequent dosing in patients with hemophilia B. The trial was registered at www.clinicaltrials.gov as NCT00716716. (*Blood.* 2012;119(3):666-672)

LONG-ACTING FACTOR IX PRODUCTS

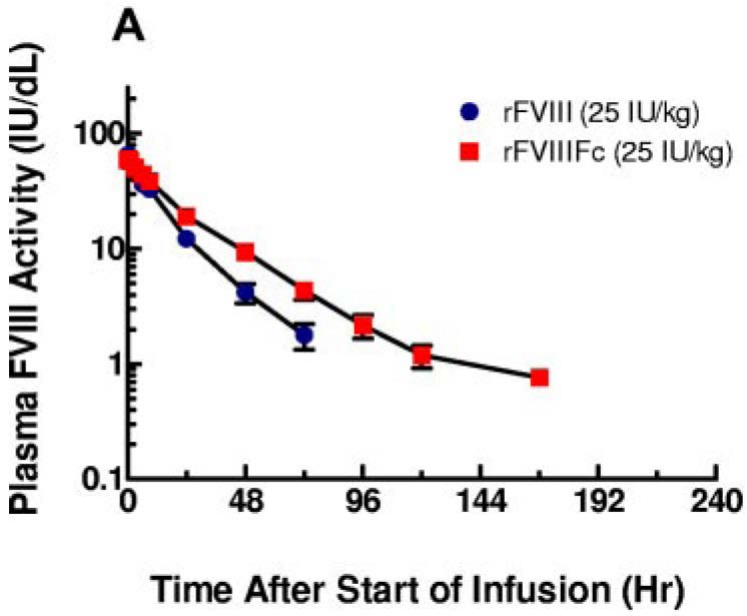
Products and manufacturer	Technology	Terminal half-life	Current stage of clinical research
N9-GP, Novo nordisk	Site-specific glycoPEGylation	93 hours	Phase III ongoing
rFIXFc, Biogen Idec	Fusion protein with the Fc fragment of IgG1	57 hours	Phase III completed
rIX-FP, CSL-Behring	Fusion protein with albumin	92 hours	Phase III ongoing

FACTOR VIII

Safety and prolonged activity of recombinant factor VIII Fc fusion protein in hemophilia A patients

Jerry S. Powell,[1] Neil C. Josephson,[2] Doris Quon,[3] Margaret V. Ragni,[4] Gregory Cheng,[5] Ella Li,[6] Haiyan Jiang,[7] Lian Li,[7] Jennifer A. Dumont,[7] Jaya Goyal,[6] Xin Zhang,[7] Jurg Sommer,[7] Justin McCue,[6] Margaret Barbetti,[7] Alvin Luk,[7] and Glenn F. Pierce[7]

Current factor VIII (FVIII) products display a half-life ($t_{1/2}$) of ~ 8-12 hours, requiring frequent intravenous injections for prophylaxis and treatment of patients with hemophilia A. rFVIIIFc is a recombinant fusion protein composed of a single molecule of FVIII covalently linked to the Fc domain of human IgG_1 to extend circulating rFVIII $t_{1/2}$. This first-in-human study in previously treated subjects with severe hemophilia A investigated safety and pharmacokinetics of rFVIIIFc. Sixteen subjects received a single dose of rFVIII at 25 or 65 IU/kg followed by an equal dose of rFVIIIFc. Most adverse events were unrelated to study drug. None of the study subjects developed anti-rFVIIIFc antibodies or inhibitors. Across dose levels, compared with rFVIII, rFVIIIFc showed 1.54- to 1.70-fold longer elimination $t_{1/2}$, 1.49- to 1.56-fold lower clearance, and 1.48- to 1.56-fold higher total systemic exposure. rFVIII and rFVIIIFc had comparable dose-dependent peak plasma concentrations and recoveries. Time to 1% FVIII activity above baseline was ~ 1.53- to 1.68-fold longer than rFVIII across dose levels. Each subject showed prolonged exposure to rFVIIIFc relative to rFVIII. Thus, rFVIIIFc may offer a viable therapeutic approach to achieve prolonged hemostatic protection and less frequent dosing in patients with hemophilia A. This trial was registered at www.clinicaltrials.gov as NCT01027377. (*Blood*. 2012;119(13):3031-3037)

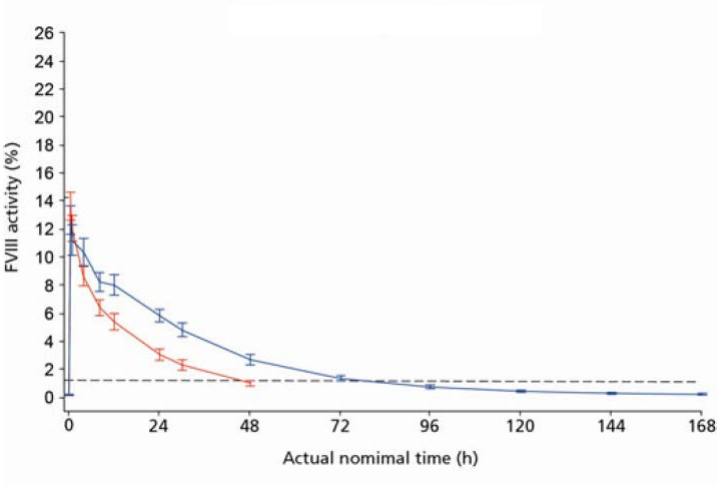


Enhancing the pharmacokinetic properties of recombinant factor VIII: First-in-man trial of glycoPEGylated recombinant factor VIII in patients with hemophilia A

A. TIEDE,* B. BRAND,† R. FISCHER,‡ K. KAVAKLI,§ S. R. LENTZ,¶ T. MATSUSHITA,** C. REA,†† K. KNOBE,‡‡ and D. VIUFF‡‡

Background: N8-GP is a recombinant FVIII with a site-directed glycoPEGylation for the purpose of half-life prolongation. *Objectives:* To evaluate the safety and pharmacokinetic profiles of N8-GP in comparison to those of the patient's previous FVIII product. *Patients/Methods:* This dose escalation trial included previously treated patients with severe hemophilia A who received one of three dose levels (25, 50, or 75 U/kg) of N8-GP and FVIII product. Each dose escalation was preceded by safety and pharmacokinetic assessment. The trial was registered at www.clinicaltrials.gov (NCT01205724). *Results:* Twenty-six patients each received one dose of their previous FVIII product followed by the same, single dose of N8-GP. N8-GP, at any tested dose, was well tolerated with a low frequency of adverse events. No new inhibitors to FVIII or N8-GP and no binding antibodies to N8-GP developed during the trial. The pharmacokinetics of N8-GP were dose-linear. The incremental recovery of N8-GP was 0.025 ([U/mL]/[U/kg]). The clearance was 1.79 mL/h/kg. The estimated time from dosing of 50 U/kg N8-GP to a plasma activity of 1% was 6.5 days (range: 3.6–7.9 days). The mean terminal half-life of N8-GP was 19.0 h (range: 11.6–27.3 h), 1.6 times longer than the patient's previous product. *Conclusions:* A single dose of up to 75 U/kg N8-GP was well tolerated in patients with hemophilia A, with no safety concerns. N8-GP had a prolonged half-life and FVIII:C activity remained above 1% for a longer compared with the patient's previous product. These results indicate that N8-GP has the potential to reduce dosing frequency during prophylaxis.

Tiede A, Brand B, Fischer R, Kavakli K, Lentz SR, Matsushita T, Rea C, Knobe K, Viuff D.
Journal of Thrombosis and Haemostasis 2013; 11:670-678



Tiede A, Brand B, Fischer R, Kavakli K, Lentz SR, Matsushita T, Rea C, Knobe K, Viuff D.
***Journal of Thrombosis and Haemostasis* 2013 2013; 11:670-678**

LONG-ACTING FACTOR VIII PRODUCTS

Products and manufacturer	Technology	Terminal half-life	Current stage of clinical research
N8-GP, Novo Nordisk	Site-specific glycoPEGylation	19 hours	Phase III ongoing
rFVIIIFc, Biogen Idec	Fusion protein with the Fc fragment of IgG1	19 hours	Phase III completed
BAY 94-9027, Bayer	Site-specific PEGylation	Data not published	Phase II/III ongoing
BAX 855, Baxter	Random PEGylation	Data not published	Phase I completed

LONG-ACTING FACTORS
Expected changes in prophylaxis patterns

	Current products (# yearly i.v. injections)		Long-acting products (# yearly i.v. injections)
Hemophilia A	150-180	→	80-100
Hemophilia B	100-120	→	30-40

FACTOR VIIa

FACTOR VIIa PRODUCTS

- Newly engineered forms of FVIIa are designed to be more potent or more persistent than regular FVIIa
- The rarity of patients with inhibitor suitable for clinical trials makes clinical validation of these of these products still unsettled

NEW BY-PASSING AGENTS (RECOMBINANT ACTIVATED FACTOR VII) FOR PATIENTS WITH INHIBITORS

Name of the product and manufacturer	Main characteristics	Current stage of clinical research	Mean half-life
~~N7-GP (Novo Nordisk)~~	~~Site-specific PEGylation~~	~~Phase I completed~~	~~15 hours (vs 3.5 for standard rFVIIa)~~
BAY 86-6150 (Bayer)	rFVIIa variant with 4 amino acid changes	Phase II/III ongoing	6 hours
PEGLip-FVIIa (Bayer)	rFVIIa formulated with PEGylated liposomes	Phase I/II completed	No difference vs standard rFVIIa

UNRESOLVED QUESTIONS

1. Half-life extension appears less attainable for FVIII than for FIX
2. What degree of extension will be required to justify a switch and a marked increase in price?
3. Issues of protein neoimmunogenicity?

TOWARDS CURE?

GENE TRANSFER

HEMOPHILIA IS CURED IN ANIMALS BY GENE THERAPY

- In mice factor VIII and IX deficiencies are corrected for the entire lifespan of the animals
- In dogs with hemophilia therapeutic levels of factor VIII and IX have been achieved for more than 8 years with a single gene transfer

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 22, 2011 VOL. 365 NO. 25

Adenovirus-Associated Virus Vector–Mediated Gene Transfer in Hemophilia B

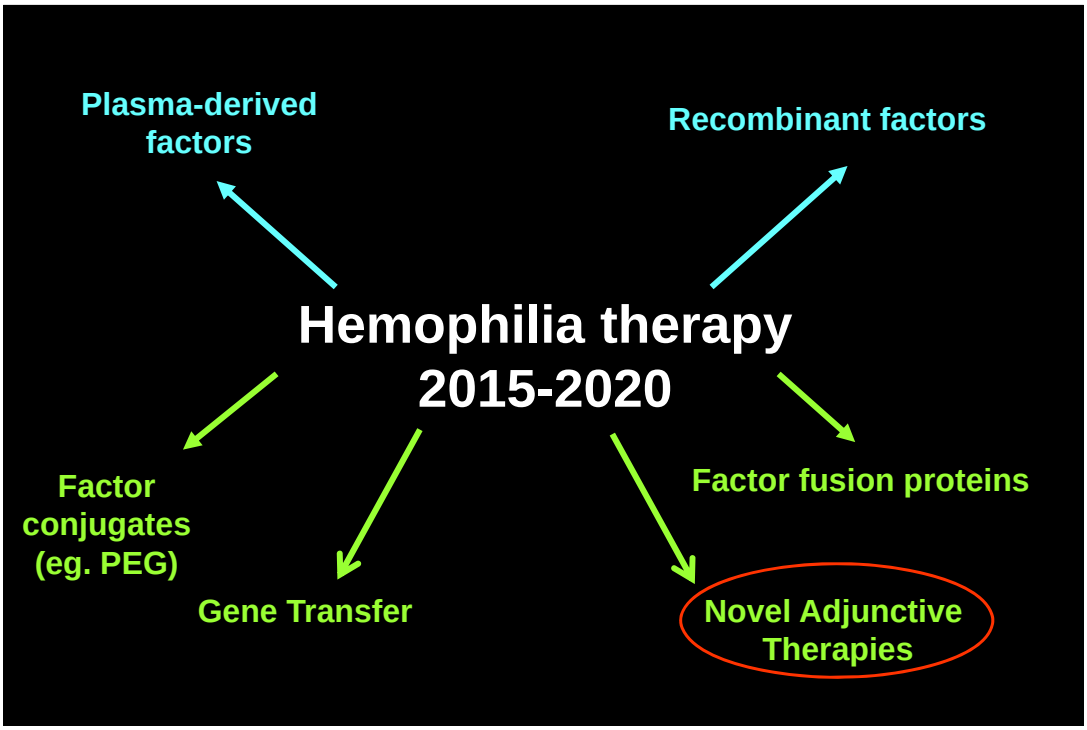
Amit C. Nathwani, M.B., Ch.B., Ph.D., Edward G.D. Tuddenham, M.B., B.S., M.D., Savita Rangarajan, M.B., B.S., Cecilia Rosales, Ph.D., Jenny McIntosh, Ph.D., David C. Linch, M.B., B.Chir., Pratima Chowdary, M.B., B.S., Anne Riddell, B.Sc., Arnulfo Jaquilmac Pie, B.S.N., Chris Harrington, B.S.N., James O'Beirne, M.B., B.S., M.D., Keith Smith, M.Sc., John Pasi, M.D., Bertil Glader, M.D., Ph.D., Pradip Rustagi, M.D., Catherine Y.C. Ng, M.S., Mark A. Kay, M.D., Ph.D., Junfang Zhou, M.D., Yunyu Spence, Ph.D., Christopher L. Morton, B.S., James Allay, Ph.D., John Coleman, M.S., Susan Sleep, Ph.D., John M. Cunningham, M.D., Deokumar Srivastava, Ph.D., Etiena Basner-Tschakarjan, M.D., Federico Mingozzi, Ph.D., Katherine A. High, M.D., John T. Gray, Ph.D., Ulrike M. Reiss, M.D., Arthur W. Nienhuis, M.D., and Andrew M. Davidoff, M.D.

N Engl J Med 2011;365:2357-65.

AAV8 VECTOR TRIAL IN HEMOPHILIA B

- With the highest vector dose one patient developed an immuno-mediate increase in transaminases, reversed by short-term corticosteroids

Nathwani et al, NEJM 2011; 365: 2352



Benefits and limitations with innovative clotting factor concentrates

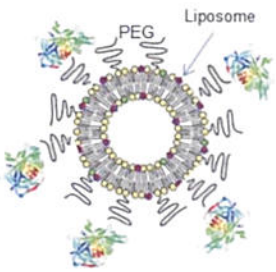
Flora Peyvandi
Haemophilia and Thrombosis Centre
University of Milan, Italy

EUROPEAN SYMPOSIUM
Optimal use of clotting factors and immunoglobulins
26-27 April 2013, Wildbad Kreuth, Germany

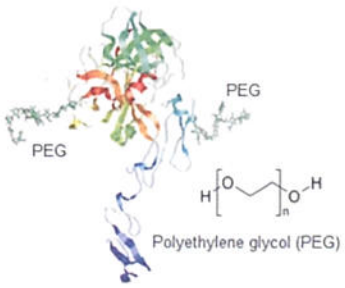
Strategies.1

Half-life extension

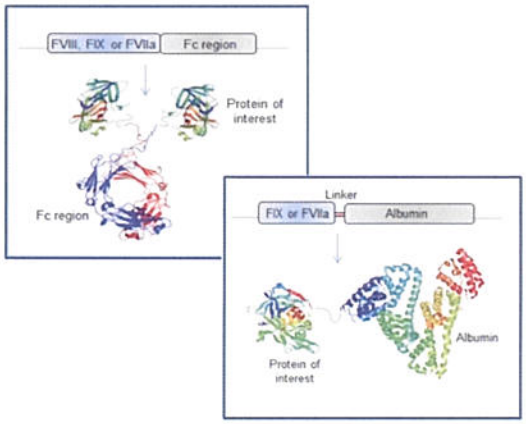
PEGylated Liposomes



PEGylation
- Random
- Site specific



Fusion protein
- Fc fragment
- Albumin



Modification of amino acid sequence

Results of Long acting products
- Clinical studies -

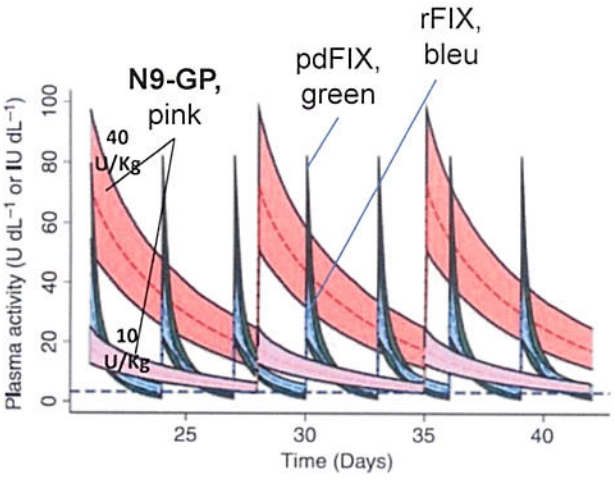
Factor IX	3 to 5-fold	- rFIX-Fc fusion - rFIX glycoPEGylated - rFIX-albumin fusion
Factor VIII	1.5 to 1,8 -fold	- rFVIII-Fc fusion - rFVIII-glycoPEGylated
rFVIIa	3 to 5-fold	- rFVIIa glycoPEGylated - rFVIIa variant with 4 amino acid changes

Peyvandi F.

Population pharmacokinetic modeling for dose setting of nonacog beta pegol (N9-GP), a glycoPEGylated recombinant factor IX

P. W. COLLINS,* J. MØSS,† K. KNOBE,‡[1] A. GROTH,§ T. COLBERG¶ and E. WATSON**

J Thromb Haemost 2012; **10:** 2305–12.



The steady-state predicted profiles for N9-GP dose regimens of 10 and 40U/kg once-weekly versus standard FIX dose regimens of 40 IU/kg rFIX (blue) or pdFIX (green) every 3 days

Peyvandi F.

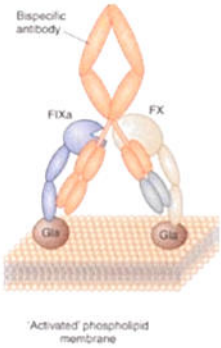
Strategies.2

Alternative Therapeutic strategies

- inhibitors of coagulation to increase the hemostatic efficacy

Inhibition of TFPI
- antibodies (anti-TFPI)
- synthetic inhibitors (aptamers)

Bispecific antibody (ACE910) against activated factor IX (FIXa) and factor X (FX)



Inhibition of APC and antithrombin (AT)
- aptamers and RNAi silencing

Peyvandi F.

Results of Alternative Therapeutic strategies
- Clinical studies -

Inhibitors of Coagulation	Product	Phase	Status	Results	Reference
TFPI	Aptamer (BAX499)	I/II (NCT01191372)	Prematurely stopped due to an increased number of bleeding events	- Increased TFPI plasma levels - Reduced thrombin generation	Dockal *et al.* ASH Annual Meeting Abstracts. 2012; 120: 1104-
	mAb 2021	I (Healthy subjects) (NCT01555749)	Completed	N/A	-
		I (Explorer 2) (NCT01631942)	This study has suspended participants recruitment (awaiting protocol amendement)	N/A	-

Inhibition of TFPI

Aptamers, ARC19499 or BAX499

Phase I clinical trial **prematurely stopped** due to an increased number of bleeding events

BAX499 induced an increase in full-length TFPI plasma levels (25 –fold higher with the highest dose of BAX499) reducing thrombin generation

- induces the release intracellularly-stored TFPI
- prolongs the circulatory half-life of full-length TFPI binding to the Kunitz 3-C terminus domain of TFPI, a region required for full-length TFPI clearance

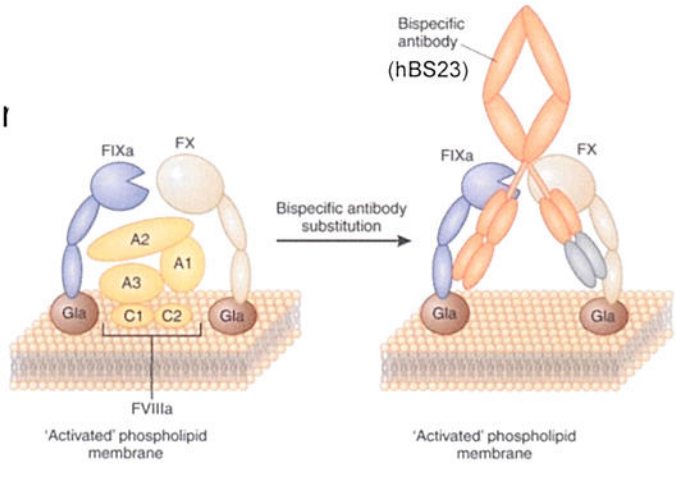
The net results of these effect is elevated plasma full-length TFPI, which even at a molar excess of BAX499 retains anti-coagulant activity

Peyvandi F.

(Dockal *et al.* ASH Annual Meeting Abstracts. 2012; 120: 1104-)

A bispecific antibody to factors IXa and X

- a humanized bispecific antibody to factor IXa (FIXa) and factor X (FX), termed **hBS23**
- restores factor VIII hemostatic activity in a hemophilia A model
- hBS23 mimics the cofactor function of FVIII

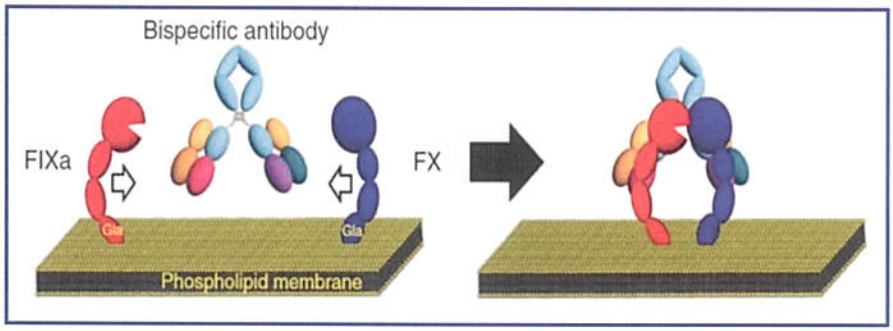


Peyvandi F.

(Lillicrap *et al* Nat Med 2012;18:1460-61)

hBS23 bispecific antibody

hBS23 binds FIXa with one arm and FX with the other placing in spatially appropriate positions, as FVIIIa does, and promote FIXa-catalyzed FX activation.



(Kitazawa *et al* Nat Med 2012;18:1570-74)

hBS23 bispecific antibody

- **hBS23** has a 2-week half-life
  - reduces injection frequency, but still required venous access
- development of a subcutaneous formulation
- reduces the immunogenicity of the humanized antibody
- A Phase I clinical study with hBS23/ACE910 has started and is currently recruiting in Japan
  (JapicCTI-121934; http//www.clinicaltrials.jp)

Evaluation of efficacy and safety

- potency assignment and laboratory monitoring
- Safety and efficacy evaluation:harmonization (EMA *vs* FDA)
- Long term safety evaluation: post registration surveillance

Peyvandi F.

Potency labeling

- define the quantity of the active substance in the vial
- guide physicians on the dose to be used for treatment
- the potency measurement of novel products may be highly dependent on the choice of assay methods and reagents

Peyvandi F.

New products potency

- Novel FVIII/FIX molecules modified will likely have similar responses as their "commercial non-modified products " in *in vitro* biological assays for potency assignment
- Units assigned *in vitro* may correlate differently with the clinical activity for the new products, particularly if the modification has changed the pharmacokinetic profile


Peyvandi F.

Potency labeling

Recommendations by the FVIII/FIX subcommittee 2012 of the scientific and standardization committee (SSC) of the ISTH (http://www.isth.org/default/index.cfm/ssc1/subcommittees-working-groups/)

- All new products should be tested against the current WHO International Standards (WHO IS)
- FVIII and FIX assays should be performed using both one-stage clotting and chromogenic methods
- the potency of modified products by the one-stage clotting method may be highly dependent on the choice of APTT reagent, e.g. silica-based and ellagic acid

(Hubbard AR. SSC/ISTH June 2012)
(http://www.isth.org/default/index.cfm/ssc1/subcommittees-working-groups/)


Peyvandi F.

Currently, pre- and post-authorisation studies are required for product registration

Pre-authorisation studies include **Efficacy and Safety trials**


Peyvandi F.

Efficacy evaluation?

- to be conducted before marketing authorisation combined with the commitment to perform post-authorisation investigation(s)
- the initial trial typically examines the pharmacokinetics of the principal active factor
- appropriate pharmacokinetic data (incremental recovery, half-life, area under the curve (AUC), and clearance)
- is measured by the ability to controll bleed rates
- clinical efficacy (e.g. prophylaxis, on demand) should be assessed during a period of a minimum of 50 EDs


Peyvandi F.

Laboratory monitoring
LONG acting rFVIII/rFIX

- Classical clotting or chromogenic assays may not be applicable or require some modifications (e.g. silica-based and ellagic acid)
- A specific reference standard is required for each novel specific product


Peyvandi F.

Bypassing agent (rFVIIa) and Alternative Therapeutic Strategies

- Global clotting assays such as TEG/RoTEM, TGA and CWA may attain greater relevance and prove to be suitable, however, **standardization** and pre-analytical challenges still need to be resolved


Peyvandi F.

Safety

Viral safety

- virus testing in manufacturing processes
- selection of donors for plasma derived products

Adverse events

- vital signs
- development of hypersesitivity/anaphilactic reactions (including against host cells proteins, excipients and residues used in manufacturing process)

Immunogenicity

- inhibitor titre immediately before first exposure, ED 10-15, ED 50-75 and if there is any suspicion of inhibitor development, continue for a minimum of 50 exposure days

Peyvandi F.

Inhibitors Assay

- **Nijmegen modified Bethesda assay** is currently the gold standard inhibitor assay, in which patient's inhibitor titres are measured relative to a "Control" mixture consisting of equal volumes of buffered normal pooled plasma and FVIII-deficient plasma (FDP)

  – Several physicochemical factors may affect the results of the test (e.g.temperature and pH)

  – Development of the alternative methods to optimize the sensitivity, specificity, reproducibility and standardisation of the assay

(Saut R. SSC ISTH June 2012) (http://www.isth.org/default/index.cfm/ssc1/subcommittees-working-groups/)

Peyvandi F.

Product	One-stage	Chromogenic assay	Antigen	TG	TGE	Bethesda/ Nijmegen method
rFVIII-Fc	X	X				X
rFVIII-GlycoPEG		X				X
rFIX-Fc	X	X	X			X
rFIX-GlycoPEG	X	X	X			X
rFIX-albumin	X	X	X			X
rFVIIa-GlycoPEG	X	X				*
rFVIIa variant	X	X		X		*
TFPI					X	

* Radioimmunoassay, plus in vitro neutralizing assays were modified from a coagulation (clot) bioassay (Scharling *et al*, Blood Coagul Fibrynol 2007;18:1433-46)

Peyvandi F.

rFVIIa variant – Alternative strategies

Vatreptacog alfa is a rFVIIa analogue with three point mutations in the protease domain

Phase 3a clinical trials demonstrated that vatreptacog alfa can stop a very high percentage of bleeding episodes, 93%, with three doses or less

However, a few patients developed anti-drug antibodies to vatreptacog alfa, including one patient with a potentially neutralising effect in one sample and the study has been terminated

Company Announcement

28 September 2012

Novo Nordisk discontinues development of vatreptacog alfa following analysis of phase 3 results

Peyvandi F.

What needs to be done in future?

- Laboratory assessment and standardisation

  (SSC Subcommittee Project is Ongoing)

- Clinical trial design in hemophilia

  (SSC Subcommittee Project is Ongoing)

- Postregistration surveillance (harmonization of data)

Peyvandi F.

SSC Subcommittee Project

"EVALUATION OF NOVEL FVIII/FIX CONCENTRATES AND FVIII-INHIBITOR BY-PASSING AGENTS WITH THROMBIN GENERATION OR OTHER ASSAYS"

The project propose to assess novel FVIII/FIX concentrates and by-passing agents:

- to understand the their haemostatic dynamics by thrombin generation (TG) and thromboelastometry (TE)

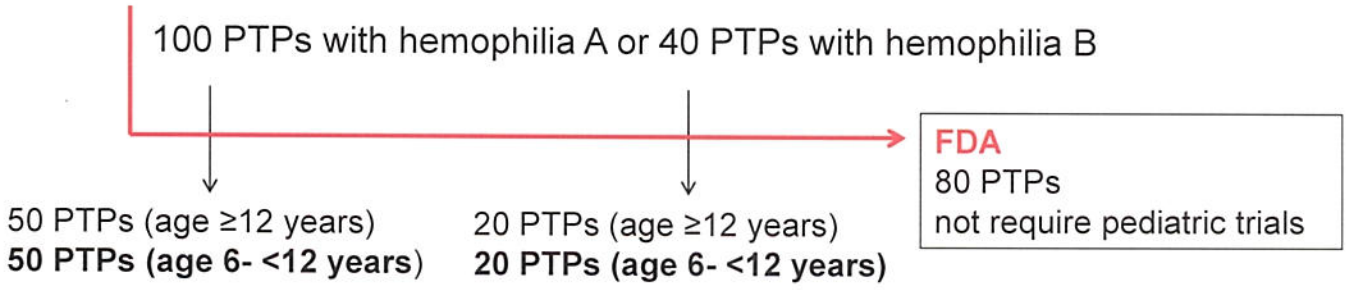
- to determine the clinical utility of TG and other assays, these tests will be performed on samples obtained from patients before and after treatment (ex-vivo study)

(http://www.isth.org/default/index.cfm/ssc1/subcommittees-working-groups/)

Peyvandi F.

Harmonization of efficacy and safety (EMA *vs* FDA)

- Numbers and types of subjects



EMA guidelines require studies in **PUPs**


Peyvandi F.

Harmonization EMA - FDA

- The discrepancy between EMA and FDA implies a severe disadvantage for European patients, because they have to wait for data stemming from studies involving children
- The lack of harmonization will increase the disparity in the treatment of patients with haemophilia
- European patients will not have access to new products at the same time as patients in the US and other regions of the world.


Peyvandi F.

Post-authorisation

- cover especially immunogenicity aspects
- number of patients is 200 (for 100 EDs)
- study participants are PTPs (e.g. 60 patients <12 years out of 200 patients)
- investigation: Clinical Efficacy, Immunogenicity and Safety

	Previous product #	Test product ED1	Test product ED10-15	Test product ED50-75	Test product ED~100
Inhibitor*	x	x†	x	x	x
Recovery	x	x	x	x	x

*after washout period (see Explanatory Note); storage of back up blood sample is recommended
#new patients = not recruited for pre-authorisation studies
†baseline inhibitor testing prior to first infusion of test product

(EMA/CHMP/BPWP/144533/2009)

Peyvandi F.

What else needs to be done in future?

- Control the cost of the novel drugs
- Make them available also for the European countries

Peyvandi F.

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European Clinical Guidelines

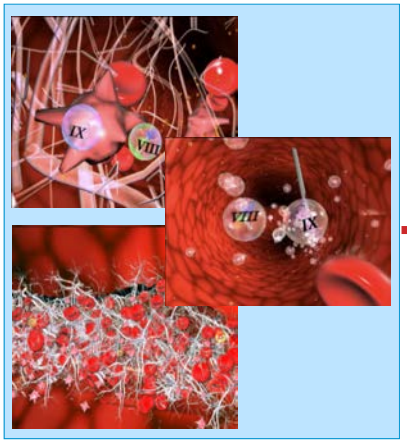
1

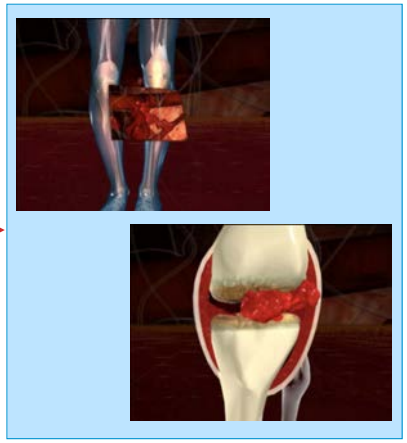
Disclosures

- Consultancy – Advisory board
  - Baxter, Bayer, Pfizer, CAF-DCF, SOBI, Ipsen, LFB, CSL-Behring, Novo Nordisk, Octapharma
- Research grants / Lecture Chairs
  - Baxter, Bayer, Pfizer, CAF-DCF, CSL-Behring, Novo Nordisk, Octapharma, Ipsen

2

Haemophilia





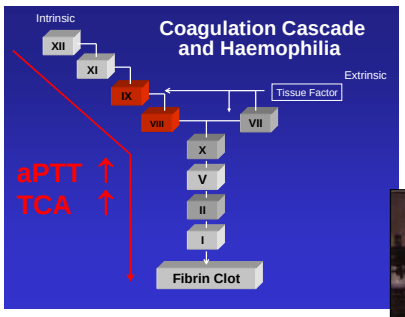
Blood Coagulation Defect

Delibitating **Arthropathy**

From the Movie « Haemophilia in 3D » by Cedric Hermans et al
www.hémophilie-ucl.be also available on YOU TUBE

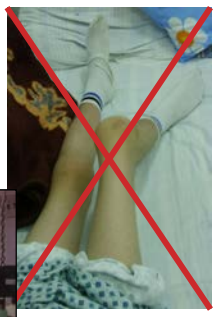
3

Treatment of Haemophilia



Coagulation defect

Regular Self-infusions
of FVIII / FIX at home
Multidisciplinary follow-up in a
comprehensive haemophilia centre

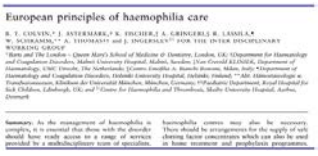


Arthropathy

4

The 10 European Principles of Hemophilia Care

1. A central hemophilia organisation with supporting local groups
2. National hemophilia patient registries
3. Comprehensive care centres and hemophilia treatment centres
4. Partnership in the delivery of hemophilia care
5. Safe and effective concentrates at optimum treatment levels
6. Home treatment and delivery
7. Prophylaxis treatment
8. Specialist services and emergency care
9. Management of inhibitors
10. Education and research


European principles of haemophilia care

Colvin BT, Astermark J, Fischer K, et al. *Haemophilia* 2008; 14: 361-374

5

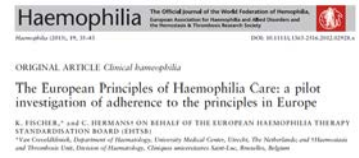
Practice versus Principles

- The level of service provision within different countries in Europe compared to the recommendations set out in the Principles of Care has recently been audited by two studies;
  - Patients' organisations
  - Physicians


Haemophilia

ORIGINAL ARTICLE

Haemophilia care in Europe: a survey of 19 countries


Haemophilia

ORIGINAL ARTICLE *Clinical haemophilia*

The European Principles of Haemophilia Care: a pilot investigation of adherence to the principles in Europe

O'Mahony B, Noone D, Giangrande PL, Prihodova L. Haemophilia care in Europe: a survey of 19 countries. Haemophilia 2011 Jan;17(1):35-40.
Fischer K, Hermans C. The European Principles of Haemophilia Care: a pilot investigation of adherence to the principles in Europe. Haemophilia 2013 Jan;19(1):35-43.

6

The European Principles of Haemophilia Care: A pilot investigation of adherence to the principles in Europe

Translation of guidelines into practice

Objective	Current standard of services for haemophilia across Europe ? Extent of adherence to the Principles of Haemophilia Care ?
Setting	European Haemophilia Therapy Standardisation Board (EHTSB) (25 haemophilia treaters from 14 European countries)
Questionnaire	Derived from the audit tool designed by the UKHCDO and the published Principles of Haemophilia Care
Participation	Completed questionnaires obtained from 21/25 (84%) members of the EHTSB, representing the situation in all 14 member countries.

7

The European Haemophilia Therapy Standardisation Board (EHTSB) Centres

Severe Haemophilia A < 1%	Severe Haemophilia B < 1%
3.052	552

8

8

Principle 1

A Central Haemophilia Organisation with Supporting Local Groups

- In each country there should be a central organisation for haemophilia care supported by centres operating at the local level
- These organizations will provide a focus for:
  - Provision of safe concentrates
  - Effective allocation of resources
  - Collection of data on concentrate usage
  - Recording of adverse reactions
  - Sharing of developments in care
  - Coordination of research

9

Adherence to Principle 1

- Central organizations of haemophilia care (mostly physicians' treatment boards), present in 11/14 (79%) of the European countries surveyed.
- Belgium, Spain and Portugal had not established such organizations.

10

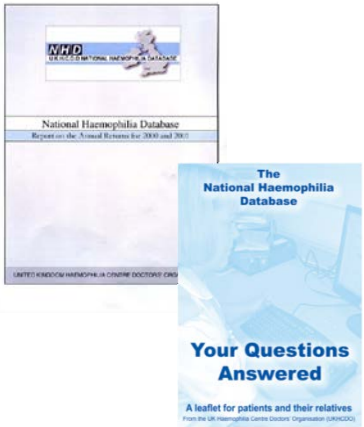
Principle 2

- **National Haemophilia Patient Registry**
  - Each country should have a national haemophilia patient registry administered by the central haemophilia organisation
  - Registries facilitate resource planning and allocation, as well as provide accurate data on patient numbers, prescribing patterns, geographical spread and adverse events

11

Adherence to Principle 2

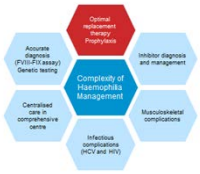
- National registries in 8/14 (57%) of the countries surveyed
- Belgium, Sweden, the Netherlands, Norway, Poland and Portugal reported that registries had not been not established in their country.
- Overall, only 7/14 (50%) countries complied with both principles 1 and 2.



12

Principle 3

- **Comprehensive Care Centres and Haemophilia Treatment Centres**
  - Comprehensive Care Centres and Haemophilia Treatment Centres should be established to ensure that people with haemophilia have access to the full range of clinical specialties and appropriate laboratory services



Wessex Haemophilia Comprehensive Care Network

13

Definitions of Comprehensive Care Centres and Haemophilia Treatment Centres

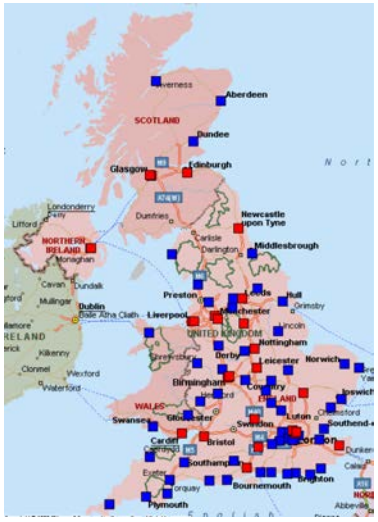
Comprehensive Care Centre (CCC)	Haemophilia Treatment Centre (HTC)
Minimum of 40 patients with severe haemophilia (FVIII/IX <1%)	No minimum number of patients specified
24 hours' specialised care available	24 hours' specialist cover
24 hours' lab service available	Lab services available (with delay)
Provide multidisciplinary comprehensive care teams, including: Employment of one full time haematologist and/or paediatrician dedicated nurse experienced physiotherapist social worker data management	Provide multidisciplinary comprehensive care teams, including: Employment of one full time hematologist and/or pediatrician Access to dedicated nurse Access to experienced physiotherapist Access to social worker Keep adequate records
Provide home treatment, prophylaxis, inhibitor treatment & ITI	In collaboration with CCC: provide home treatment, prophylaxis, inhibitor treatment & ITI
Access to OBGYN, orthopedics, dental care, genetics	In collaboration with CCC: provide access to OBGYN, orthopedics, dental care, genetics
Carry out clinical audits (internal essential, external desirable)	Carry out internal clinical audits
Adhere to consensus guidelines,	Adhere to consensus guidelines,
and provide medical education,	and provide medical education,
Perform and/or initiate research	-

14

Adherence to Principle 3

- All 14 countries surveyed had designated CCCs.
- Every country with the exception of Sweden had HTCs; only Sweden had just CCCs.
- In 9/14 (64%) of countries, all patients with haemophilia were seen in either a CCC or HTC; the exceptions were Belgium, Germany, Poland, Portugal and Switzerland.
- Some moderate and mild patients were treated in other hospitals or private practices.

UK Haemophilia Centres



Comprehensive Care Centres

Haemophilia Centres

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Adherence to Principle 3 (Centre Level)

- The total patient number / centre ranged from 55 to 1317.
- 81% of centres cared for 40 or more adults with severe haemophilia.
- Only 47% of centres cared for 40 or more children with severe haemophilia.
- All centres stored and issued FVIII/IX concentrates, and monitored clotting factor consumption in patients on home treatment programmes.
- Laboratory facilities varied across centres. At night, however, testing for FVIII/IX activity levels was only available in 18/21(86%) centres.
- 71% centres had molecular diagnostic testing for mutations on-site at the hospital.

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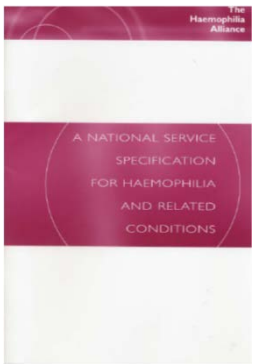
Summary of adherence to Principles 1,2 and 3 and 7 according to country

Country	No of Centres	Principle 1 Central Organisation	Principle 2 Patient Registry	Principle 3 All patients treated in CCC/HTC	No of CCC/HTC per Million inhabitants	Principle 7 % of Children on prophylaxis	Principle 7 % of Adults on prophylaxis
Belgium	1	No	No	No	0.83	75-100	50-75
France	1	Yes	Yes	Yes	0.71	75-100	1-25
Germany	2	Yes	Yes	No	0.89	75-100	50-75
Greece	1	Yes	Yes	Yes	0.37	75-100	1-25
Italy	3	Yes	Yes	Yes	0.81	75-100	1-25
Netherlands	2	Yes	No	Yes	0.78	75-100	50-75
Norway	1	Yes	No	Yes	0.40	75-100	50-75
Poland	1	Yes	No	No	0.84	75-100	1-25
Portugal	1	No	No	No	3.77	75-100	1-25
Slovakia	1	Yes	Yes	Yes	7.78	75-100	1-25
Spain	3	No	Yes	Yes	0.91	75-100	1-25
Sweden	1	Yes	No	Yes	0.32	75-100	75-100
Switzerland	1	Yes	Yes	No	1.27	75-100	1-25
United Kingdom	2	Yes	Yes	Yes	1.06	75-100	50-75
	Total 21	79% Yes	57% Yes	64% Yes	Median 0.84 IQR0.62-1.11		

Principle 4

- **Partnership in the Delivery of Haemophilia Care**
  - Clinicians and patient representatives should be part of national and/or regional haemophilia care decision making in partnership with ministries of health and social affairs, as well as those organisations that deliver haemophilia care via a formal mechanism such as a National Haemophilia Co-ordinating Group



18

Adherence to Principle 4

- About one third of the 14 countries had formal mechanisms in place to ensure collaboration.
- Government health bodies were involved to some degree in all countries.
- Clinicians were strongly involved in national or regional care decision-making in all countries with the exception of Belgium and Poland, where clinicians were only involved to some degree.

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Principle 5

- **Access to Safe and Effective Concentrates at Optimum Treatment Levels**
  - People with haemophilia should have access to safe and effective replacement factor treatment concentrates at optimum treatment levels
  - This improves physical health and reduces the psycho-social and economic impact of this bleeding disorder on the patient. It also reduces the amount of long-term support required from family, community and government

20

Adherence to Principle 5

- No constraints in dosage of prescribed factor concentrate.
- All countries used plasma-derived factor VIII (pd-FVIII) and all except Poland used recombinant factor VIII (r-FVIII).
- All countries used pd-FIX.
- r-FIX was used in all countries except Slovakia and Poland.
- Only the UK had a national guideline concerning the prescribing of recombinant concentrates for all patients.
- Five other countries had a policy of prescribing recombinant concentrates for children.

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Principle 6

- **Access to Home Treatment and Delivery**
  - Home treatment and home delivery should be available in each country to facilitate immediate and effective treatment
  - This results in a reduction in hospital visits, prevents short- and long-term disability and allows those with haemophilia to have the freedom to lead lives that are as normal as possible

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Adherence to Principle 6

- Home treatment was supported and taught by all centres.
- 11 centres directly or indirectly provided treatment by trained personnel at the patient's own home; 10 centres did not.

23

Principle 7

- **Access to Prophylactic Therapy**
  - Prophylactic treatment should be available to people with haemophilia as it has been shown to prevent and improve chronic joint disease
  - Prophylaxis also promotes health and social well-being

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Proportion of patients on prophylaxis according to country and centre

	Nr of countries N=14		Nr of centres N=21	
% of patients on prophylaxis	Children	Adults	Children (19 centres)*	Adults (21 centres)
0%				-
1-25%		8 (57%)		8 (38%)
26-50%				5 (24%)
51-75%		5 (36%)		6 (28%)
76-100%	14 (100%)	1 (7%)	21 (100%)	2 (10%)
* two centres did not treat children				

25

Principle 8

- **Specialist Services and Emergency Care**
  - Haemophilia care requires the co-ordination of a number of services to make sure that the particular needs of those with haemophilia are met
  - In critical situations, people with haemophilia need immediate access to treatment as well as skilled care through Accident & Emergency departments and to the range of specialists required to ensure their safety

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Adherence to Principle 8

- All centres were able to provide day care for patients with haemophilia.
- In all centres prompt review could be provided by junior staff within 1 h, with senior medical staff available for treatment advice on a 24 h basis.
- **Paediatric care was less organized in some centres (Paediatricians in staff in 9/19 centres).**
- Overall, a designated physiotherapist was available in 14 (67%) centres.
- A designated orthopaedic surgeon was available in 14/21 (67%) centres.

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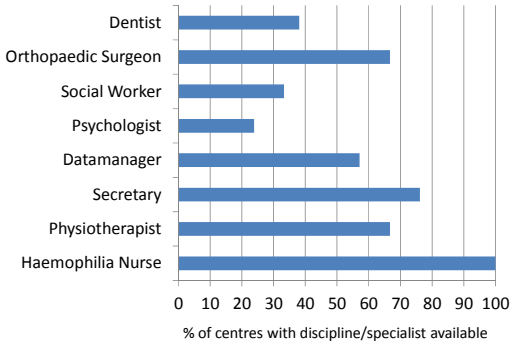
Availability of disciplines involved in care at centre level



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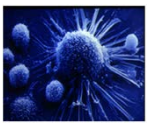
Principle 9



- **Management of Inhibitors**
  - Some people with haemophilia develop “inhibitors”, when their bodies inactivate the replacement clotting factor treatment. Those affected need to have immediate access to optimum treatments
  - Where appropriate, immune therapy induction therapy (ITT) and the management of bleeding should be administered by clinicians with the necessary expertise, in hospitals with appropriate clinical and laboratory resources

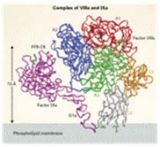
29

Adherence to Principle 9

- The median number of patients with inhibitors per centre was eight (range 0–41).
- In all centres all patients with inhibitors had access to immune tolerance induction (ITI).

30

Principle 10



- **Education and Research**
  - Recruitment and education of physicians in the area of thrombosis and haemostasis is an important task for the future to secure high quality care
  - Further research into haemophilia is also required

www.participatetoinnovate.com
Participate to improve the future of hemophilia therapy

31

Adherence to Principle 10

- Haemophilia centres were usually associated with a university.
- 18 of the 21 centres were part of a University Hospital.
- All undertook teaching about haemophilia and all centres were engaged in clinical trials or research studies.
- In addition, 10 centres reported that they had initiated studies.

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Conclusions

- ☺ The Principles of Haemophilia Care were generally applied throughout Europe.
- ☺ A crude estimate of the number of centres per 1 million of population shows considerable variation.
- ☺ Clotting factor concentrates were available, but purchasing strategies varied.
- ☺ Home treatment was taught everywhere.
- ☺ Prophylaxis was available for all children but not for all adult patients.
- ☺ All patients had access to immune tolerance induction (ITI).

33

Conclusions

- ☹ National registries were not used everywhere.
- ☹ Not all moderate and mild haemophilia patients were treated in designated centres.
- ☹ At centre level, dedicated physiotherapists, formal paediatric care and 24 h FVIII/FIX assays were lacking in some.

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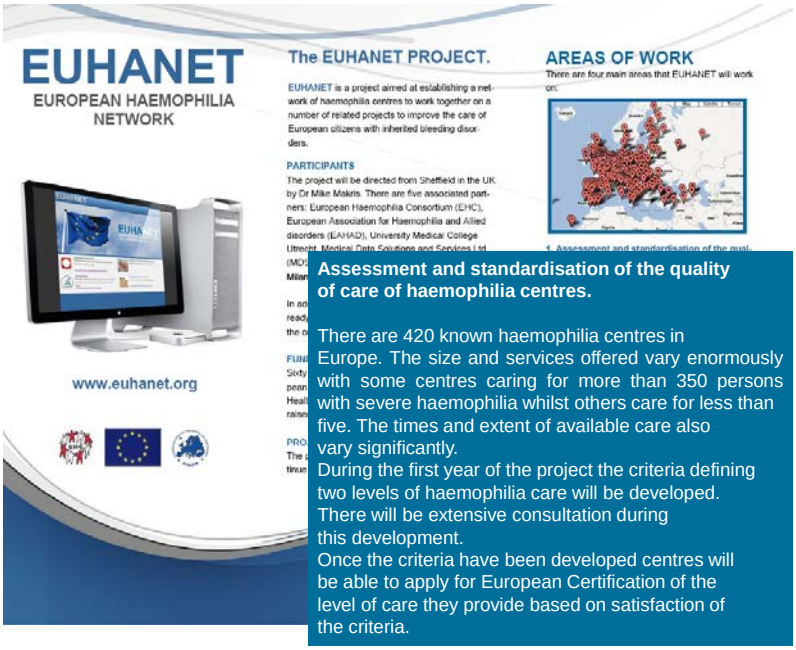
EUHANET
EUROPEAN HAEMOPHILIA NETWORK
www.euhanet.org
The EUHANET PROJECT.
EUHANET is a project aimed at establishing a network of haemophilia centres to work together on a number of related projects to improve the care of European citizens with inherited bleeding disorders.
PARTICIPANTS
The project will be directed from Sheffield in the UK by Dr Mike Makris. There are five associated partners: European Haemophilia Consortium (EHC), European Association for Haemophilia and Allied disorders (EAHAD), University Medical College Utrecht, Medical Data Solutions and Services Ltd (MDSAS) and Fondazione IRCCS Ca' Granda in Milan.
In addition 84 centres from 26 countries have already committed to participating and were part of the original funding application.
FUNDING THE PROJECT
Sixty percent of the funding is provided by the European Commission via its Executive Agency for Health and Consumers (EAHC) and the rest will be raised from industry.
PROJECT DURATION
The project started on 1st June 2012 and will continue until 31st May 2015.
AREAS OF WORK
There are four main areas that EUHANET will work on:
1. Assessment and standardisation of the quality of care of haemophilia centres.
There are 420 known haemophilia centres in Europe at locations shown on this map. The size and services offered vary enormously with some centres caring for more than 350 persons with severe haemophilia whilst others care for less than five. The times and extent of available care also vary significantly.
During the first year of the project the criteria defining two levels of haemophilia care will be developed. There will be extensive consultation during this development.
Once the criteria have been developed centres will be able to apply for European Certification of the level of care they provide based on satisfaction of the criteria.

35


EUHANET
EUROPEAN HAEMOPHILIA NETWORK
www.euhanet.org
The EUHANET PROJECT.
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Thank you for your attention

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EAHAD

Annual meeting

European Association for Haemophilia and Allied Disorders

EAHAD

European | Association | Haemophilia | Allied Disorders

BRUSSELS – BELGIUM

26-28 February 2014

www.eahad2014.com

38

European Regulatory Perspective
on
Clinical Trials in Haemophilia

Dr. Anneliese Hilger
Paul-Ehrlich-Institut

EUROPEAN SYMPOSIUM
Optimal use of clotting factors and immunoglobulins
26-27 April 2013, Wildbad Kreuth, Germany

Agenda

- Legal Background
- Definitions
- Clinical Guidelines FVIII/FIX
- Clinical Concept Aspects
- Conclusion

Legal Background

General Requirements on CT

- Dir. 2001/20/EC – GCP introduction
  - Definitions
  - compliance with GCP and GMP
  - CT application procedure (NCA+EC)
  - Labelling
  - Notification of adverse events
  - amendments
- Dir. 2005/28/EC…..more details: IB,inspection

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Definitions (1)

GCP

Good Clinical Practice is a set of internationally recognised ethical and scientific quality requirements which must be observed for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects.

Compliance with this good practice provides assurance that the rights, safety and well-being of trial subjects are protected, and that the results of the clinical trials are credible.

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Definitions (2)

- **Clinical trial**
  Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy
- **Conduct of a clinical trial**
  Before commencing any clinical trial, the sponsor shall be required to submit a valid request for authorisation to thecompetent authority of the Member State in which the sponsor plans to conduct the clinical trial.
  The sponsor may not start a clinical trial until the Ethics Committee has issued a favourable opinion and inasmuch as the competent authority of the Member State concerned has not informed the sponsor of any grounds for non-acceptance.

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Clinical Guidelines FVIII/FIX

Guidance on the Clinical Investigation/core SmPCs of recombinant and plasma-derived FVIII and FIX:

- GL pd FVIII+FIX (CPMP/BPWG/198/95) 1996
- CoreSmPC pd+rk FVIII/FIX (CPMP/BPWG/1619+1625/99)2000
- GL recombinant FVIII+FIX (CPMP/BPWG/1561/99) 2001
- **EMA Class review on rFVIII** 2003-2005
- Concept paper 2004/2005
- **Expert meeting on inhibitors EMA** 2006
- **Paediatric Regulation** (EC) No 1901/2006
- First public consultation GL+coreSmPC 2007
- Stakeholder meeting 2008
- Second public consultation 2009
- CHMP adoption in 07.2011/in operation 02.2012

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Efficacy aspects

- Clinical response will be assessed by patient and physician
  (none, moderate, good, excellent)
- Surgery
  5 patients with at least 10 surgeries (including major surgeries) =efficacy of haemostasis, blood loss, transfusion requirements + consumption (number of infusions and IU/kg per month and per year, as well as IU/kg per event (prophylaxis, on-demand, and surgery).

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Safety aspects

- PTPs are most suitable to study product-related immunogenicity
- Modified Nijmegen method of Bethesda assay performed in a central laboratory
- Inhibitor definitions: low titer ≥0,6 BU
  high titer > 5 BU
- Regular Inhibitor monitoring following a predefined schedule

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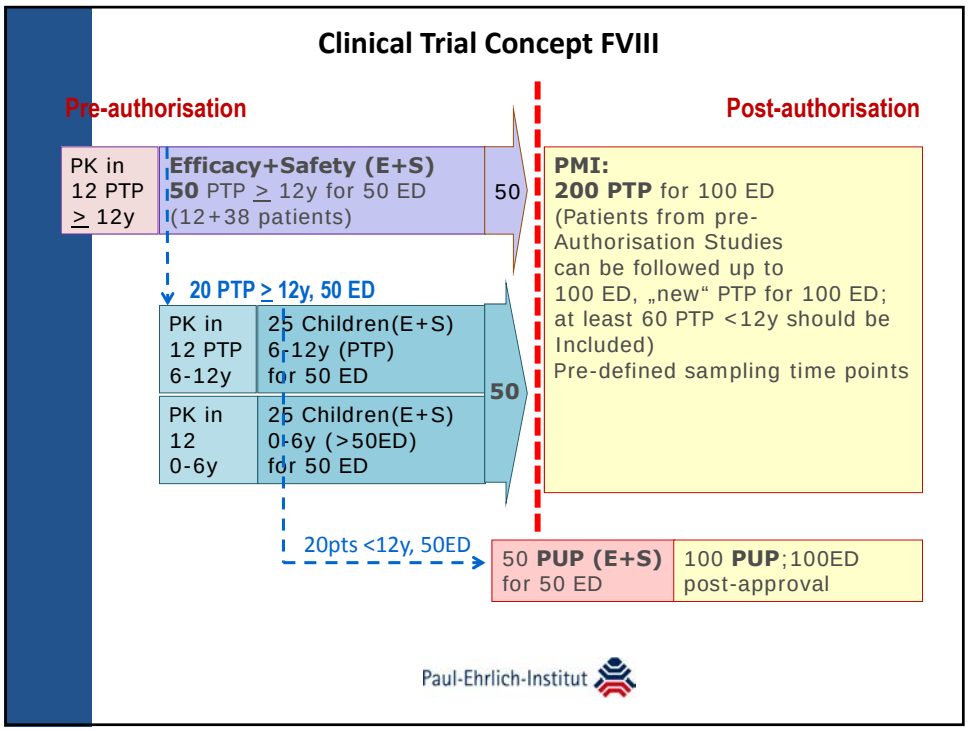

Previous Guideline	Current Guideline	Remarks
50 PTP > 12y (incl. 12 PTP for PK and 5 PTP for surgery)	**50** PTP > 12y (incl. 12 PTP for PK and 5 PTP for surgery)	Remains unchanged
20 children **< 6y**, to be started before MA	**50** children **0-12**y	Acc. Paediatric Regulation / PIP
PUP study not mandatory	**50** PUP for **novel** products (increased to 100 PUP follow up)	According to inhibitor review 2005 and included in the PIP
Post-authorisation: no specific number of patients required	**200** patients to be followed for 100 ED	According to inhibitor review 2005

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ClinTrials.gov

CT Haemophilia	no
total	313
observational	82
interventional	230
closed	166
open	64
recruiting rk	19
Enrolment planned:	1250

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- Children study available before MA – delayed access to novel products for adults in EU?
  →FVIII/FIX basically used in children; off-label use needs to be avoided, conduct of studies in children after MA difficult, convincing novel products…
- Investigation in PUP
  →novel products, careful approach to collect E+S data under controlled conditions

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Conclusion

- **European GL FVIII/FIX**
  -harmonized requirements for MA
  -patient numbers
  -enrolment criteria
  -study duration (ED)
- **Adequately characterized MP for children**
  -PK, efficacy and safety
- **Adaptive Marketing authorisation**
  -stepwise approach
  -balancing the minimum data needed for MA against patient availability
  -comprising adults and children; pre- and post MA data

Letter to the editor- comment on: Evolution of the European guidelines for the clinical development of factor VIII (PM Mannucci) Haemophilia (2013), 19, 349-350

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Registries

Mike Makris
Sheffield, UK

Haemophilia: types of registries

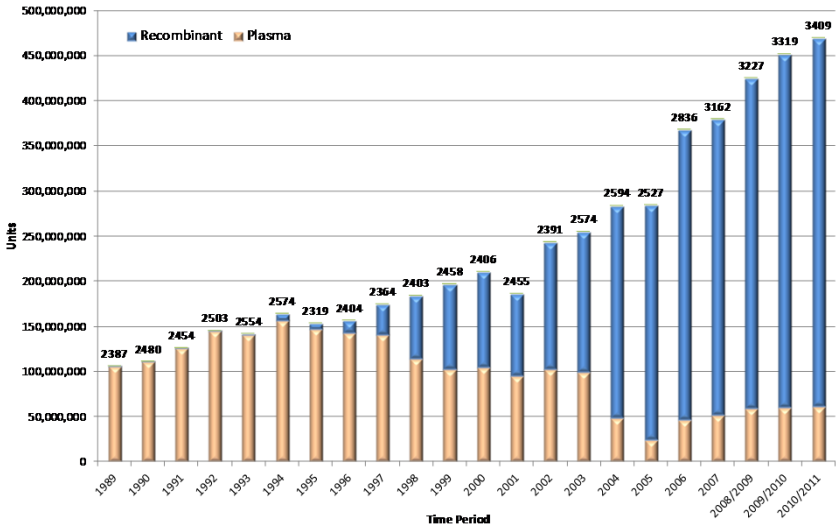
- Registered patients
  - National, regional, local
  - Example: UKHCDO
- Study specific
  - Prospective or cross sectional
  - Examples: RODIN and INSIGHT
- Adverse events
  - International, national
  - Example: EUHASS

UKHCDO National Database

UK Haemophilia Centre Doctors Organisation (UKHCDO)

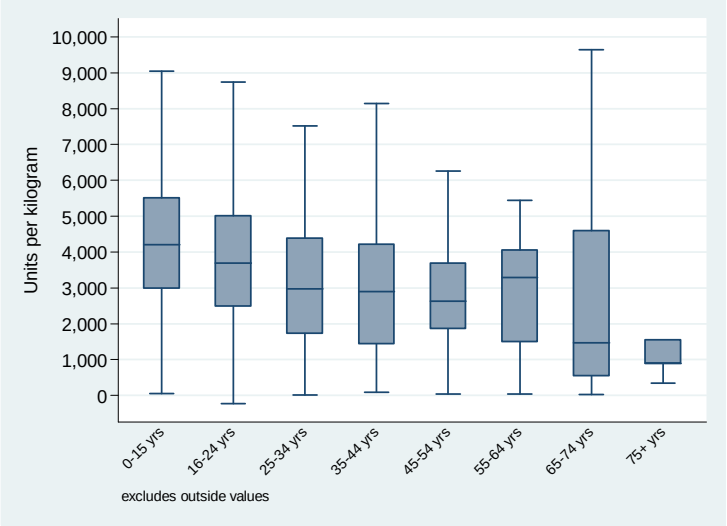
- 1968: UKHCDO formed.
  - Decision to form a UK registry from the start
- 1969: first report issued
- UK population: 61 million
- 26 Comprehensive care haemophilia centres
- 61 Haemophilia centres
- Virtually all UK patients with bleeding disorders and their treatments registered from birth to death since 1968

FVIII usage by UK Haemophilia Centres



FVIII by commissioning group

Median factor VIII units used per kilogram body weight per year in Severe Haemophilia A patients, 2010/11



UKHCDO Database: Patients with Alloantibodies (Inhibitors)

Coagulation Defect	Number of Patients ever known to have an inhibitor by disease severity								
	≤ 1 iu/dl			>1 and <5 iu/dl			≥ 5 iu/dl		
	In Reg *	Inhib. Pts	%	In Reg *	Inhib. Pts	%	In Reg *	Inhib. Pts	%
Haemophilia A	1906	395	20.72%	529	35	6.62%	3032	59	1.95%
Haemophilia B	416	16	3.85%	236	0	0.00%	513	0	0.00%
von Willebrand disease	120	5	4.17%	160	2	1.25%	7991	6	0.08%

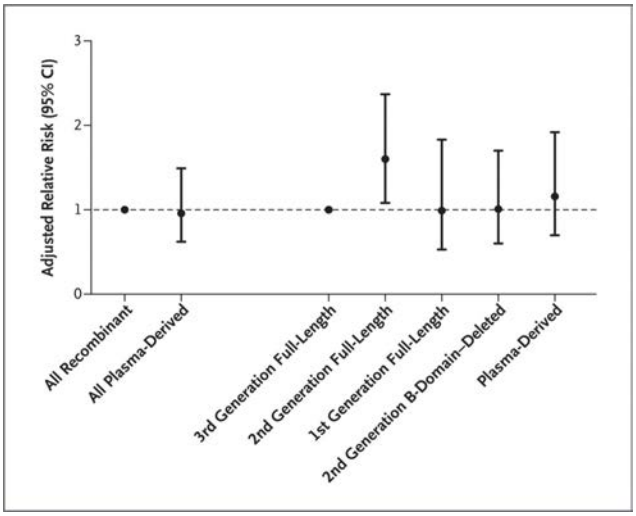
Coagulation Defect	Patients with a current inhibitor between April 2011 and March 2012 by disease severity								
	≤ 1 iu/dl			>1 and <5 iu/dl			≥ 5 iu/dl		
	In Reg *	Inhib. Pts	%	In Reg *	Inhib. Pts	%	In Reg *	Inhib. Pts	%
Haemophilia A	1906	142	7.45%	529	10	1.89%	3032	20	0.66%
Haemophilia B	416	11	2.64%	236	0	0.00%	513	0	0.00%
von Willebrand disease	120	4	3.33%	160	2	1.25%	7991	3	0.04%

RODIN Study Registry

RODIN Registry

- All severe haemophilia A newborns
- 2000-2010
- Data up to 75 exposure days
- Prospective, 29 haemophilia centres
- Detailed information collected
- 574 patients recruited
- 177 inhibitors (32.4%)

Adjusted Relative Risk of Inhibitor Development, According to the Type of Factor VIII Product



Gouw SC et al. N Engl J Med 2013;368:231-239.

EUHASS Adverse Event Registry

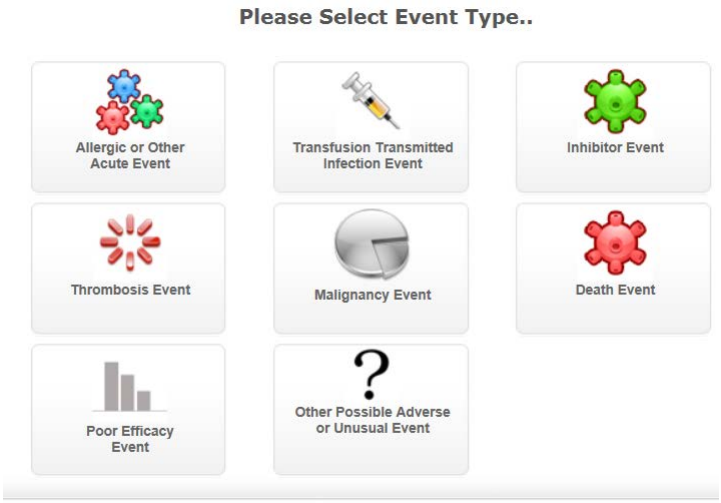
EUHASS

(European Haemophilia Safety Surveillance)

- Adverse event surveillance scheme
- European
- Sentinel centres
- Prospective
- Electronic
- English language
- Started 1st Oct 2008

EUHASS Participating Centres n=84

EUHASS: data on adverse events



www.euhass.org
Makris M, et al. Thromb Res 2011; Suppl 2:22

Patients for Surveillance

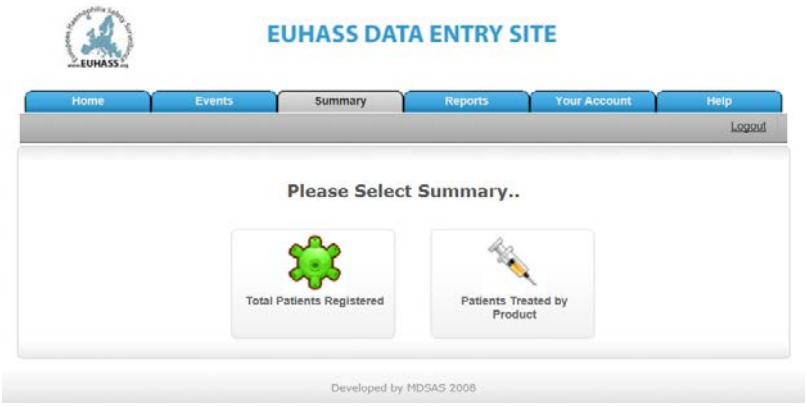
- Haemophilia A and B – all severities
- All VWD 2, 3 and severe type 1 (<15% VIII:RCo)
- Other coagulation factor deficiencies

- Excluded: acquired disorders, platelet disorders

Data submitted

- **Event specific**
  - Generic and event specific questions
  - Events reported live when they occur, or
  - 3 monthly
- **Cumulative data on surveyed population**
  - Annually
  - By diagnosis
  - By clotting factor concentrate

EUHASS: No. of patients at risk



Concerning inhibitors:
→Incidence (cumulative incidence or rate)
→Incidence according to product
→PUPs and PTPs

EUHASS Data: First 3 Years

1 Oct 2008 – 30 Sept 2011

- 74 haemophilia centres
- 26 European countries
- **29,692 patients**

(Year 4 is 1.10.11-31.12.12)

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EUHASS Patients Under Surveillance

	Total	Severe	Concentrate treated during the year
Haemophilia A	**14,467**	**6,210**	**7,617**
Haemophilia B	**3,073**	**1,063**	**1,458**
Other bleeding disorders	12,152	1,784	1,698
Total	**29,692**	**9,057**	**10,773**

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	Total	Severe	Concentrate /FFP treated during the year
Afibrinogenemia	57		30
Hypofibrinogenemia	146		17
Dysfibrinogenemia	392		23
Factor II deficiency	17	10	3
Factor V	372	88	27
Factor VII	1642	341	149
Factor X	372	88	56
Factor XI	1626	243	62
Factor XIII	164	99	96
α2 antiplasmin	37		0
Factor V+VIII	49	14	5
Factor II+VII+IX+X	22	4	4

Concentrates Used: 61 Different Products

Recombinant

- Advate, 1905
- Kogenate, 1426
- Helixate, 758
- ReFacto AF, 1064
- BeneFix, 899

Bypass agents

- FEIBA, 215
- Novoseven, 389

Others, eg

- Emoclot DI, 301
- Fanhdi, 473
- Immunate, 507
- Octanate, 185

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Acknowledgement

- All the centre directors, data managers and nurses at the participating centres

- Funders: EU and Baxter, Bayer, Biotest, CSL Behring, Grifols, LFB, Novo Nordisk, Octapharma, Pfizer
- Enis Muminovic
- Estelle Gilman

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A look at
Primary Immunodeficiencies Patients Access and Unmet Needs

Jose Drabwell
President

Clinical use of coagulation factors & immunoglobulins meeting

26-27 April 2013

Contents

1. IPOPI a brief introduction
2. Primary Immunodeficiencies
3. Treatment Unmet Needs
4. Patient Needs and Outlooks
5. Conclusions

1. IPOPI a brief introduction

- IPOPI is the Association of national patient organisations dedicated to improving awareness, access to early diagnosis and optimal treatments for primary immunodeficiency patients worldwide

1. IPOPI a brief introduction

Board of Directors

Jose Drabwell, Chair (UK)

Martine Pergent, Vice-Chair (France)

Sven Fandrup, Treasurer (Denmark)

Marcia Boyle (USA)

1. IPOPI a brief introduction

Dragana Koruga (Serbia)

Maria Michelfelder (Sweden)

Christine Jeffery (Australia)

Roberta Pena (Argentina)

Joy Rosario (South Africa)

Vicky Modell (USA – JMF Strategic Partner)

1. IPOPI a brief introduction

Medical Advisory Panel (MAP)

Dr. Teresa Espanol, Chair (Spain)

Prof. Ewa Bernatowska (Poland)

Prof. Andrew Cant (UK)

Dr. Esther de Vries (Netherlands)

Dr. Monika Esser (South Africa)

Prof. Amos Etzioni (Israel)

Prof. Alain Fischer (France)

Dr. Jose Franco (Colombia)

Prof. Luigi Notarangelo (Italy/USA)

Prof. Alessandro Plebani (Italy)

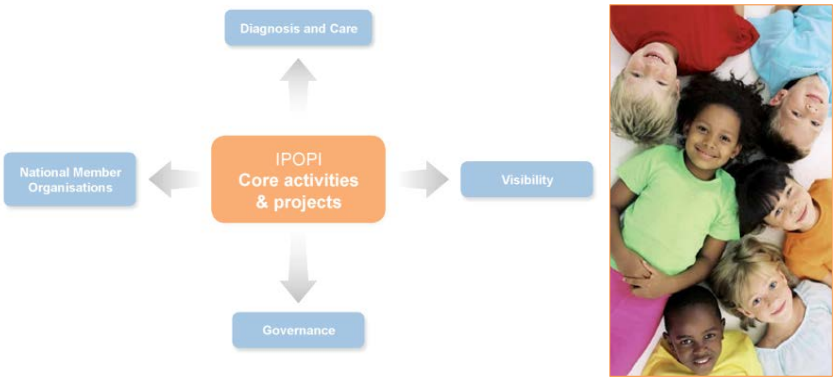
Prof. Surjit Singh (India)

Dr. Klaus Warnatz (Germany)

1. IPOPI a brief introduction

	Staff
Johan Prévot	Executive Director
Magda Lourenço	Communications and NMO Programme Officer
Carla Morgado	Executive Assistant
Carol Tavener	Bookkeeping & Administration
Clare Glynn	Financial consultant
David Watters	Consultant - Projects

1. IPOPI a brief introduction



2. Primary Immunodeficiencies

- Primary immunodeficiencies occur in persons born with failed immune systems
- Hereditary or genetic defects,
- Can affect anyone, regardless of age or sex.
- They vary in severity depending on whether one or several parts of the immune system are non functional (innate or adaptive)
- It is estimated that there are over 200 different primary immunodeficiencies, defined in 8 different groups

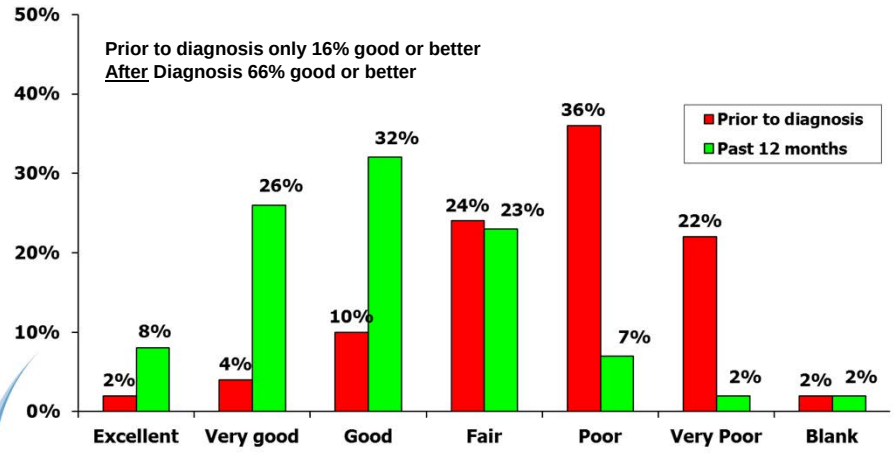
2. Primary Immunodeficiencies

- Primary immunodeficiencies are RARE disorders
- It is conservatively recognized they are within the range as defined by the European Union
- Prevalence varies according to diagnosis rates from country to country
- PIDs are massively UNDER DIAGNOSED in most countries. Patients are treated for their symptoms rather than for the cause of their symptoms
- Treatment options: IG therapy, BMT, Gene Therapy...

3. Treatment

- Antibody deficiencies are the most prevalent form of PIDs – 65% (ESID Registry). Treatment: IG therapy
- PID patients who require life long IG replacement therapy will:
  - Each have an individualised dose of Ig to prevent infections
  - Each have a unique trough IgG level to prevent bacterial infection
  - Not every product will suit every patient : Not generic!

3. Treatment



Q10. Would you describe his/her health in the 12 months prior to diagnosis…..? BASE: Those who are currently using IVIG or SCIG Therapy N=955

Q61. Would you describe his/her health in the past 12 months as…..? BASE: Those who are currently using IVIG or SCIG Therapy N=955

Source: 2008 IDF National Patient Treatment Survey

3. Treatment

- The level at which IgG trough levels are protective are:
  - Variable – no single level overall on which healthcare providers can insist
  - Person dependent – as in a healthy population
  - Some patients may need more than others (ie XLA...)
  - Might be variable during life-time; ie: infections / complications

3. IG Therapy in PIDs

- It is therefore very difficult to talk about ideal or gold treatment level!
- **Treatment regimen will vary between 0.4-1ish g/kg/month**
- Improved patient survival in connection to higher dosing has been demonstrated (Orange meta analysis 2010, Lucas et al 2010, Quinti et al 2010...)

3. Future PID IG treatment needs

- It is estimated that 75-80% of PID patients do not have access to appropriate therapy on a worldwide basis
- Prevalence of PID ranges from region to region
- Assuming a conservative prevalence of 1/5,000* patients for PADs (**in the US prevalence has been estimated to be 1/1,200*) , or 200 per million population
- Potentially, 1.4 million people living with a PID worldwide of which a majority would require IG therapy

3. Treatment

•Let us assume, based on a worldwide prevalence of 1.4 million PID patients likely to need IG therapy, the total treatment level needs per year, should all these patients be able to access appropriate levels of care....

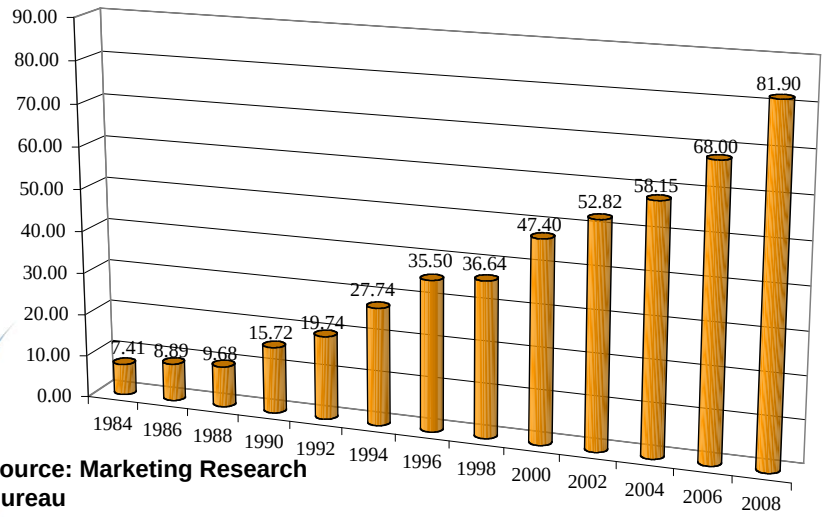
Dosage in g/kg/month: 0,4	Dosage in g/kg/month: 0,7
Average weight adult/children: 40kg	Average weight adult/children: 40kg
0.4 x 40 = 16gr/month	0.7 x 40 = 28gr/month
16gr/m x 12 = 192gr/y	28gr/m x 12 = 336gr/y
1.4mo X 192gr = 269 tons	1.4 mo X 336gr = 470 tons

3. Treatment

•Let us assume, based on a recent survey of IPOPI's NMOs in 33 countries with a total number of estimated patients of 290,881, the total treatment level needs per year, should all these patients be able to access appropriate levels of care....

Dosage in g/kg/month: 0,4	Dosage in g/kg/month: 0,7
Average weight adult/children: 40kg	Average weight adult/children: 40kg
0.4 x 40 = 16gr/month	0.7 x 40 = 28gr/month
16gr/m x 12 = 192gr/y	28gr/m x 12 = 336gr/y
290,881 X 192gr = 55tons	290,881X 336gr = 98 tons

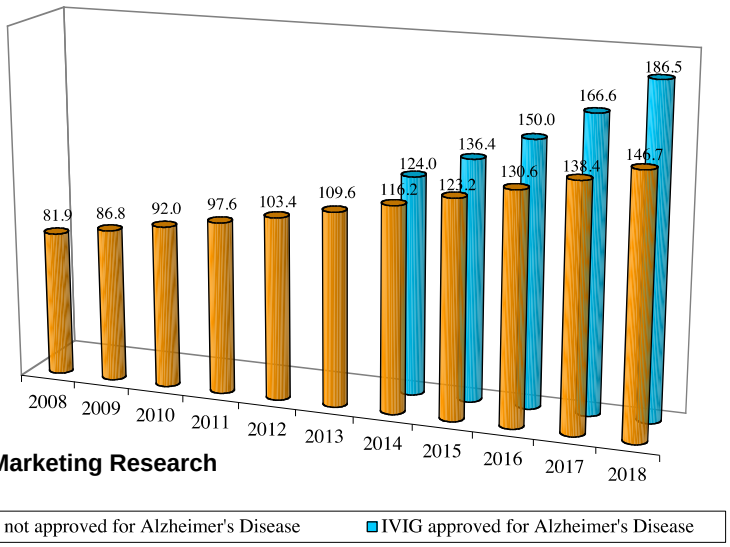
WORLDWIDE DEMAND FOR POLYVALENT INTRAVENOUS IMMUNE GLOBULIN (IVIG) 1984 - 2008 (Metric Tons)



Source: Marketing Research Bureau

GLOBAL DEMAND FOR POLYVALENT INTRAVENOUS/SUBCUTANEOUS IMMUNE GLOBULIN (IVIG/SCIG) WITH/WITHOUT ALZHEIMER'S DISEASE TREATMENT APPROVAL IN 2015 - 2008 TO 2018

(Metric Tons)



Source: Marketing Research Bureau

IPOPI PID Patient Needs & Outlooks Survey

A Report based on 300 patient questionnaires

Report Prepared by BRYTER

Background & objectives

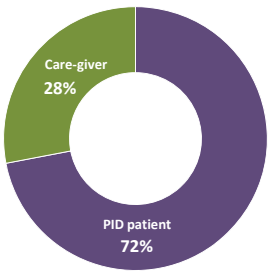
Research goals and objectives

- The study has been designed to provide detail on the current landscape, outlook and needs of patients in relation to their circumstances, outlooks and treatment needs with PID
- This study explores the patient experience of PID, covering aspects from treatment and unmet needs to the impact of PID on daily and social life.
- The conjoint section asked respondents to evaluate a number of treatment options in rotation to establish unmet needs.
- Sample:
- N=300: Patients & Care-givers of people with PID and treated with immunoglobulins. Sample sourced through national member organisations (NMOs) affiliated to the International Patient Organisation for Primary Immunodeficiencies (IPOPI). Sample was self-selecting amongst those invited by the NMOs.

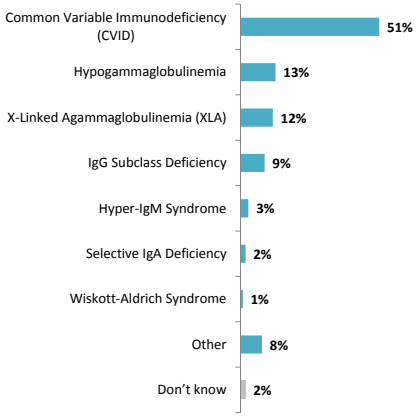
Country	Groups	Interviews
UK	A, B	59
Sweden	A	34
Canada	C	31
France	A, B	31
Germany	A, B	31
Spain	A, B	22
Portugal	A	21
Argentina	C	15
Brazil	C	13
South Africa		10
Colombia	C	9
Italy	A, B	9
Switzerland	A	4
Belgium	A	2
New Zealand		2
Poland	A	2
Australia		1
Austria	A	1
Hungary	A	1
India		1
Netherlands	A	1

7 in 10 survey respondents are patients with the remaining made up by care givers. CVID is the most widely represented diagnosis of PID.

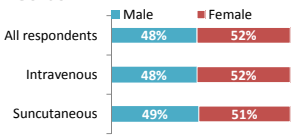
Role in relation to PID



Patient Diagnosis



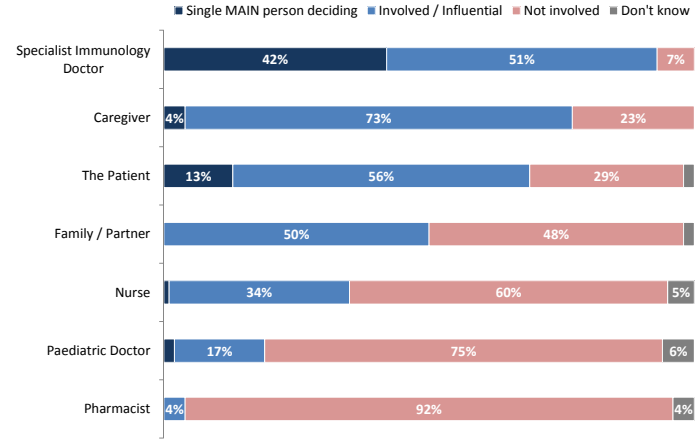
Gender



P1: Which of the following best describes your role In relation to PID?
D1: And what is your specific diagnosis/ What is the diagnosis of the PID patient you care for?
Q.C0b/Q.C3: Are you ... Male or Female
Base: All Respondents (300)

For 42%, immunology specialists are the main decision maker regarding how Ig therapy is administered. However, around 70% of patients and 77% of caregivers were involved in the decision-making process

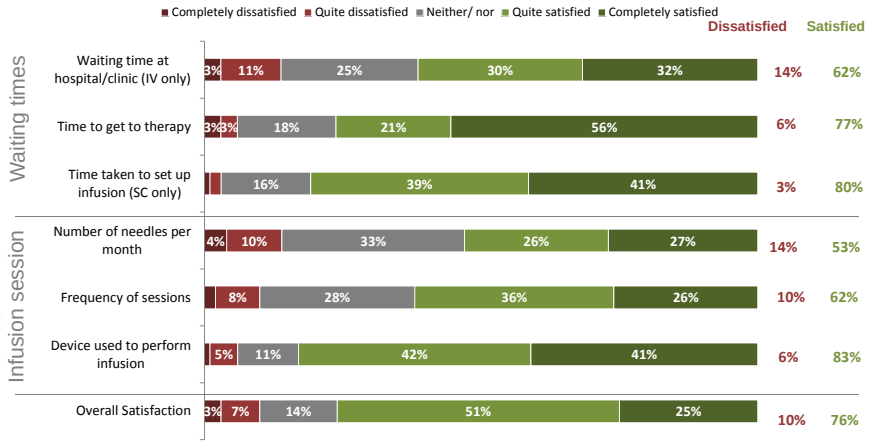
Decision makers for route of administration



D5a. Thinking about the decisions and selection of the current therapy... Who was involved in choosing how the therapy is administered?
Base: All Respondents (300)

Overall, three quarters (74%) are satisfied with their treatment. However, 1 in 5 (18%) are dissatisfied with the number of needles to contend with each month

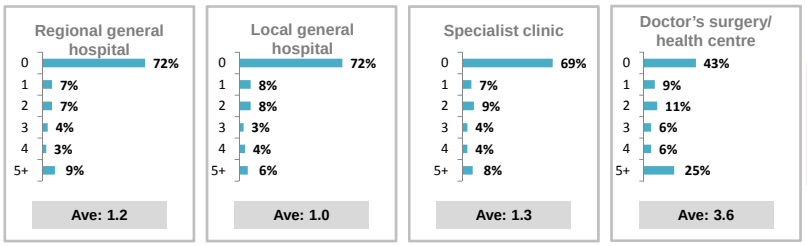
Satisfaction with aspects of current treatment



D19a: How satisfied are you with the following...
Base: All Respondents (300), SubC only (134), IV only (160)

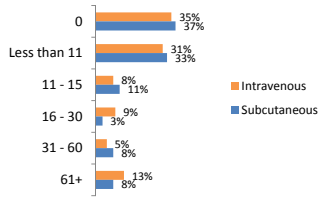
Sixty-six percent (using intravenous Ig) and 70% (using subcutaneous Ig) report missing 10 or fewer work/school days during the past 6 months. Of these, 35% (using intravenous Ig) and 37% (using subcutaneous Ig) missed 0 days

Unscheduled visits in relation to PID in last 12 months



There was no difference in the number or unscheduled visits based on the type of administration (IV vs. SubC)

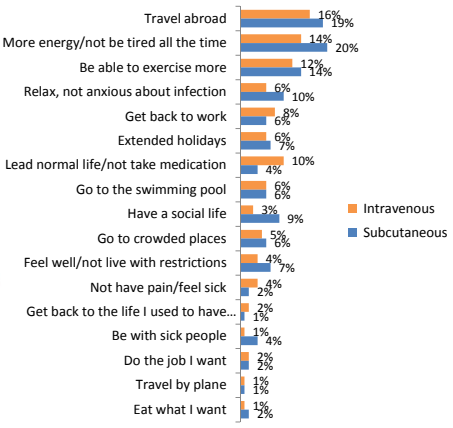
Days missed at work/education due to ill health in last 6 months



H4: In the last 12 months, how many unscheduled or emergency visits have you/the patient made to each of the following in relation to PID?
H5: And how many days have you/the patient missed at work/education due to ill health in the past six months?
Base: All Respondents (300)

PID patients would like to take part in 'everyday' activities: travelling / going abroad was mentioned by most (19%) of subcutaneous patients as the one thing they would like to be able to do, but don't feel they can because of PID

One thing patient would LIKE to be able to do but don't feel they can, because of PID (spontaneous mentions)



"Travel to countries very far away."

"Have enough energy for a full day and going out at night without needing a nap and early night!"

"Travel for over 2 weeks without the need to bring medical equipment or make advanced planning."

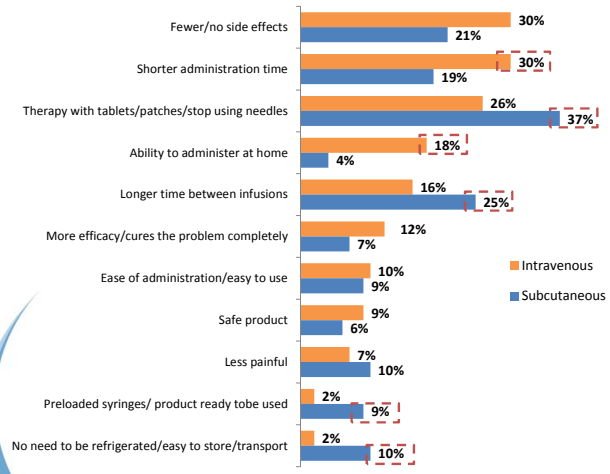
"Get back to life I used to have before I was diagnosed with PID."

"I would like to meet other people even during times there's a lot of flu etc. Don't like trying to avoid crowded places etc. because the risk for infection."

H6: In your opinion, what is the one thing you would LIKE to be able to do but don't feel you can, because of PID? MULTIPLE RESPONSE
Base: All Respondents (300)

Intravenous and subcutaneous patients differ regarding the features they look for in an ideal product to treat PID.

Features of an ideal treatment for PID (spontaneous mentions)



Compared to subcutaneous patients, a significantly higher share of intravenous patients mentioned **'shorter administration time'** and **'ability to administer at home'** as a feature of an ideal product.

Among subcutaneous patients **'longer time between infusions'** features more often as an attribute of an ideal product. 9% of them would like to use **'preloaded syringes'**.

Significant difference between intravenous and subcutaneous therapy:

D21: Thinking about future PID treatments imagine you were working with a medical design team what two features would you look for in the ideal product?
Base: All Respondents (300), Intravenous (160), Subcutaneous (134)

Amongst both intravenous and subcutaneous patients, the positive elements of their current treatment (e.g. intravenous – less frequent infusions needed) seem to have more weight in the decision about how therapy is administered

Importance of attributes by current route of administration (intravenous vs. subcutaneous)

Conjoint analysis

	All Respondents	Current Intravenous	Current Subcutaneous
Convenience around scheduling	15%	13%	18%
Dosing frequency	19%	24%	14%
Where you take the treatment	22%	17%	29%
Number of needle sticks per treatment	20%	24%	15%
Time to take each treatment	23%	23%	23%

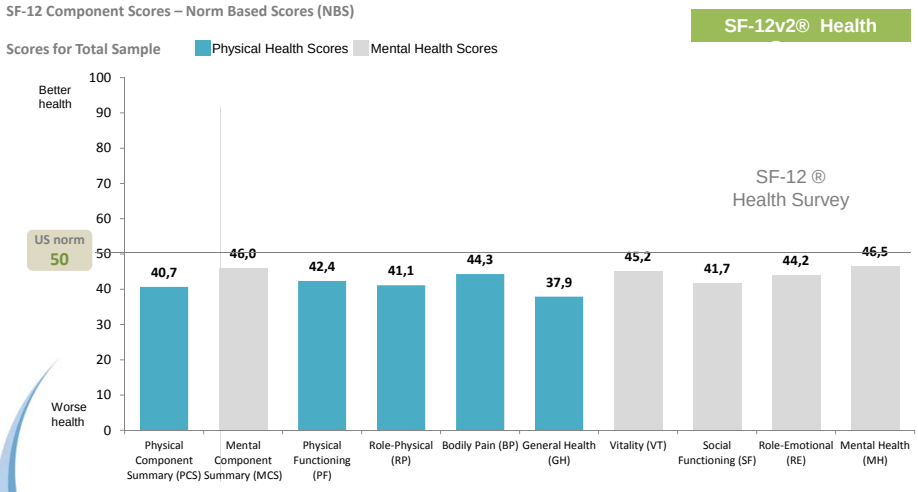
Colour coding

- High
- Average to high
- Average
- Low

The colour coding indicates whether a score of the subgroup is higher or lower compared to the score at total level.

Base: All Respondents (300)

PID patients are below US norms across Physical and Mental elements



F1. In general, would you say your health is… F2. Does your health now limit you in these activities. F3: During the past 4 weeks, how much of the time have you had any of the following problems with your work/other regular daily activities as a result of your physical health? F4 During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)? F5: During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework?)
F6: How much time during the past 4 weeks … F7 During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)? Base: All Respondents who are PID patients (216)

Conclusions IPOPI Survey – Patient Needs and Outlooks

IV and SubC treatments are roughly split 50/50 across the surveyed countries

Immunology Specialist physicians are the decision makers choosing administration route in 2 in 5 cases with patients and or caregivers being secondary influencers.

Impact of treatment

Sixty-six percent of patients (using intravenous Ig) and 70% (using subcutaneous Ig) report missing 10 or fewer work/school days during the past 6 months. Of these, 35% (using intravenous Ig) and 37% (using subcutaneous Ig) missed 0 days. While 39% report no pain, 50% report moderate pain; 48% report problems with daily activities. Patients' mental well-being is affected too: 61% report no anxiety/depression, while 39% identify moderate or extreme anxiety/depression (averages were below population norms across physical and mental QoL elements)

One in five IV patients have tried SubC whilst 8 in 10 SubC patients have tried IV

IV patients who had tried SubC were most likely to have stopped because of side effects (61%) and wanting longer between doses (32%). SubC patients who had previously tried IV most commonly stopped because of inconvenience of going to the centre (51%), wanting to treat at home (43%) or because it was recommended they change (48%). 33% said side effects

Side effects in IV and SC patients

95% of SubC experience swelling / bumps at infusion site but this causes a large impact for just 7%. 7% experience pain at infusion sites but to a large extent for just 5%. Headaches are most prominent for IV patients (51% experience) and these have a large impact on life for 11%

Conclusions IPOPI Survey – Patient Needs and Outlooks

Main area where IV & SC patients would like treatments to be improved	34% of IV patients believe headaches are the most important area to improve. For SubC patients, pain at the infusion site and swelling at the infusion site are priorities for improvement though 19% say it is 'highly important' to focus on headaches too.
IV & SC patients views on ideal treatment	Spontaneously 30% of IV patients said they wanted a treatment with less side effects compared to 21% of SubC patients. SubC patients were most likely to say a therapy without needles (37%) and more time between infusions (25%). IV patients also mentioned a shorter admin time (30%) and the ability to administer at home (18%)
Preference analysis showed relatively level importance around attributes in choosing treatments	Drivers of choice were time to take each treatment (23%), site of treatment - at home vs. medical centre (22%), number of needle sticks (20%), dosing frequency (19%) and convenience on scheduling (15%).
A preference was shown for self-administration at home, infrequent, quick to administer dosing and few needle sticks	Half of IV respondents (52%) would prefer a SubC type therapy similar to those available. This would be preferable for 91% of existing SubC respondents.

4. Patients Access and Unmet needs

a. Austria - Lack of knowledge/awareness by GPs. Doctor to Doctor – no diagnosis. Immunologists are paediatricians – no specialist for adults.
b. Cyprus – No immunologist, No clinic, No nurse.
c. France – Problem with choosing home therapy. Hospital tenders, not always assured of the same product. IG delivered to hospital, patients travel to hospital to collect product then go home to infuse. Pharmacists believe IGs are generic – therefore only 1 brand in stock, despite the French national guideline (circulaire) which states hospitals should provide a range of therapies in view of patients tolerability patterns and the fact Igs are not generics. .

4. Patients Access and Unmet needs

- Germany - Very low rate of diagnosis, small number of immunologists. Can take up to 3-4 months to get an appointment. Problems with Health Insurance Companies due to high costs of treatment.
- Greece – Shortage of IV and SCIG. 40% less available. Not sufficient for all patients. Due to economic crisis no response from MOH.
- Holland – No choice in product, depends on contract between hospital and pharmaceutical company. 2014 change in payment structure for IG and treatment.

4. Patients Access and Unmet needs

- Italy – Infusion pumps not paid for by Health Service, although sometimes hospitals supply or companies. Anxiety that NHS may change due to present financial situation.
- Russia – Children diagnosed with SCID, WA and CGD are declared disabled (treatment from the state incl. high cost drugs under the social assistance programme). Less severe PIDs such as CVID, HAE etc do not have the protection of being “disabled”, so have to get Compulsory Medical Insurance – State managed. Adults with PID, this diagnosis is not recognised, so hospitalisation for pneumonia, TB or any other major infection is looked upon as a cure after treatment.

4. Patients Access and Unmet needs

- Serbia – Adults not receiving adequate treatment, 5-10 gram per month, trough levels below 6. Hospitals say IG too expensive and claim they do not receive payment from insurance companies.
- Spain – Very good NHS , treatment all free, but lately hospitals are only providing one IVIG product, not taking into consideration patients history.

Conclusions – Unmet Treatment Needs

- The large majority of patients with a primary immunodeficiency currently do not have appropriate access to care & diagnosis
- Delays in diagnosis and inappropriate treatment result in recurring life-threatening or life-impairing infections
- Resulting in an inability to function properly (socio-economic impact on education, professional lives..) and poor quality of life
- PID is one indication amongst many others which are treatable with IG therapy but a top priority indication given its life saving replacement role in PID patients, as supported by numerous studies and various IG demand management mechanisms (UK DMP, CEDIT..)

Conclusions – Unmet Treatment Needs

- As the demand for IG therapy keeps growing for new indications, and the diagnosis rates of PID patients increase...
- Future distribution of IG therapy will need to be tightly regulated in order to allow those patients whose lives depend entirely on this therapy to have priority access at all times.

Focus on clinical care and diagnosis


IPOPI
THANK YOU
www.ipopi.org
Report Prepared by BRYTER

Contents

- Primary vs Secondary Immune Deficiencies
- Severe Combine Immune Deficiencies – pre stem cell transplantation & often post transplant
- Complex / combined immune deficiencies
- Primary Antibody Deficiencies - complete and partial
- Secondary immunodeficiencies

Primary

- Without an obvious cause
- Due to an intrinsic defect in genes
- Usually present in infancy or early childhood
- Groups depend on nature of defect e.g severe affecting both parts of adaptive immune system [T and B lymphocytes] or less severe e.g. affecting only antibody production [B cells]

Secondary

- Associated with an underlying cause e.g lymphoma, thymoma, so usually obvious symptoms of malignancy/ detectable on CT imaging
- Medications in history e.g. anticonvulsants, anti-rheumatics, Rituximab, chemotherapy, immunosuppression
- After transplantation e.g. solid organ or HSCT

Warning signs of primary immunodeficiency

Children	Adults
Patholological Susceptibility to Infections : Unusual pathogens, localisation, course, intensity, frequency: Suspicion of PID in adults: >3 infections/year lasting longer than 3-4 weeks	
Immunodysregulation: granulomas, autoimmunity, recurrent fever, eczema, lymphoproliferation, chronic diarrhea, increased frequency of malignant tumors	
Failure to thrive	***Loss of body weight (>10%)***
Suspicious family history: Consanguinity, proven immunodeficiency or increased susceptibility to infections in the family, early child death, vaccination complications	

Basic laboratory: Blood count: lymphopenia, neutropenia, hypogammaglobulinemia IgG,A,M
Advanced diagnostic lab : Complement (CH50,C3,C4), IgG-subclasses, specific antibody (Diph, Tet, pneumococcal antigens), lymphocyte panel, cytotoxicity, proliferation, genetics

AWMF Leitlinie S2k Nr. 027/050: Diagnostik von primären Immundefekten, 12/2011

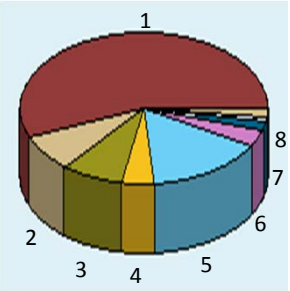
IUIS Klassifikation of PID

(IUIS Update 2011) (Al-Herz; 2011) N>200

1. Combined T and B cell deficiency
2. Predominant B cell deficiency (AMS)
3. Other well defined immunodeficiency syndromes (WAS, AT, Di George a.o.
4. Immunodysregulation syndromes
5. Defects of phagocyte number and function
6. Defects of natural immunodeficiency
7. Autoinflammatoy syndromes Syndrome
8. Complement deficiency

ESID PID Registry 2012:
16,547 patients

Diagnosis:	2012:	
1. Predominant antibody disorders	**56.14%**	**(n=9,289)**
2. Predominant T cell deficiencies	**7.82%**	**(n=1,294)**
3. Phagocytic disorders	**8.43%**	**(n=1,395)**
4. Complement deficiencies	**4.14%**	**(n=685)**
5. Other well defined PIDs	**14.92%**	**(n=2,468)**
6. Autoimmune & immune dysregulation syndromes	**3.98%**	**(n=659)**
7. Autoinflammatory syndromes	**2.05%**	**(n=339)**
8. Defects in innate immunity	**1.02%**	**(n=169)**
9. Unclassified PIDs	**1.50%**	**(n=249)**
Total number of patients:	**100.00%**	**(n=16,547)**

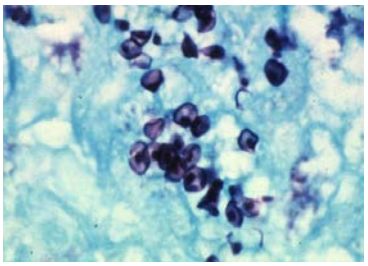


List of some PRIMARY DEFECTS (now > 200 syndromes) in many guidelines for Ig therapies

Combined Complex Deficiencies:

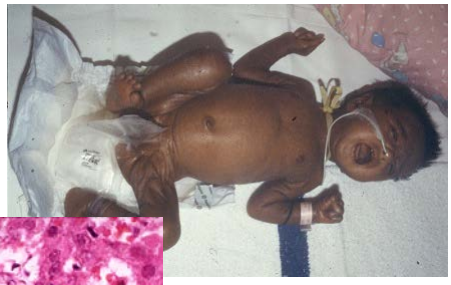
- SCID (all prior to + after BMT, if B cells do not reconstitute)
- Wiskott-Aldrich syndrome (if severe immunodeficiency)
- Ataxia-telangiectasia
- Short-limbed dwarfism or cartilage-hair hypoplasia
- X-linked lymphoproliferative syndromes (possible benefit)
- 22q11 deletion syndromes (if severe antibody deficiency)
- Hyper-IgE syndromes

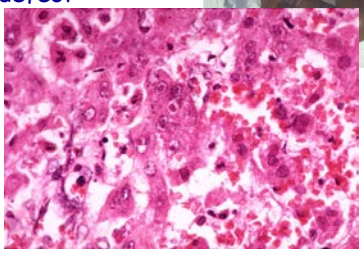
Case: Severe Combined Immune Deficiency



Bronchoalveolar lavage
Pneumocystis = T cell defect

Severe chest infection since 4 months – diarrhoea and poor weight gain





Liver histology
CMV hepatitis with characteristic owl's eye inclusion bodies
= T cell defect

No detectable serum Igs = B cells defect too

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All infants with SCID need Human Stem Cell Transplantation [HSCT]

Ig treatment:

1. Pre- stem cell transplant – sterile conditions, antibiotics, antifungals and IMMUNOLOGLOBULIN
2. After HSCT, many continue to need IMMUNOLOGLOBULIN if B cells are not reconstituted- test = rise in serum IgG, IgA and IgM with specific abs after immunisation

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- Secondary immunodeficiencies: Drugs, lymphoid malignancies or post-anti CD20 monoclonal abs

Complex combined immunodeficiencies

Combined Immune Deficiencies
- Children with other organs affected e.g Wiskott Aldrich with thrombocytopenia
- Variable use of Ig –for surgery/therapies causing infections

CD40 ligand Deficiency
- Children and adults affected
- Markedly shortened life span if not treated with Ig
- HSCT for new cases in infants and children but variable in adults – not all need HSCT

Di George syndrome
- Mainly T cells low – and complicated by autoimmunity
- A few require Ig therapy

Familial Hemphophagocytic Lymphohistiocytosis /MAS
- Defective exocytosis of lytic vesicle from CTL, NK

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Primary Antibody Deficiency (PAD) Syndromes

1.	X-linked Agammaglobulinemia (M.Bruton), AR	(10%)
2.	Hypogammaglobulinemias:	(90%)
	Common variable Immunodeficiency	
	Hyper-IgM-Syndromes	
	Selektive IgA-deficiency	
	IgG-subclass deficiency	
	Kappa-light chain deficiency	
	Selective antibody deficiency (SAD)	
	Transitory hypogammaglobulinemia of infancy	
3.	Good Syndrome	

Peter, Pichler, Müller-Ladner „Klinische Immunologie „ 2012

Differential diagnoses of PADs:

- XLA – no IgG/IgA/IgM; no antibodies; no B cells
- CVID – low serum IgG and IgA; little /no antibody responses
- IgA and IgG subclass deficiencies – low/normal IgG, no IgA; some ab responses but usually no pneumoccocal abs
- Specific antibody deficiencies – normal serum IgG, IgA and IgM but failure of one type of Imx only – usually no pneumococcal abs
- Transient hypogamma of infancy – low Igs but good abs responses
- Selective IgA deficiency – no IgA but good IgG abs to all Imx

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Common Variable Immunodeficiency (CVID):

The most frequent form of PAD in adults and a diagnosis of exclusion.

Definition: Heterogenous primary antibody deficiency
8-10% are by now genetically defined

Diagnostic criteria (www.esid.org):

1) Hypogammaglobulinemia: marked decrease of IgG (2 SD < mean for age) marked decrease in either IgA and/or IgM
2) Onset of immunodeficiency at greater than 2 years of age
3) Absent isohemagglutinins and/or poor response to vaccines

Epidemiology and clinical phenotype of CVID

Epidemiology:

Incidence: 1:25.000/year;

male:female =1:1

15-20% familial: 80% AD, 20% AR

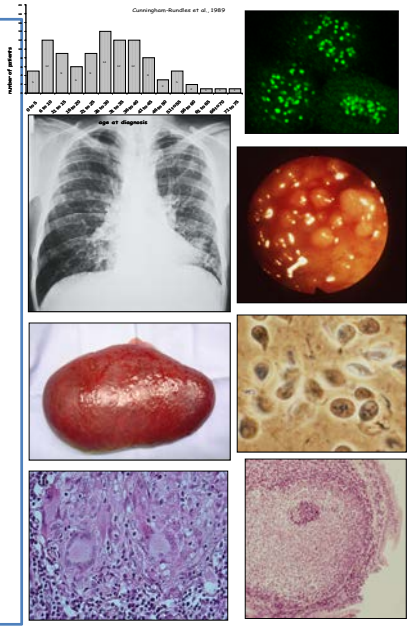
Disease onset:

Early : 2-6 years (10-20%)

Late: young adult (80-90%)

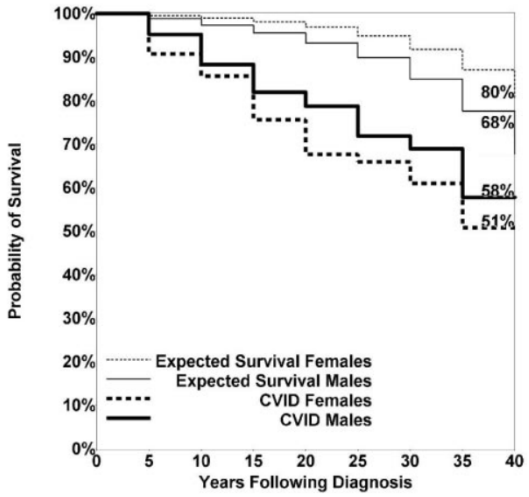
Clinical symptoms

- URTI, bronchitis, pneumonias	**>95%**
- Diarrhea, H. pylori gastritis	**40-50%**
- NLH, Lambliasis, celiac disease	**30%**
- Autoimmunity (AIHA,ITP, RA..)	**30%**
- Splenomegaly, Lymphoproliferation	**50%**
- Sarcoid-like granulomas	**10-20%**
- Malignancies	**10%**



Life exspectancy of CVID

(ES Resnick et al 2011)

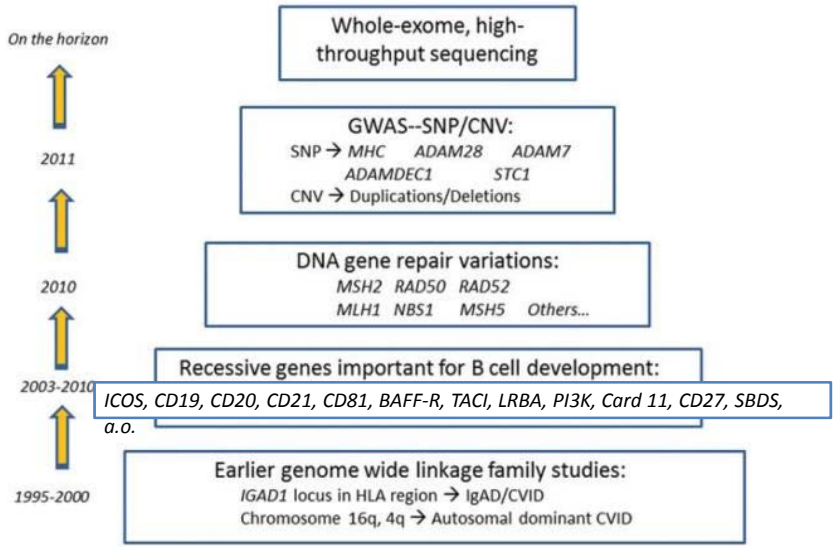


Prognostically relevant Lab findings in CVID

Parameter, Lab finding, cell type	Prognosis effect	Ref
Normal IgM	good	Resnick 2011
Very low IgG	poor	Resnick 2011
Complete absence of vaccine-induced specific antibodies	poor	Goldacker 2007
Low B cells	poor	Resnick 2011
Low/absent switched memory B cells	poor	Wehr et al 2008
High transitional B cells	poor	Wehr et al 2008
High $CD21^{low}$ B cells	poor	Rakhmanov 2009
Low CD4+ T cells and Low CD4+CD45RA	poor	Giovannetti 2007

Attempts at deciphering genetics of CVID

(Park et al 2012, Salzer et al 2012)



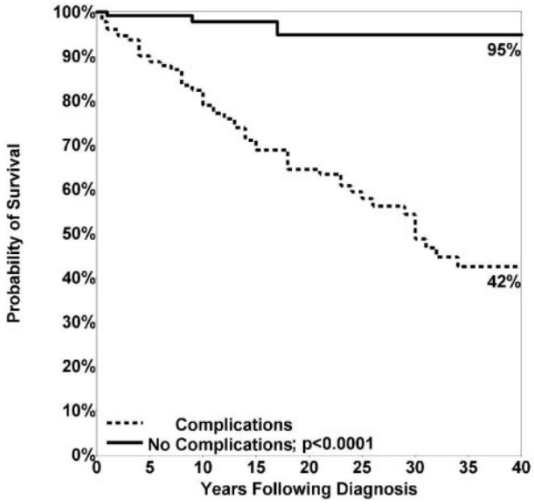
Selected complications in 473 CVID patients followed over 4 decades in 1 center

(ES Resnick, C Cunningham-Rundles 2012)

Associated condition	N	Per cent
Infections only (without complications)	151	31.9
Chronic lung disease	135	28.5
Bronchiectasis	53	11.2
Autoimmunity	134	28.6
Immune throbocytopenic purpura (ITP)	67	14.2
Autoimmune hemolytic anemia (AIHA)	33	7.0
Gastrointestinal disease	73	15.4
Malabsorption	28	5.9
Inflammatory bowl disease	20	4.2
Chronic liver disease /hepatitis	43	9.1
Granulomatous disease	46	9.7
Malignant disease (Lymphoma 39, Cancer 33)	72	15.2

Survival of uncomplicated and complicated CVID

(ES Resnick et al 2011)



Infections only

Infections plus complications

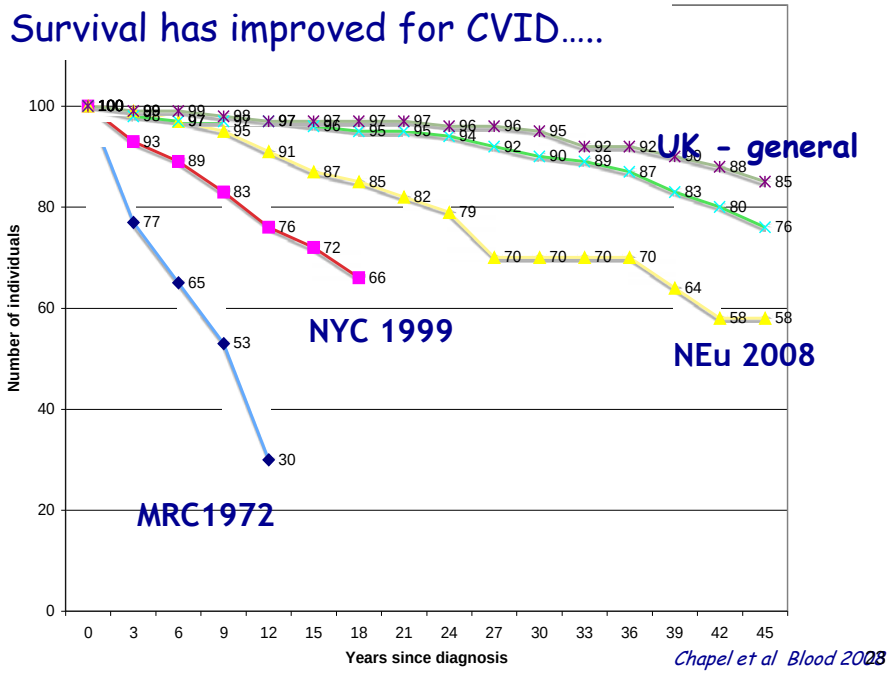
Complications	HR	p
Any	10.96	<0.0001
GI disease	2.78	<0.004
Liver disease	2.48	<0.003
Lymphoma	2.44	<0.01
Chronic lung dis	2.06	<0.01
Malabsoprtion	2.06	<0.022

What about Ig treatment for these conditions….

Common variable immunodeficiencies disorders [CVIDs] - commonest symptomatic PAD

- Replacement Ig therapy is life-saving and required life-long – no known cure
- Along with improved management, better compliance and monitoring, physiotherapy, has extended life expectancy if no disease-related complications
- EVIDENCE – plenty!

Survival has improved for CVID…..



Treatment for partial antibody deficiencies:

- *IgA with IgG subclass deficiencies*
- *Specific antibody deficiencies*

1. Try prophylactic antibiotics
2. IF in doubt, agree a 12 month trial with monitoring before starting
3. EVIDENCE – Expert opinion, though data now being collected

Immunoglobulin deficiencies that do NOT usually require immunoglobulin therapy

1. Selective IgA deficiency

2. Transient Hypogammaglobulinemia of Infancy

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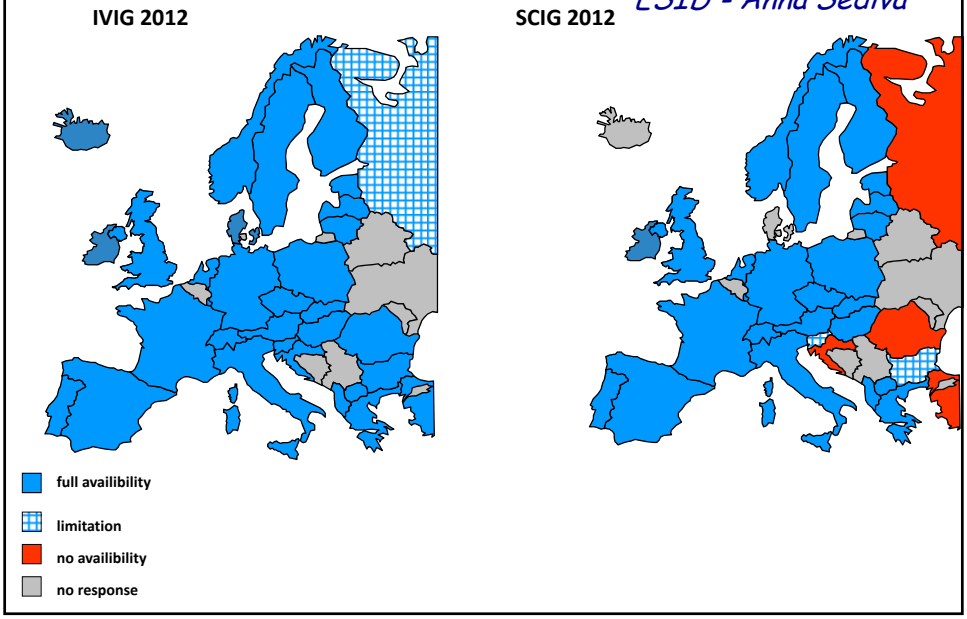
EUROPE IMMUNOGLOBULIN MAP 2012

ESID - Anna Sediva



Immunglobulin-Replacement Therapy in PID

(ESID Register 2010)

PID Typ	Patients (n)	Under IVIG/SCIG	% IVIG/SCIG
Agammglobulinämie	551	501	90.9
CVID	1.669	1.457	87.3
Hyper-IgM (CSR -Defekte)	222	129	58.1
XLP-Syndrom	38	20	52.6
HLA-Klasse II Defekt	36	18	50.0
SCID (T -B- Defekte)	153	72	47.1
SCID (T- B+ Defekte)	162	65	40.1
T-Zell-Defekte unklassifiziert	104	45	44.2
Wiskott-Aldrich-Syndrom	243	107	44.0
Chron. mucokutane Candidiasis	32	8	25.0
CD4 Defekt	42	10	23.8

Immunglobulin-Replacement Therapy in PID
(ESID Register 2010)

PID Typ	Patients (n)	Under IVIG/SCIG	% IVIG/SCIG
Unclear immunodeficiency	135	40	29.6
Hyper-IgE Syndrome	142	36	25.4
DNA breakage disorders	385	89	23.1
Hypo-γ-globulin. (non-CVID)	2.333	482	20.7
Fam. Hämophagozytose	55	11	20.0
ALPS	89	13	14.6
LAD	30	2	6.7
DiGeorge	273	12	4.4
Congenital Neutropenie	272	11	3.7
Chron. Granulomatose (CGD)	327	12	3.7

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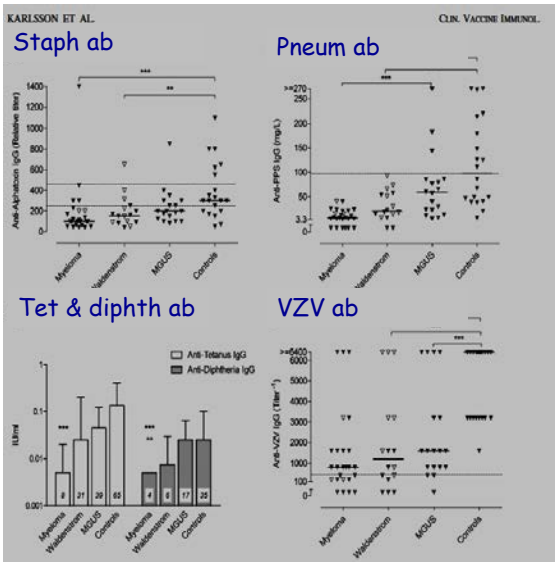
Secondary antibody deficiencies: Drugs, post-anti CD20 monoclonal abs, lymphoid malignancies

- Anticonvulsants – valproate, carbamezipine; **if no Imx responses + serious infection,** may need transient Ig if prophylactic antibiotics fail
- Rituximab – long-term outcome unclear. Some are slow to recover polyclonal responses ? Imx responses if serious/recurrent moderate infections; may need transient Ig – **data needed**
- Lymphoid malignancies:
  - Chronic lymphocytic leukaemia
  - Multiple myeloma
  - Monoclonal gammopathy of unknown significance – "MG without other features"

Lymphoid malignancies

- Not all patients need Ig – all depends on selection
- Those referred for rec / serious infections:
  1. Test Imx responses with protein and carbohydrate vaccines (as for PIDs)
  2. If low Igs and Imx failure, consider prophylactic antibiotics
  3. If infections persist/antibiotics contra-indicated, consider trial of Ig for 12 months and monitor infections
  4. Check neutrophils and trough IgG regularly
  5. Review Ig and dose if more chemotherapy considered

Imx responses in CLL, WM & myeloma patients:



24 different pathogens in elderly patients with MM (n=25), WM (n=16), and MGUS (n=18) and in age-matched controls (n=20).

Karlsson et al 2011

CLL – also variable; poor polysaccharide responses and poor to conjugate vaccine too

Sinisalo et al 2007

Guidelines for Ig in myeloma – no new data

- Randomized placebo-controlled study in **plateau-phase** patients IVIg 0.4 g/kg monthly for 1 year showed significant reductions in frequency and severity of infections, but **only in patients who responded poorly to pneumococcal immunization** *Chapel et al 1994*

- *Guideline for Supportive care in multiple myeloma.*

  'For those with repeated infectious complications, prophylactic measures i.e. **antibiotics, antivirals or IVIg is recommended** … and can significantly improve the wellbeing of myeloma patients in disease progression as well as remission."

  Ludwig and Zoier 2007

Myeloma and HSCTx Retrospective study from one centre
Prophylactic IVIg *during* autologous haemopoietic stem cell transplantation for multiple myeloma is not associated with reduced infectious complications
Blombery, et al 2011

Meta-analysis:
IVIg prophylaxis in CLL and MM: systematic review and meta-analysis.
"On the basis of the available data, IVIG cannot be recommended routinely for patients with CLL or MM with **hypogammaglobulinemia and/or recurrent infections and should be considered on individual basis**." *Raananai et al 2009*

Conclusions

- Regular immunoglobulin substitution should be considered in selected CLL & myeloma patients
- Those who suffer from recurrent infections……
- But not in those without any history of infectious complications …. ?
- So why not take Imx responses as the criteria – but need good age-matched healthy and disease controls
- When to test – at diagnosis. Cover chemotherapy and HSCTx with prophylactic abx?
- Meanwhile IgG levels are the best surrogate since prior infections depend on exposure and virulence of pathogen

Thank you to:

NIHR Oxford Biomedical Research Centre

EU funded 4th, 5th & 7th FP programmes

Primary Immunodeficiency Association
Jeffrey Modell Foundation

Baxter Healthcare, Biotest, Talecris. LFB

Research Co-ordinator
Mary Lucas

Oxford collaborators– Alex Rice, Smita Patel, Siraj Misbah, Niall Moore,

Collaborators for CVIDs: Czech Republic, Italy, UK, France, US, Sweden, Germany and Netherlands

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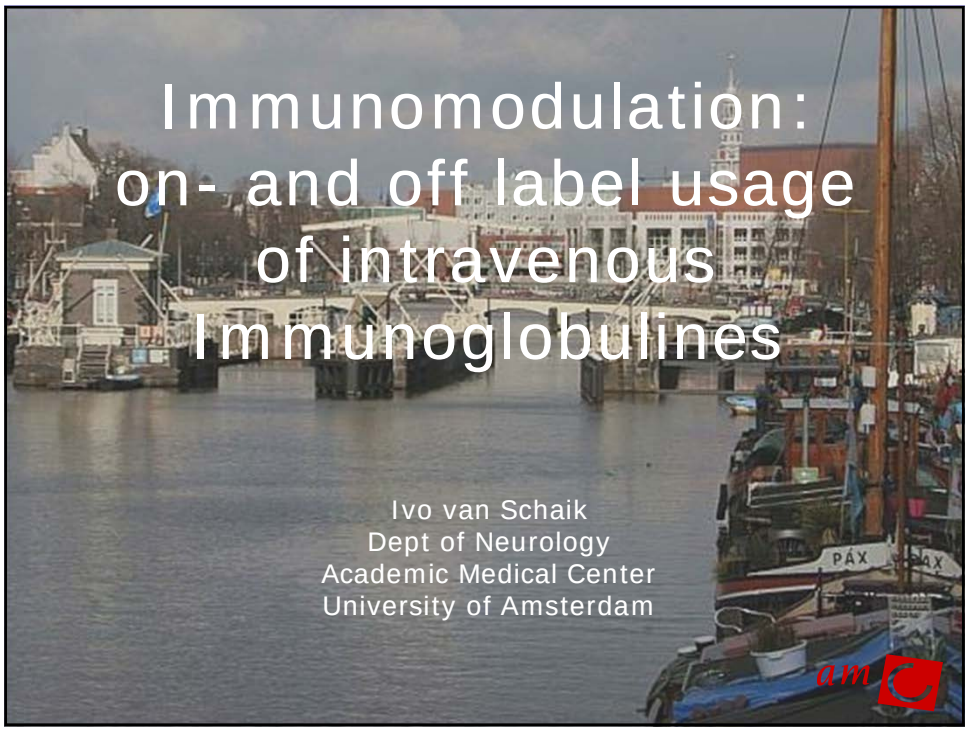


Important issues

- Where do we stand with on- and off label use
- Label: separate for each product or more generic
- Shortage
  - How should we rank priority in use
  - Alzheimer's disease
- IVIg versus SCIg
  - Safe, effective?
- What should get priority in research
  - Health technology assessments
  - Biomarkers
  - IgG levels

On label indications for IVIg

Established therapeutic role

- Guillain–Barré syndrome (GBS)
- Idiopathic thrombocytopenia purpura (adults/children)
- Kawasaki disease

- Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) (2 products)
- Multifocal Motor Neuropathy (MMN) (1 product)

off label indications for IVIg

Established therapeutic role

- Dermatomyositis/polymyositis
- Myasthenia gravis
- Lambert Eaton myasthenic syndrome
- Neonatal haemachromatosis
- Stiff person syndrome

off label indications for IVIg

Reasonable evidence for therapeutic role

- Acute disseminated encephalomyelitis (ADEM)
- Acute treatment of humoral rejection after solidorgan transplantation
- ANCA positive systemic vasculitis
- Autoimmune haemolytic anemia
- Evans syndrome = autoimmune haemolytic anemia with immunethrombocytopenia
- Foeto-maternal/neonatal alloimmune thrombocytopenia
- Haemophagocytic syndrome
- Idiopathic thrombocytopenia purpura (<16 years)
- IgM (IgA, IgG) MGUS and Anti-myelin-associated glycoprotein (MAG) neuropathy
- Immunobullous diseases (dermatology)
- Multipele sclerosis
- Opsoclonus myoclonus ataxie
- Neuromyotonia
- Post transfusion purpura
- Toxic epidermal necrolysis and Stevens-Johnson syndrome
- Toxic shock syndrome

off label indications for IVIg

Class IV evidence only

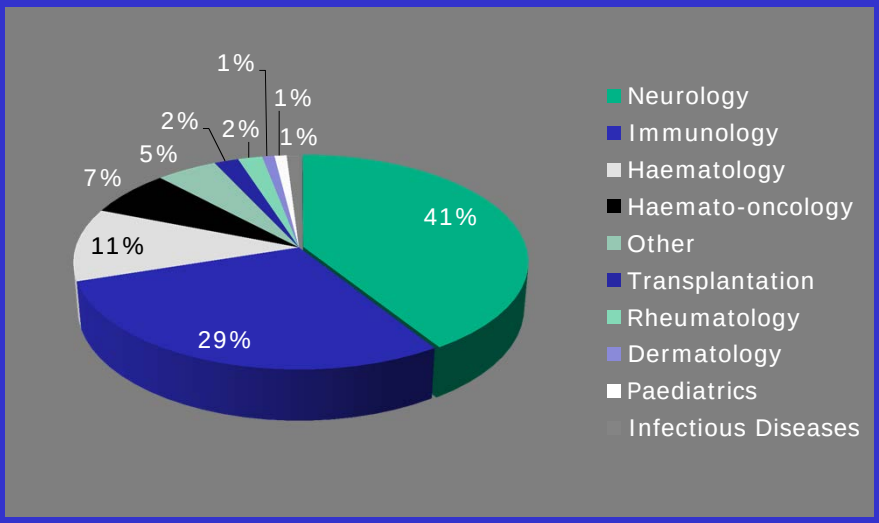
- Acute leukaemia in children
- Alzheimer's disease
- Autoimmune congenital heart block
- Autoimmune neutropenia
- Autoimmune uveitis
- Catastrophic antiphospholipid syndrome
- Coagulation factors inhibitors (acquired haemophilia)
- Devic disease (NMO, aquaporin-4 antibody disease)
- Intractable childhood epilepsy
- Graves Ophtalmopathy
- Haemolytic disease of the newborn
- Hashimoto encephalopathy
- HIV in children
- Myocarditis in children
- Limbic encephalitis (nonparaneoplastic, potassium channel antibody mediated)
- PANDAS = paediatric autoimmune neuropsychiatric disorder associated with streptoccocal infections
- Paraneoplastic syndromes: POEMS, subacute sensory neuronopathy, cerebellar degeneration, limbic encephalitis
- Pure red cell aplasia
- Pyoderma gangrenosum
- Scleromyxedema
- Sjogren's syndrome
- Solid organ transplantation
- Susac syndrome (CNS vasculitis)
- Systemic capillary leak syndrome and sepsis

off label indications for IVIg

At present no supportive evidence

- Acute optic neuritis
- Atopic dermatitis/eczema
- Haemolytic uraemic syndrome
- HIV/AIDS in adults
- Recurrent foetal loss (with and without antiphospholipid syndrome)
- Systemic lupus erythematosus (SLE)

Volume of IVIg used for each specialism



Second National Immunoglobulin Database Report (2010–2011) NHS

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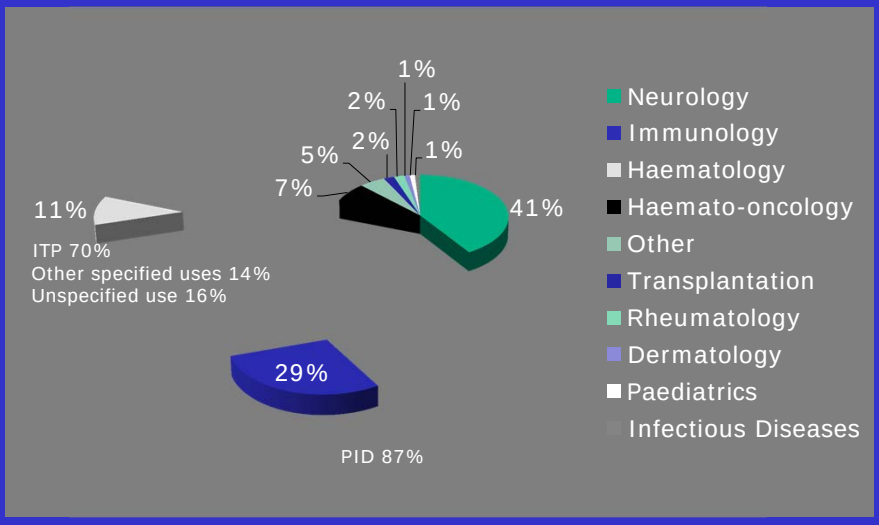
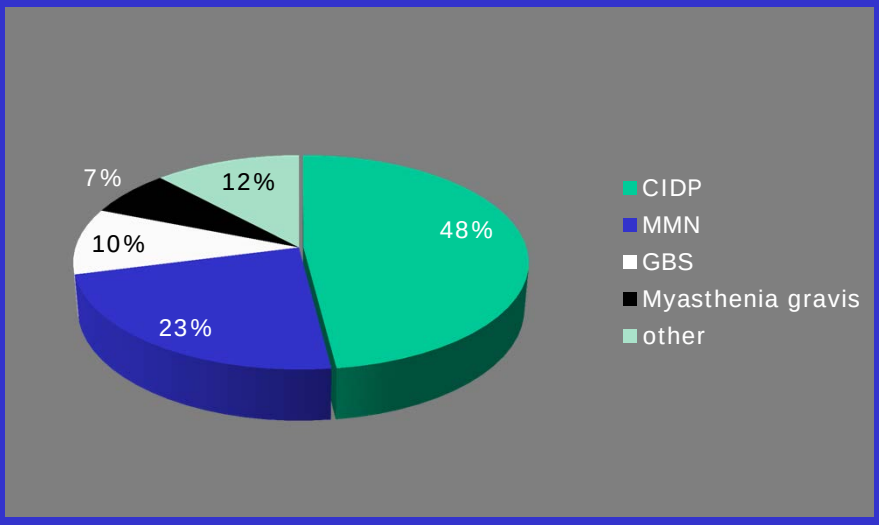


Second National Immunoglobulin Database Report (2010–2011) NHS

Volume of IVIg used in specific neurologic conditions



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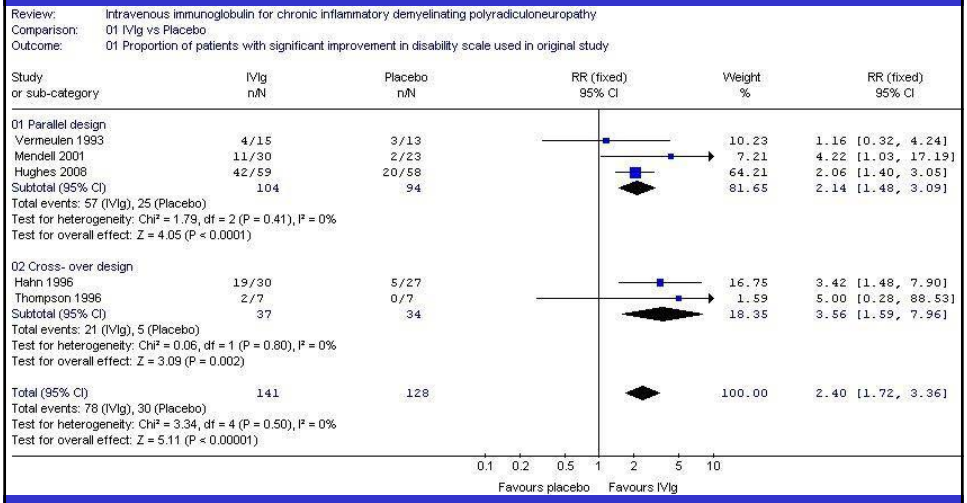
Systematic review IVIg (2)



Absolute risk difference	32% (95% CI 21 to 43)
Number needed to treat	3 (95% CI 2.3 to 4.8)

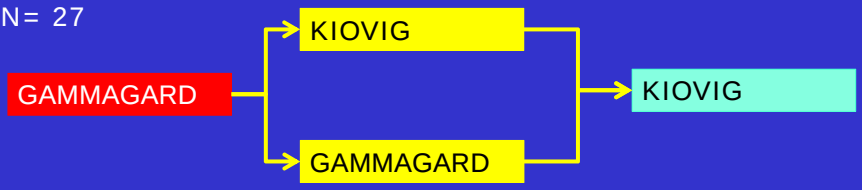
Research paper

Randomised controlled trial comparing two different intravenous immunoglobulins in chronic inflammatory demyelinating polyradiculoneuropathy

K Kuitwaard,[1] L H van den Berg,[2] M Vermeulen,[3] E Brusse,[1] E A Cats,[2] A J van der Kooi,[3] N C Notermans,[2] W-L van der Pol,[2] I N van Schaik,[3] S I van Nes,[1] W C J Hop,[4] P A van Doorn[1]

J Neurol Neurosurg Psychiatry 2010;81:1380-1381.

N= 27



This trial demonstrated equal clinical efficacy between a freeze-dried and a liquid IVIg preparation for maintenance treatment of CIDP

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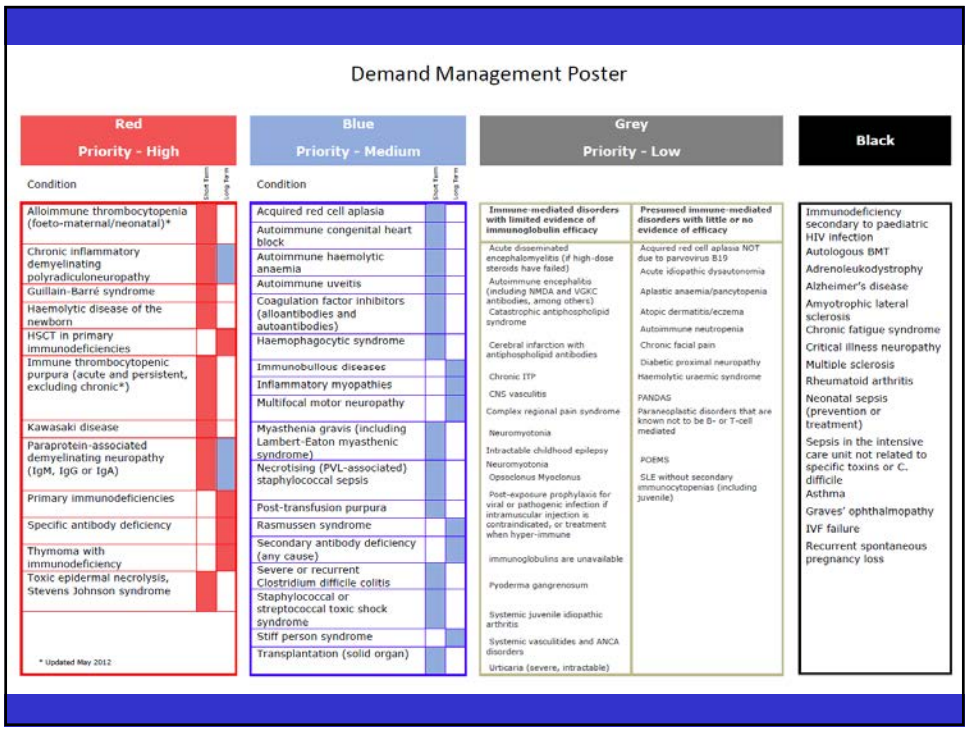
- Label: separate for each product or more generic
- Shortage
  - How should we rank priority in use
  - Alzheimer's disease
- IVIg versus SCIg
  - Safe, effective?
- What should get priority in research
  - Health technology assessments
  - Biomarkers
  - IgG levels



IVIg for Alzheimer's disease

- 3 small clinical trials in mild-to-moderate AD
- one uncontrolled trial
  - N=5, 1·2 g/kg IVIg every 4 weeks for 6 months
  - concentration of total Aβ decreased in CSF and increased in blood compared with baseline
  - patients had no cognitive deterioration
- another uncontrolled trial
  - N=8, 0·4–2·0 g/kg per month for 6 months
  - Same results
- one placebo-controlled (saline) multiple dose study
  - N=24, 0·2 g/kg or 0·4 g/kg once every 2 weeks or 0·4 g/kg or 0·8 g/kg per month for 6 months
  - 0·4 g/kg every 2 weeks treatment group had the best outcome
  - no decline in cognitive and functional measures

Intravenous immunoglobulin for treatment of mild-to-moderate Alzheimer's disease: a phase 2, randomised, double-blind, placebo-controlled, dose-finding trial

Richard Dodel, Axel Rominger, Peter Bartenstein, Frederik Barkhof, Kaj Blennow, Stefan Förster, Yaroslav Winter, Jan-Philipp Bach, Julius Popp, Judith Alferink, Jens Wiltfang, Katharina Buerger, Markus Otto, Piero Antuono, Michael Jacoby, Ralph Richter, James Stevens, Isaac Melamed, Jerome Goldstein, Stefan Haag, Stefan Wietek, Martin Farlow, Frank Jessen

Lancet Neurol 2013; 12: 233–43

- N= 58
- Safe tolerability and good
- no effect on concentration of Aβ1-40, except for 0·4 g/kg/2wk
- effect in favour of placebo for the clinical dementia rating score
- The decrease across all treatment groups was much the same as the decrease in the natural course of Alzheimer's
- Study limitations:
  - small size of each treatment group
  - large variations in disease trajectories
  - duration of 6 months
  - too advanced disease
- not possible to rule out that IVIg might not be effective in AD
- Longer studies with larger N needed

Important issues

- Where do we stand with on- and off label use
- Label: separate for each product or more generic
- Shortage
  - How should we rank priority in use
  - Alzheimer's disease
- IVIg versus SCIg
  - Safe, effective?
- What should get priority in research
  - Health technology assessments
  - Biomarkers
  - IgG levels

Why is ScIg interesting?

- IgG peak levels will be lower, trough levels higher
  - a more constant IgG level
  - reduced wearing off
- Improve quality of life
  - Patient autonomy, self administration in home setting
  - No need for venous access
  - Reduced hospitalisation
  - No need for health care personnel
- Improved side effect profile
  - less and less severe systemic side effects
- Lower cost

- Problems
  - Volumes to be administered sc
  - Local side effects
  - Frequency of administration

SCIg in CIDP and MMN

	CIDP	MMN
Köller, J Neurol 2006	1	2
Lee, Muscle & Nerve 2008	2	
Magy, J Peripher Nerv Syst 2008	15	
Eftimov, J Peripher Nerv Syst 2009		10
Harbo, Eur J Neurol 2009		9
Harbo, Neurology 2010		(5) + 1
Dacci, Neurol Sci 2010		(1)
Cocito, J Peripher Nerv Syst 2011	5	
Misbah, J Peripher Nerv Syst 2011		8
Total	23	30

SCIg in CIDP

	Good outcome	Preference for SC	remark
Köller, 2006	1/1	1/1	Oral steroids ↓; FU 6 months
Lee, 2008	2/2	-	Mycophenolate; FU 8 months & 2 years
Magy, 2008	13/15	-	Extremely low dose, abstract, not published, FU 13 weeks
Cocito, 2011	5/5	4/5	6 months
Total	21/23	5/6	

Conflicts of interest

- PATH trial (CSL-Behring)
  - Chair of steering committee

Important issues

- Where do we stand with on- and off label use
- Label: separate for each product or more generic
- Shortage
  - How should we rank priority in use
  - Alzheimer's disease
- IVIg versus SCIg
  - Safe, effective?
- What should get priority in research
  - Health technology assessments
  - Biomarkers
  - IgG levels

Is IVIg cost-effective in CIDP?

Blackhouse *et al. Cost Effectiveness and Resource Allocation* 2010, **8**:14
http://www.resource-allocation.com/content/8/1/14

COST EFFECTIVENESS AND RESOURCE ALLOCATION

RESEARCH Open Access

Cost-utility of Intravenous Immunoglobulin (IVIG) compared with corticosteroids for the treatment of Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) in Canada

Gord Blackhouse*[1,2], Kathryn Gaebel[1,3], Feng Xie[1,2,3], Kaitryn Campbell[1,2], Nazila Assasi[1,2], Jean-Eric Tarride[1,2,3], Daria O'Reilly[1,2,3], Colin Chalk[4], Mitchell Levine[2,3] and Ron Goeree[1,2,3]

Biomarkers for disease activity and predicting response

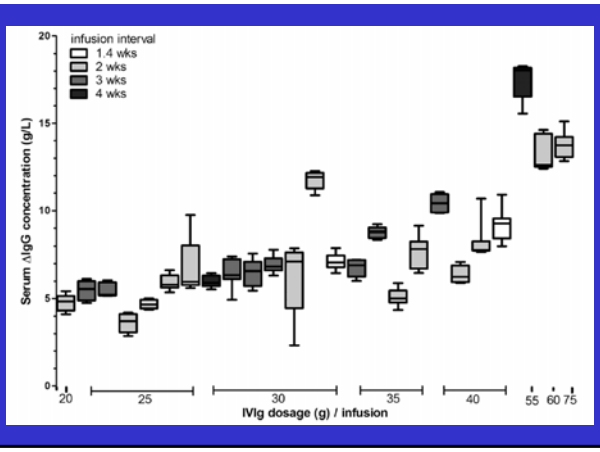
- Association between IVIg responsiveness and a single nucleotide polymorphism (SNP) corresponding to transient axonal glycoprotein 1 (TAG-1)
  - Iijima M., et al. Single nucleotide polymorphism of TAG-1 influences IVIg responsiveness of Japanese patients with CIDP. Neurology 2009;73(17):1348-1352
- Treg numbers increased to normal levels after IVIg treatment in GBS; no results for CIDP
  - Chi LJ., et al. Abnormality of circulating CD4(+)CD25(+) regulatory T cell in patients with GBS. J Neuroimmunology 2007;192(1-2),206-214
- IVIg dose dependent decline of number and cytotoxic function of NK-cells
  - Bohn AB., et al. The effect of IgG levels on the number of natural killer cells and their Fc receptors CIDP. European J Neurol. 2011;18(6):919-924

J Neurol Neurosurg Psychiatry 2013 Neuromuscular

SHORT REPORT

Serum IgG levels in IV immunoglobulin treated chronic inflammatory demyelinating polyneuropathy

Krista Kuitwaard,[1] Pieter A van Doorn,[1] Marinus Vermeulen,[2] Leonard H van den Berg,[3] Esther Brusse,[1] Anneke J van der Kooi,[2] W-Ludo van der Pol,[3] Ivo N van Schaik,[2] Nicolette Notermans,[3] Anne P Tio-Gillen,[1,4] Wouter van Rijs,[1,4] Teun van Gelder,[5] Bart C Jacobs[1,4]



Important issues

- Where do we stand with on- and off label use
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  - How should we rank priority in use
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  - Safe, effective?
- What should get priority in research
  - Health technology assessments
  - Biomarkers
  - IgG levels

Wildbad Kreuth III
Optimal Use of Immunoglobulins
A Regulator's Perspective

DISCLAIMER
Any opinions/recommendations presented are my own and
do not necessarily reflect those of any official body

What is optimal use?

Diagnostic GL

Diagnosis uses <5% of hospital costs,
but influences 60% of decision making

CEBM Oxford, 2013, Mathew Thompson

Therapy GL

Symptomatic, curative, prophylactic,
1st, 2nd, 3rd line

Product

Directive 2002/98/EC
Ph. Eur. Monographs

Investigational GL
B/R

HTA GL
REA

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Investigational GLs

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000388.jsp&mid=WC0b01ac0580032ec8

22 July 2010
EMA/CHMP/BPWP/94033/2007 rev. 2
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg)

15 November 2012
EMA/CHMP/BPWP/410415/2011 rev 1
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the clinical investigation of human normal immunoglobulin for subcutaneous and/or intramuscular administration (SCIg/IMIg)
Draft

Deadline for comments: 3rd June 2013

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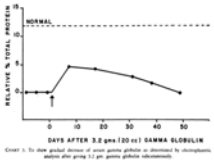
What evidence suffices?

James Lind (1716 – 1794)
Scottish military surgeon
1st RCT → cure for scurvy

Col. Ogden Bruton (1908 – 2003)
US military
1952 discovery + treatment of agammaglobulinemia based on one case followed over 5 years



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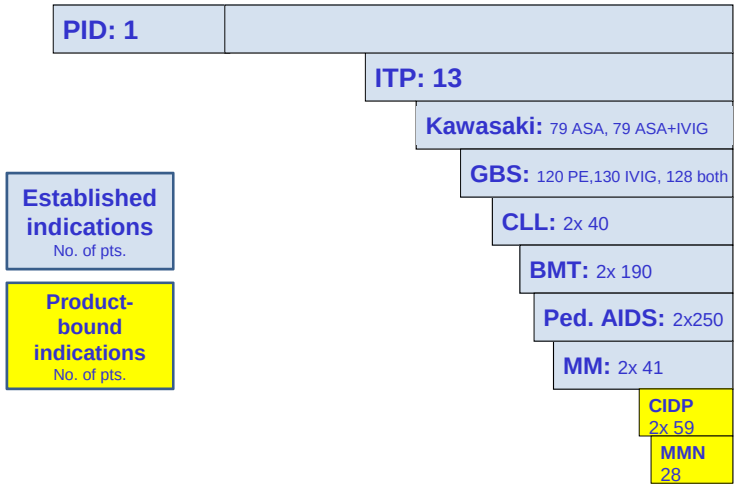
History of Authorised Indications



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Off-label = not optimal

Alzheimer's Disease / Inflammatory myopathies / Lambert–Eaton myasthenic syndrome /Myasthenia gravis / Neonatal haemochromatosis / Stiff person syndrome / Anti-neutrophil cytoplasmic antibody (ANCA)-positive systemic necrotising vasculitis / Autoimmune haemolytic anaemia (AIHA) / Bullous pemphigoid , Pemphigus foliaceus (PF) and Pemphigus vulgaris (PV) / Cicatricial pemphigoid (CP) or mucous membrane pemphigoid (MMP) / Evans syndrome - autoimmune haemolytic anaemia (AIHA) with immune thrombocytopenia / Foeto-maternal/neonatal alloimmune thrombocytopenia / Haemophagocytic syndrome / IgM paraproteinaemic neuropathy / Acute antibody-mediated rejection and steroid-resistant rejection following solid organ transplantation / Multiple sclerosis / Opsoclonus myoclonus ataxia / Post-transfusion purpura / Toxic epidermal necrolysis / Toxic shock syndrome / Acute leukaemia in children / Autoimmune congenital heart block / Autoimmune neutropenia / Autoimmune uveitis / Catastrophic antiphospholipid syndrome / Coagulation factor inhibitors / Devic disease (neuromyelitis optica) / Intractable childhood epilepsy, Rasmussen syndrome / Graves ophthalmopathy / Haemolytic disease of the newborn / Hashimoto encephalopathy / HIV in children / Myocarditis in children / Limbic encephalitis /Paediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS) / Pure red cell aplasia / Pyoderma gangrenosum / Scleromyxedema / Sjogren's syndrome / Susac syndrome / Systemic capillary leak syndrome (SCLS) and Sepsis

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Off-label = not optimal

- *The off-label use of IVIG has dramatically increased during the past 10 years, although for most of these autoimmune and inflammatory diseases well-controlled clinical trials are missing and much of the rationale for using IVIG under these circumstances is based on case studies.*
- Schwab, Nimmerjahn, nature.com/reviews/immunol MARCH 2013 | VOLUME 13

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History of revision of IVIG GL

2001 PEI optimal use conference
2004 BPWP discussions
2005 Concept Paper
2006 EMA Workshop
2007 Workshop Report
2008 Revision
2009 Stakeholders Meeting
2010 Publication
2011 Effective

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Columns of evidence

Product compliance with relevant Ph. Eur monographs

PK, efficacy and safety in PID and ITP → Established indications

Data on new indications

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1. Harmonize PID Guidance with FDA ? Mostly

40 - 50 PID pts. (20 children)
12 months duration
1°: SBI < 1/pt./y
2°: IgG trough levels, days off school/work, other infections, antibiotics, hospitalisations
PK in 20 adult PID patients
Safety: TEAEs

2. Update ITP model ? Yes

Rodeghiero, Blood, 3/**2009**; 113:11; 2386-2393
Standardization of terminology, definitions and outcome criteria in ITP of adults and children: report from an international working group

3. Paediatric update ? Not really

No new efficacy data for "established indications"
Include adolescents in congenital AIDs
Extrapolation from adult data for paediatric CIDP, MG and GBS

Paediatric WS 2011 for IVIGs, SCIGs/IMIGs
8 MAHs: 41 studies
→ no major differences in AEs between adults + children

4. Take on board new indications ?

Well, sort of...

Published literature indicates a positive effect of IVIgs in particular in MMN, CIDP, and MG exacerbations

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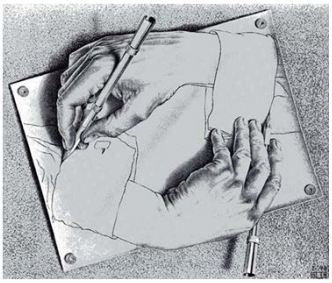
GL finished?



- CIDP, MMN = „established“ indications ?
- New indications? How many trials/brands are necessary?
- How can one most beneficially use existing evidence?
- Should priorities be set? If so, by whom?

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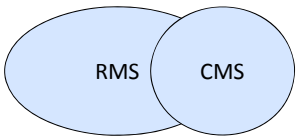
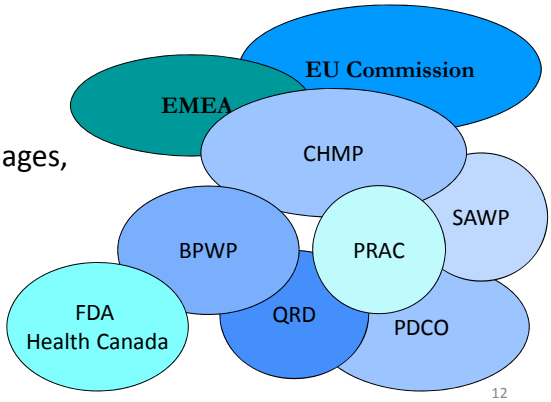
Regulatory development

1999:
10% IVIG clinical AR 14 pages



2013:
SCIG clinical AR 300 pages,
380 emails



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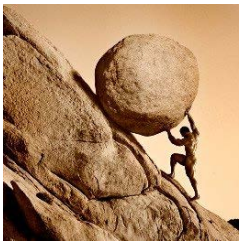
Outlook

Industry should perform studies together

Trial designs should use the existing data

Agencies should co-operate
to simplify regulation

If new indications were to pose threats to
supply – how should we prioritize indications?



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Kreuth III

The UK Immunoglobulin Demand Management Plan

W A Carrock Sewell

Path Links Immunology | University of Lincoln
Centre for Immunoglobulin Therapy

carrocksewell@nhs.net
www.immunoglobulin-therapy.org

Thanks

- Department of Health
- IVIG Advisory Panel
- MD-SAS

Dr Rob Hollingsworth
Head of NHS Medical Data Solutions and Services (MDSAS)
The Works Business Centre
Manchester M12 4JD

Tel. No.: 0161 277 7917
Email: rob.hollingsworth@nhs.net

- Note: My *personal* view only

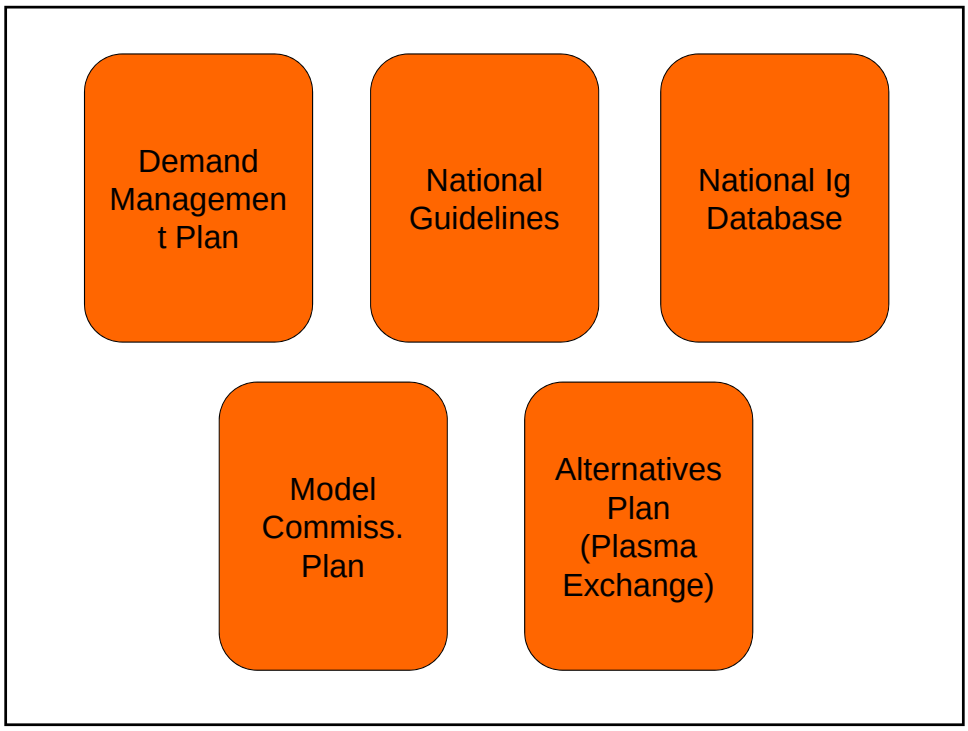
www.ivig.nhs.uk

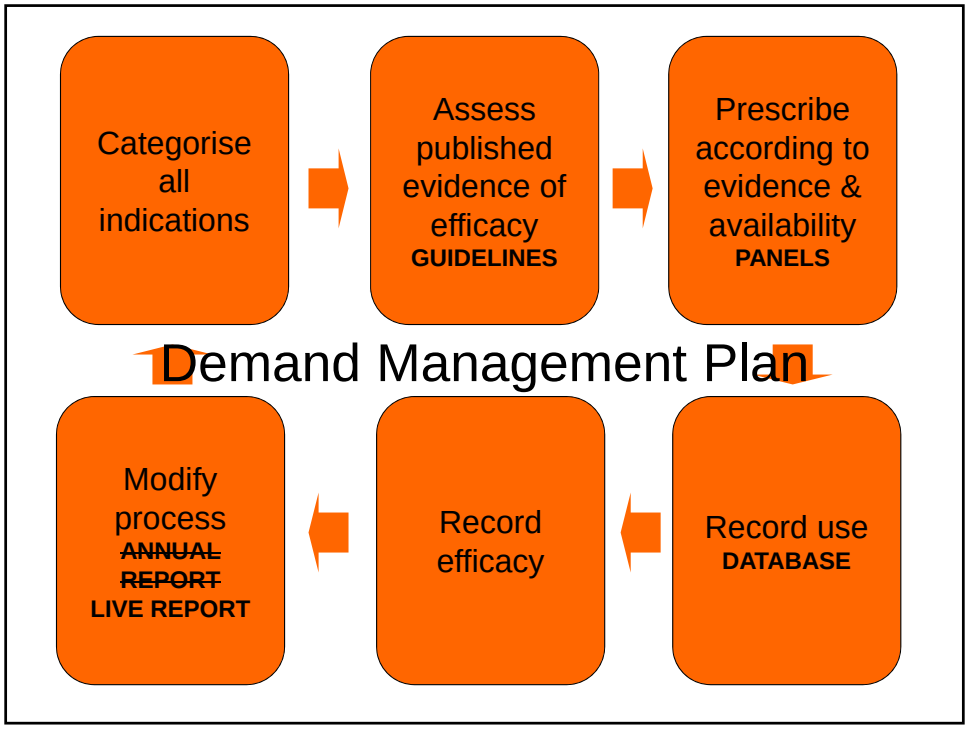
Baxter: Gammagard • HCV

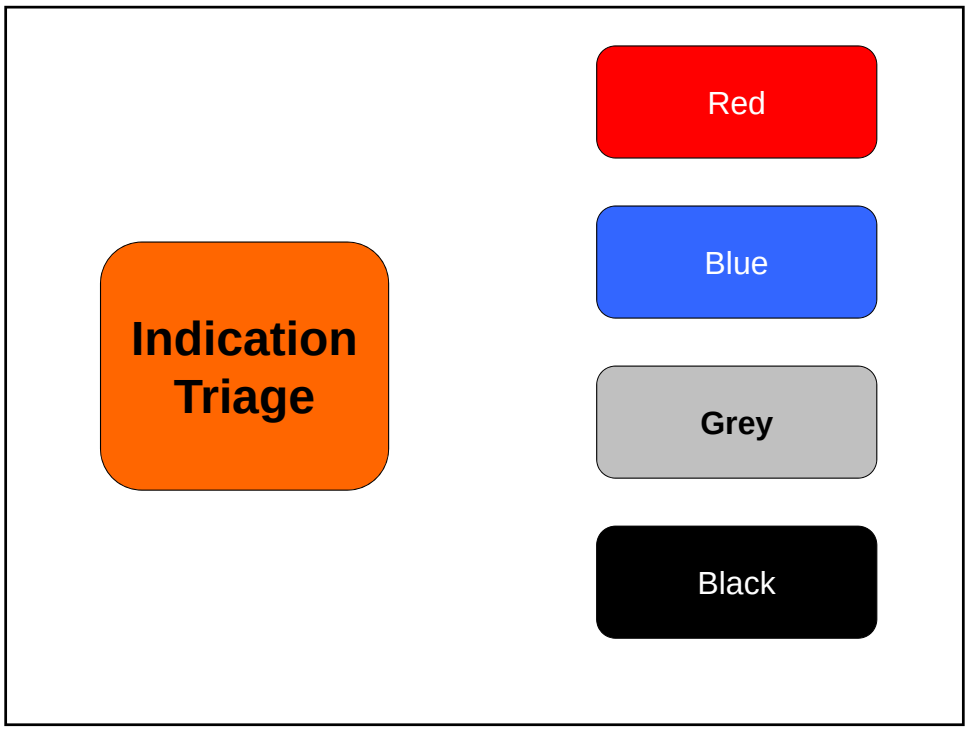
BPL • vCJD • No UK IVIG

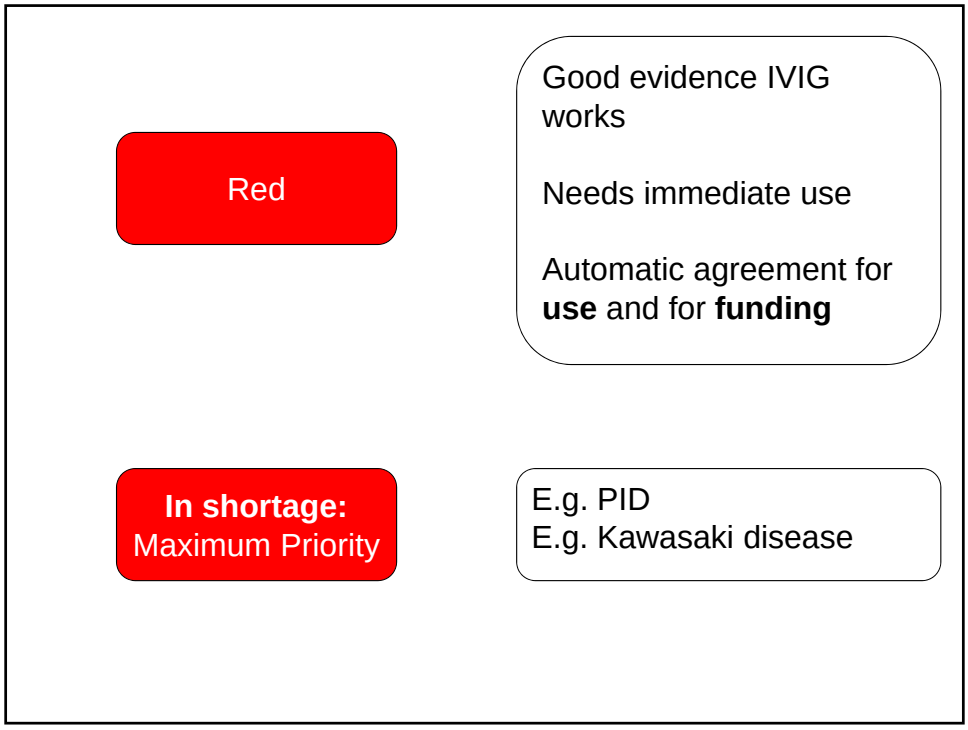
Various: Zero availability

UK = vulnerable


Demand Management Plan
National Guidelines
National Ig Database
Model Commiss. Plan
Alternatives Plan (Plasma Exchange)

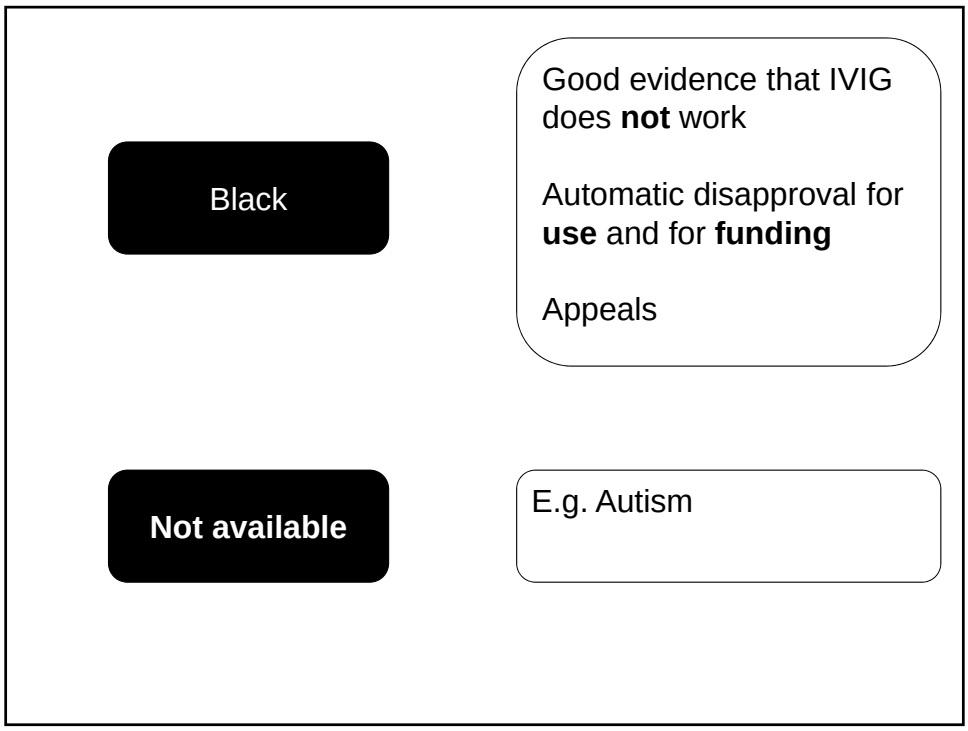

Categorise all indications
Assess published evidence of efficacy
GUIDELINES
Prescribe according to evidence & availability
PANELS
Demand Management Plan
Modify process
~~ANNUAL REPORT~~
LIVE REPORT
Record efficacy
Record use
DATABASE


Indication Triage
Red
Blue
Grey
Black

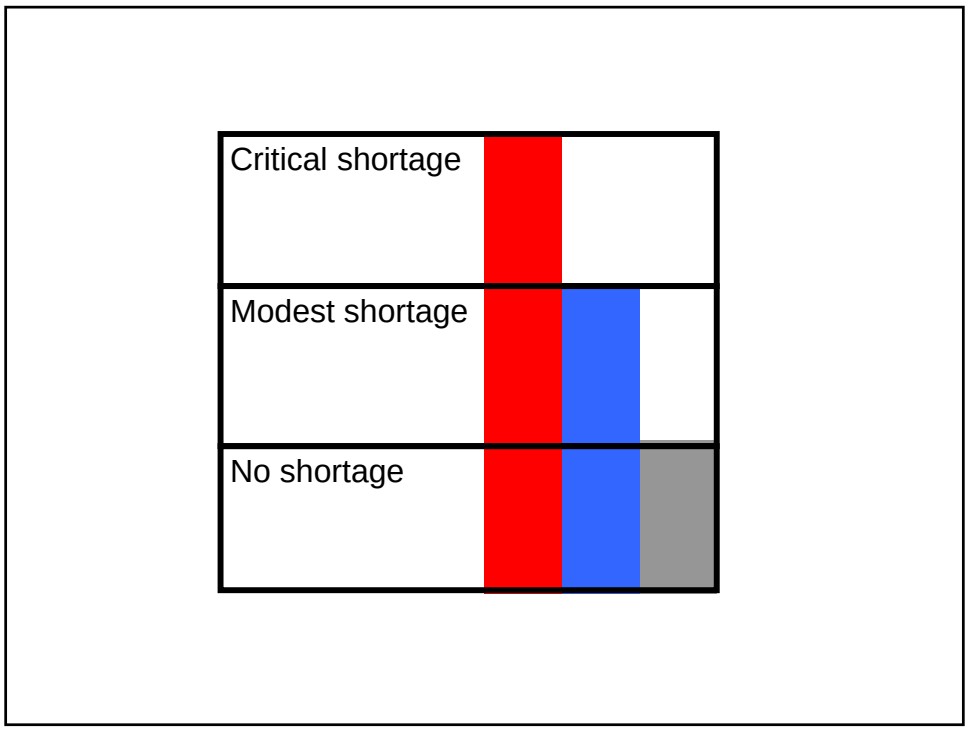

Red
Good evidence IVIG works
Needs immediate use
Automatic agreement for use and for funding
In shortage: Maximum Priority
E.g. PID
E.g. Kawasaki disease

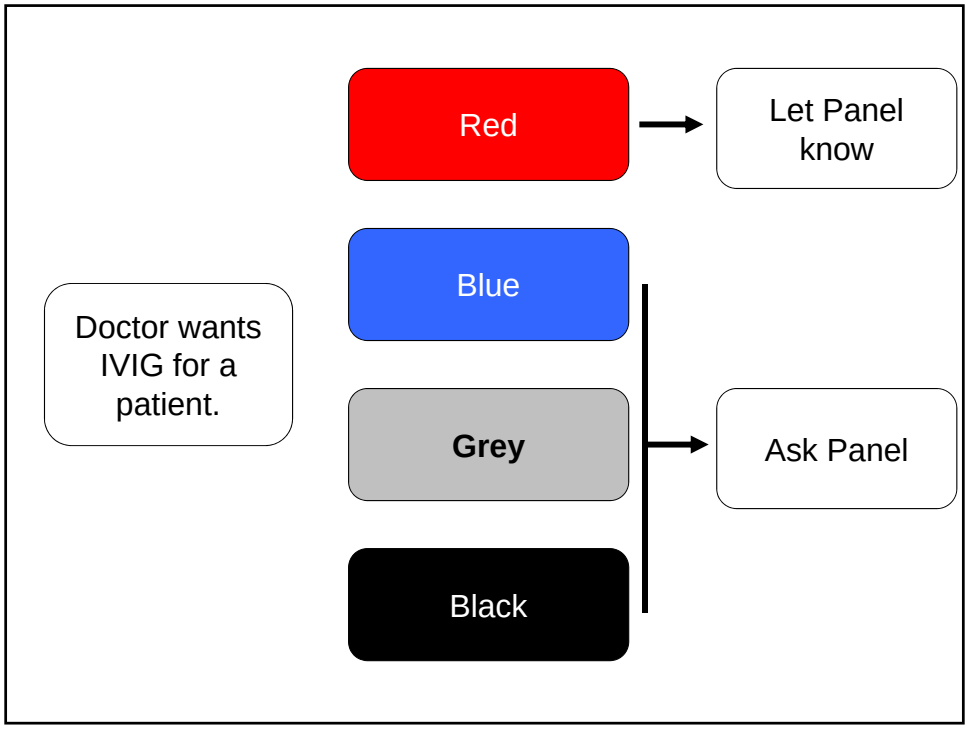
Blue	Good evidence IVIG works in **selected cases** but other drugs may be better. Automatic agreement for **use** and for **funding,** **IF PANEL AGREES**
In shortage: Medium Priority	E.g. Some neuropathies

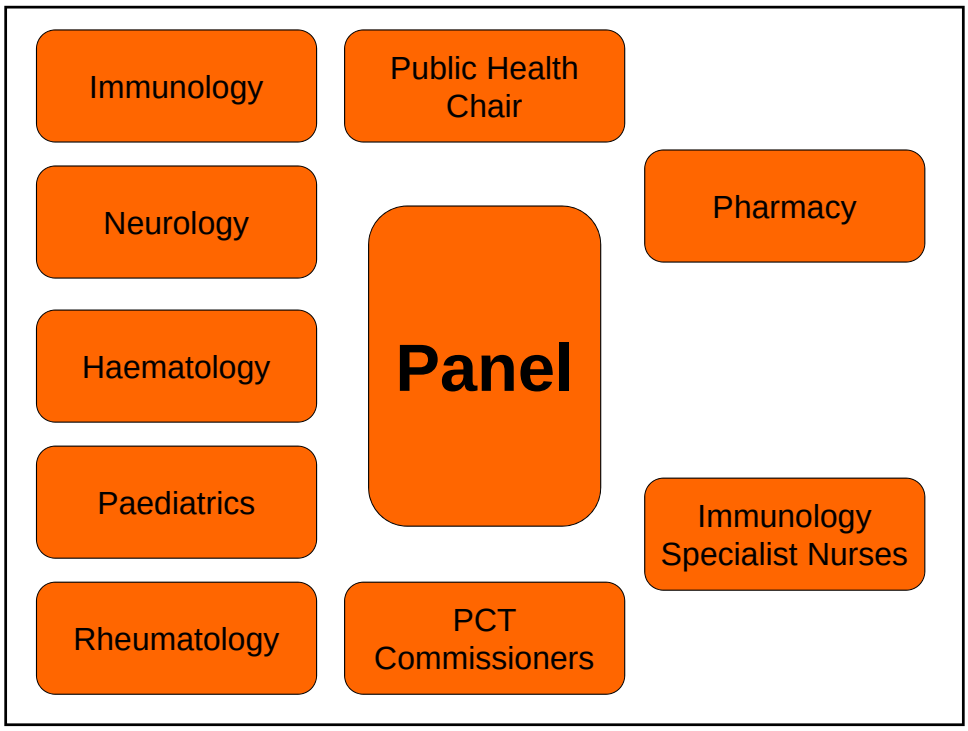
Grey	Some evidence IVIG works, or disease very rare, or not listed Panel has to approve **use** and PCT has to agree **funding**
In shortage: Lowest Priority	E.g. vasculitis

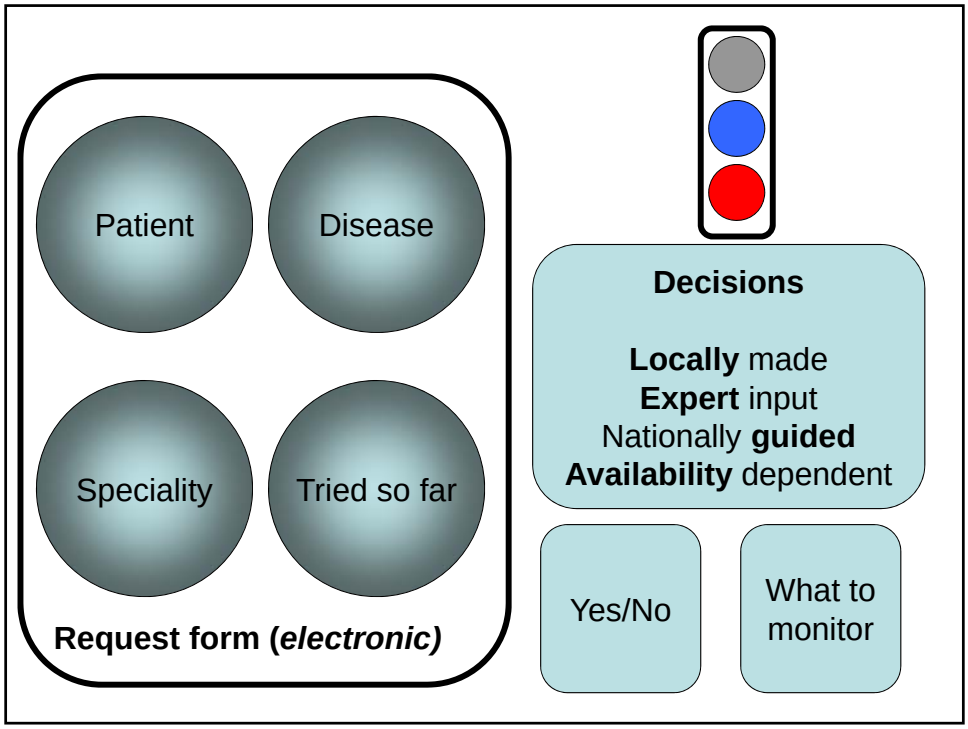


Condition	Treatment		Recommendation, evidence grade*
	Short term	Long term	
Immunology			
Impaired specific antibody production	No	Selected	C, III
Kawasaki disease	Yes	No	A, Ia
Primary immunodeficiencies	selected	Yes	B, IIb
Haematology			
Acquired red cell aplasia caused by parvovirus B19	Selected	No	C, III
Adult HIV-associated thrombocytopenia	Selected	No	A, Ib
Alloimmune thrombocytopenia – fetal therapy (treatment to the mother)	Yes	No	C, III
Alloimmune thrombocytopenia – neonatal therapy	Selected	No	C, III
Autoimmune (acquired) haemophilia	Selected	No	C, III
Autoimmune haemolytic anaemia	Selected	No	C, III
Autoimmune thrombocytopenia (see ITP)	Selected	No	A, Ia
Evans' syndrome	Selected	No	C, III
Haemolytic disease of the fetus and newborn (isoimmune haemolytic jaundice in neonates)	Selected	No	C, III
Haemophagocytic lymphohistiocytosis/ haemophagocytic syndrome	Selected	No	C, III
Idiopathic thrombocytopenic purpura – paediatric (<16 years)	Selected	No	A, Ib
Idiopathic thrombocytopenic purpura – adult	Selected	No	A, Ia
Post transfusion purpura	Selected	No	C, III


Critical shortage
Modest shortage
No shortage


Red
Let Panel know
Blue
Doctor wants IVIG for a patient.
Grey
Ask Panel
Black


Immunology
Public Health Chair
Neurology
Pharmacy
Haematology
Panel
Paediatrics
Immunology Specialist Nurses
Rheumatology
PCT Commissioners


Patient
Disease
Speciality
Tried so far
Request form (electronic)
Decisions
Locally made
Expert input
Nationally guided
Availability dependent
Yes/No
What to monitor

Local decision

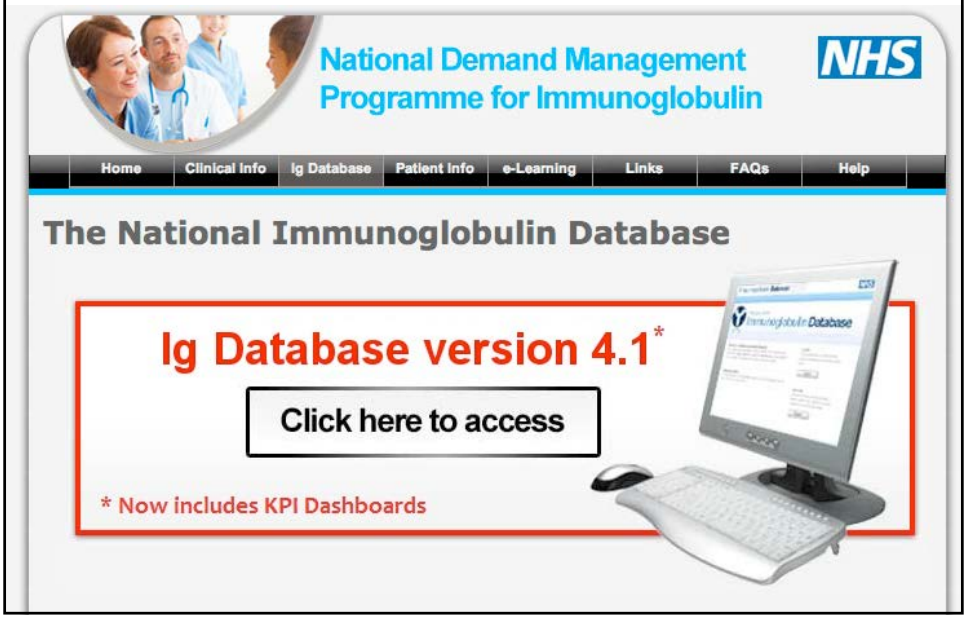
Non-compliance?

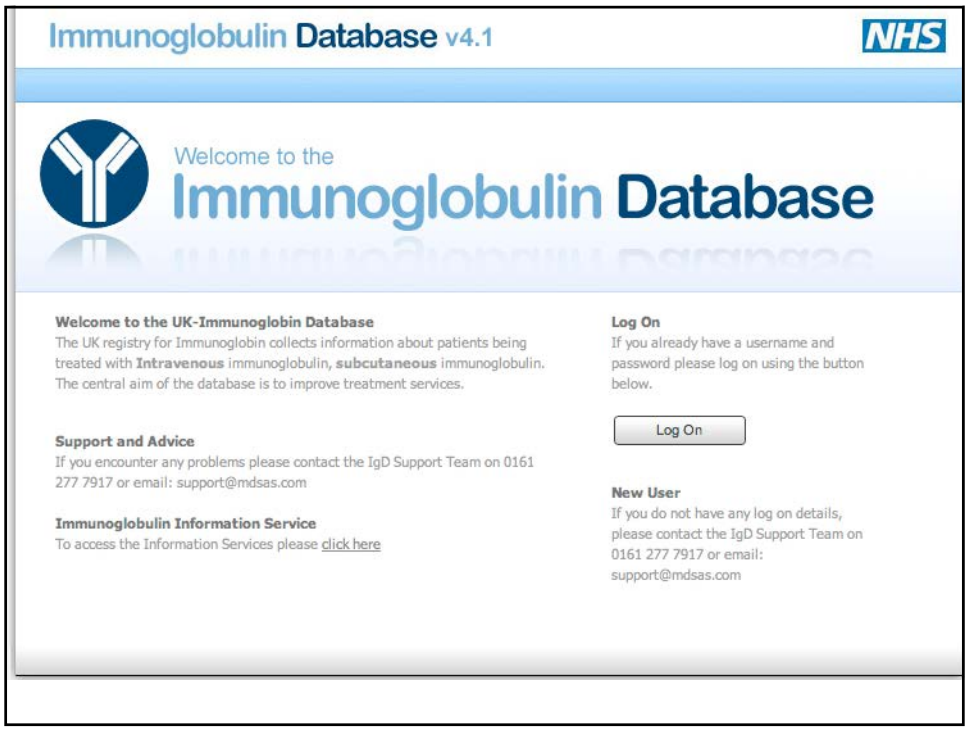
€

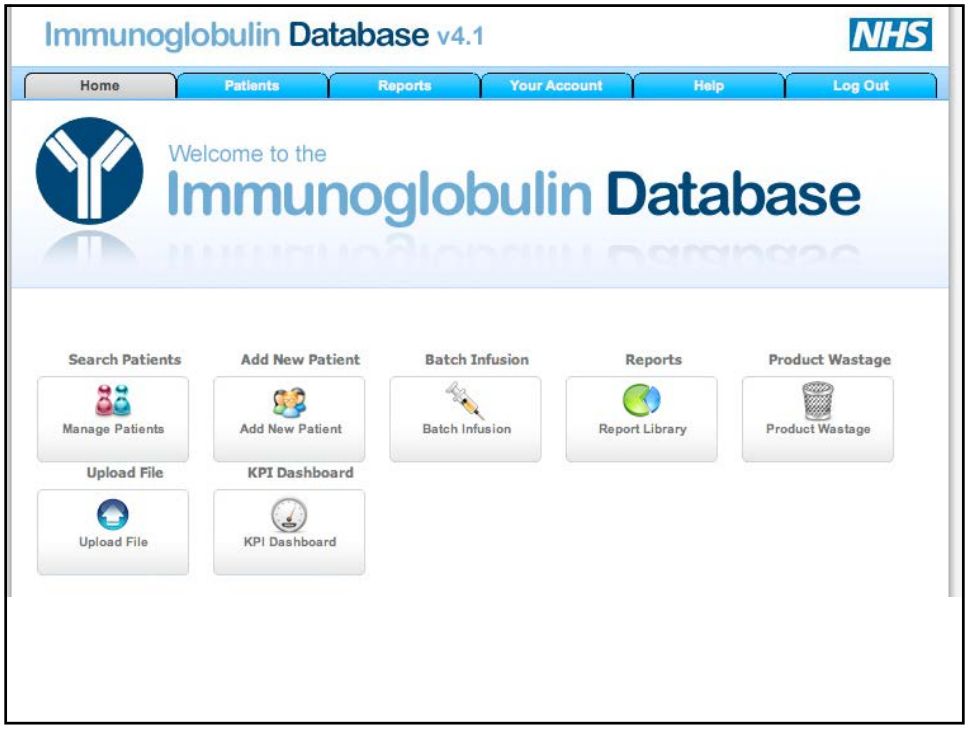
"Variable supply, high product costs, and an increasing demand for both established and off-label indications have made the Department of Health's development of a management programme for intravenous immunoglobulin use in the United Kingdom essential."

Fitzharris P, Hurst M. *BMJ* 2008; 337:a1851

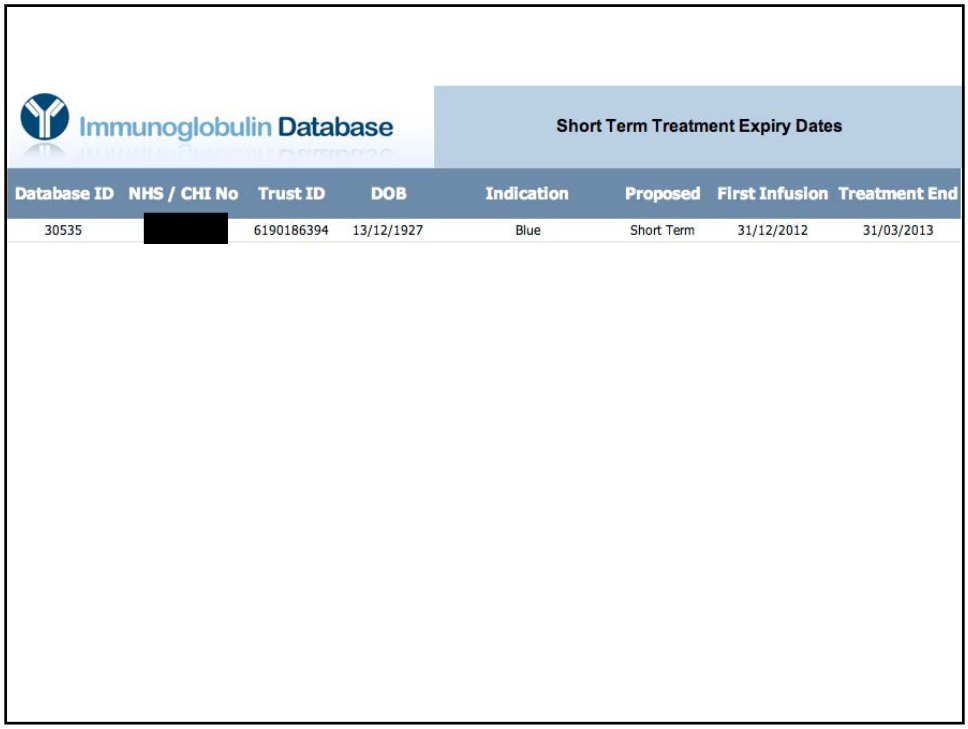
www.ivig.nhs.uk

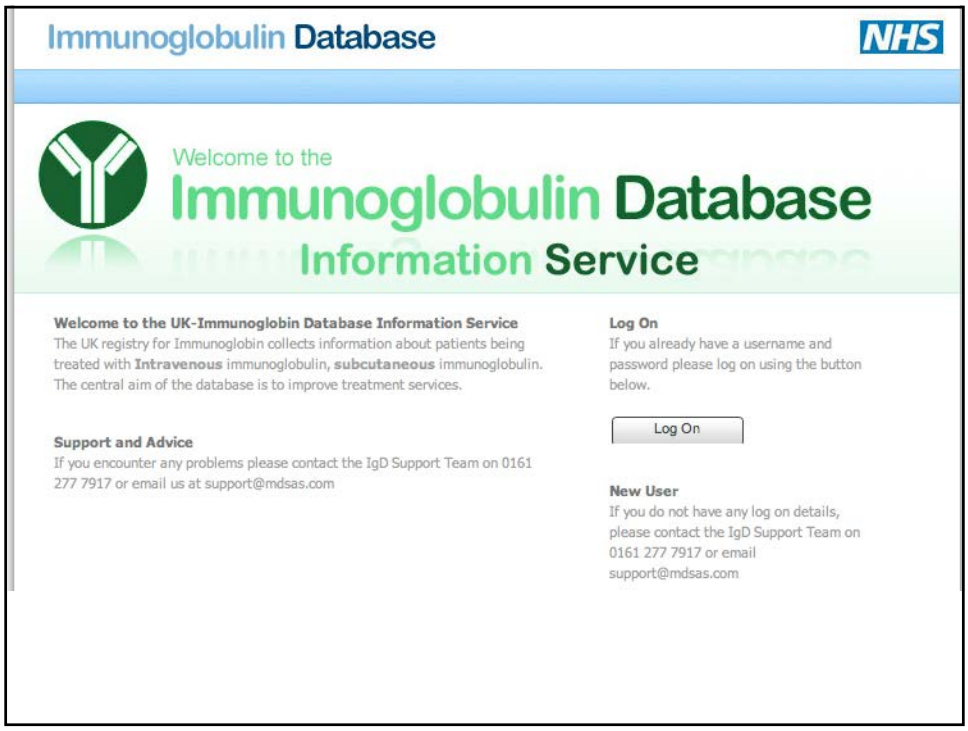


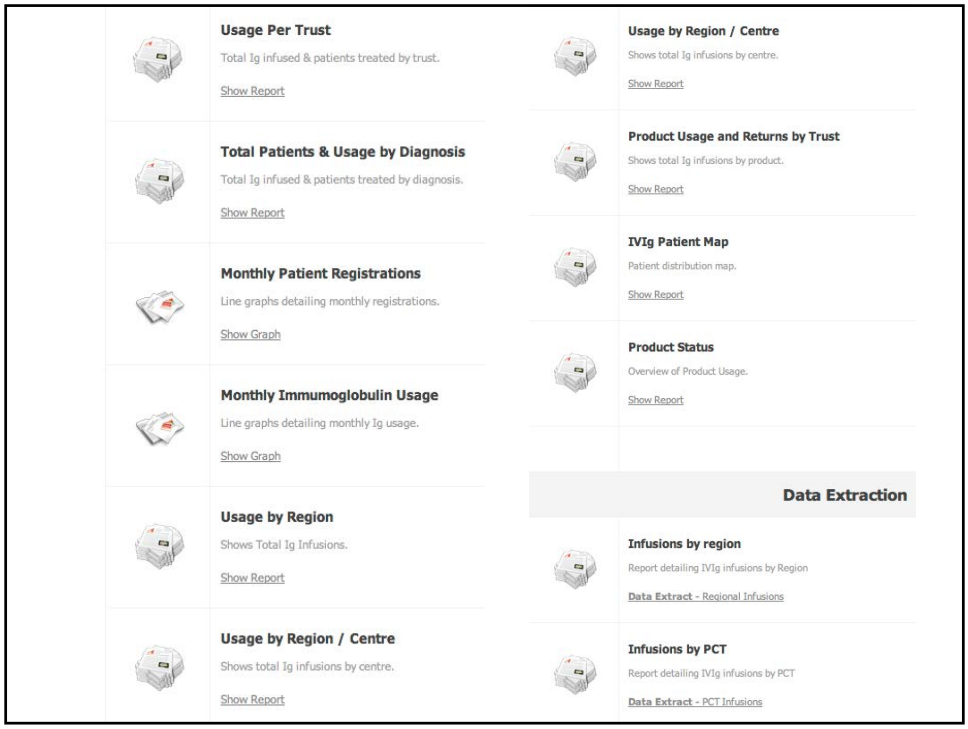

Immunoglobulin Database v4.1
NHS
Welcome to the
Immunoglobulin Database
Welcome to the UK-Immunoglobin Database
The UK registry for Immunoglobin collects information about patients being treated with Intravenous immunoglobulin, subcutaneous immunoglobulin. The central aim of the database is to improve treatment services.
Support and Advice
If you encounter any problems please contact the IgD Support Team on 0161 277 7917 or email: support@mdsas.com
Immunoglobulin Information Service
To access the Information Services please click here
Log On
If you already have a username and password please log on using the button below.
Log On
New User
If you do not have any log on details, please contact the IgD Support Team on 0161 277 7917 or email: support@mdsas.com


Immunoglobulin Database v4.1
NHS
Home
Patients
Reports
Your Account
Help
Log Out
Welcome to the
Immunoglobulin Database
Search Patients
Manage Patients
Add New Patient
Add New Patient
Batch Infusion
Batch Infusion
Reports
Report Library
Product Wastage
Product Wastage
Upload File
Upload File
KPI Dashboard
KPI Dashboard


Immunoglobulin Database v4.1
NHS
Home
Patients
Reports
Your Account
Help
Log Out
Reports Menu
Centre Infusions
Centre Infusions Grouped by Patient
Centre Infusion Data for Commissioners
Monthly Net Usage
Patients with missing GP Code
List of all Registered Patients
List of Treated Patients
Product Usage
Patient Follow-ups
Manage Follow Ups **New**
Short Term Expiry **NEW**
Centre Chart Reports
Centre Infusions Export
Diagnosis List


Immunoglobulin Database
Short Term Treatment Expiry Dates
Database ID
NHS / CHI No
Trust ID
DOB
Indication
Proposed
First Infusion
Treatment End
30535
[redacted]
6190186394
13/12/1927
Blue
Short Term
31/12/2012
31/03/2013


Immunoglobulin Database
NHS
Welcome to the
Immunoglobulin Database
Information Service
Welcome to the UK-Immunoglobin Database Information Service
The UK registry for Immunoglobin collects information about patients being treated with Intravenous immunoglobulin, subcutaneous immunoglobulin. The central aim of the database is to improve treatment services.
Support and Advice
If you encounter any problems please contact the IgD Support Team on 0161 277 7917 or email us at support@mdsas.com
Log On
If you already have a username and password please log on using the button below.
Log On
New User
If you do not have any log on details, please contact the IgD Support Team on 0161 277 7917 or email support@mdsas.com


Usage Per Trust
Total Ig infused & patients treated by trust.
Show Report
Total Patients & Usage by Diagnosis
Total Ig infused & patients treated by diagnosis.
Show Report
Monthly Patient Registrations
Line graphs detailing monthly registrations.
Show Graph
Monthly Immumoglobulin Usage
Line graphs detailing monthly Ig usage.
Show Graph
Usage by Region
Shows Total Ig Infusions.
Show Report
Usage by Region / Centre
Shows total Ig infusions by centre.
Show Report
Usage by Region / Centre
Shows total Ig infusions by centre.
Show Report
Product Usage and Returns by Trust
Shows total Ig infusions by product.
Show Report
IVIg Patient Map
Patient distribution map.
Show Report
Product Status
Overview of Product Usage.
Show Report
Data Extraction
Infusions by region
Report detailing IVIg infusions by Region
Data Extract - Regional Infusions
Infusions by PCT
Report detailing IVIg infusions by PCT
Data Extract - PCT Infusions

Immunoglobulin Database

Number of Patients & Usage by Condition
01/01/2012 to 31/12/2012

Condition	Grams	Patients
Primary immunodeficiencies	745489	2301
Chronic inflammatory demyelinating polyradiculoneuropathy	568428	973
Other Conditions	544135	2795
Multifocal motor neuropathy	292082	406
Immune thrombocytopenic purpura - Acute	155543	991
Guillain–Barré syndrome	113393	720
Myasthenia gravis	86464	389
Secondary antibody deficiencies	76596	438
Inflammatory myopathies	46601	145
Immune thrombocytopenic purpura - Persistent	35687	180
Transplantation (Solid Organ)	20772	162
Paraprotein-associated demyelinating neuropathy (IgG or IgA)	20481	40
Stiff person syndrome	17710	45
Specific antibody deficiency	13087	48
Alloimmune thrombocytopenia	11350	38
Kawasaki disease	10098	266
Staphylococcal toxic shock syndrome	10012	90
Coagulation factor inhibitors	8430	17
Immunobullous diseases	7884	18
Haemophagocytic syndrome	7779	64
Toxic epidermal necrolysis, Stevens Johnson syndrome	6650	41
Necrotising (PVL-associated) staphylococcal sepsis	4392	39
Severe or recurrent Clostridium difficile colitis	4209	99
Rasmussen syndrome	4018	13
Acquired red cell aplasia	2710	17
Thymoma with immunodeficiency	1655	7
Haemolytic disease of the fetus and newborn	1346	104

Immunoglobulin Database

Usage Per Trust & Treated Patients
01/01/2013 to 18/03/2013

Trust	Grams	Patients
UNIVERSITY COLLEGE LONDON HOSPITALS NHS FOUNDATION TRUST	34835	150
ROYAL FREE HAMPSTEAD NHS TRUST	26986	186
THE NEWCASTLE UPON TYNE HOSPITALS NHS FOUNDATION TRUST	22543	177
SALFORD ROYAL NHS FOUNDATION TRUST	18356	106
SHEFFIELD TEACHING HOSPITALS NHS FOUNDATION TRUST	17836	123
LEEDS TEACHING HOSPITALS NHS TRUST	15785	156
OXFORD RADCLIFFE HOSPITALS NHS TRUST	14679	108
BARTS AND THE LONDON NHS TRUST	14181	99
NOTTINGHAM UNIVERSITY HOSPITALS NHS TRUST	12671	122
SOUTH TEES HOSPITALS NHS TRUST	10785	69

Show me the patients with antibody deficiency on IVIG in my region

Show me the patients on one particular IVIG product in England

Success

- Rational use of IVIG
- Can track in emergency
- Better understanding

Forecasting allows

- Product diversity
- Product continuity
- Purchasing: price & **quality**

Improvements

- Simplify, simplify, simplify
- Electronic requesting
- Data: local or national?

Posters

Downloadable at:

http://www.edqm.eu/medias/fichiers/posters_kreuth_iii.pdf

Bibliographies

EUROPEAN SYMPOSIUM
OPTIMAL USE OF CLOTTING FACTOR CONCENTRATES AND IMMUNOGLOBINS
26-27 APRIL 2013, WILDBAD KREUTH, GERMANY
HAEMOPHILIA WORKSHOP

HAEMOPHILIA A

TRENDS IN TREATMENT OF HAEMOPHILIA A:

PATIENT NEEDS, RESEARCH AND DEVELOPMENT, NEW THERAPIES

Mary-Ann Eichmann

OVERVIEW

- BACKGROUND
- ISSUES
- METHODS
- RESULTS
- CONCLUSION

BACKGROUND

– Status quo of research in hemophilia

– Identification of gaps

– Structured literature research in „Pubmed“ and „ClinGov“

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ISSUES

1. Expected additional clinical and patient relevant benefits associated with innovative clotting factor concentrates and innovative therapeutical approaches compared to standard haemophilia treatment?

2. Status quo of new therapy modalities (patient tailored, low dose prophylaxis, gene therapy).

3. Research in haemophilia: clinical trials for market authorization, investigator initiated trials and registries.

METHODS

Structured Literature Search

Inclusion criteria

- Haemophilia A
- Factor VIII
- Time frame: 2009-01-01 – 2012-12-31
- Original article
- Clinical trials
- Registries
- Therapy / Therapeutic use

Exclusion critieria

- Blood coagulation factor inhibitors
- Reviews
- Case reports
- Editorials
- Comments
- Letters

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METHODS

Concept for Search

- Search in database „PubMed“
- More sensitive search with MeSH terms (medical subject headings) and subheadings
- Combining search terms with Boolean Operators
- Search literature in regard to questions
  - title
  - abstract
  - full text
- Studies are assessed by levels of evidence
  - Cochrane classification
- Search in ClinicalTrials.gov

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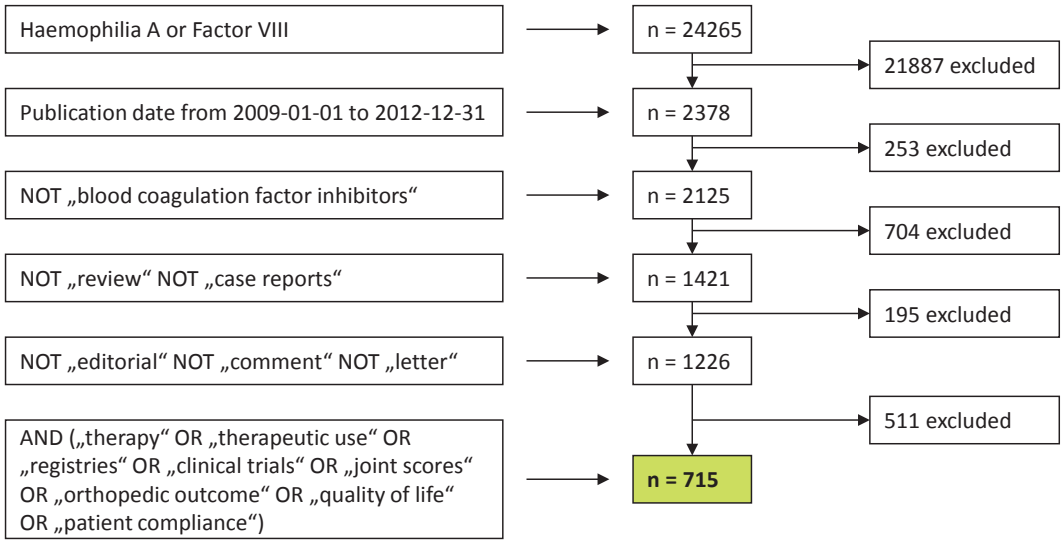
PubMed Search

(2013-02-17)



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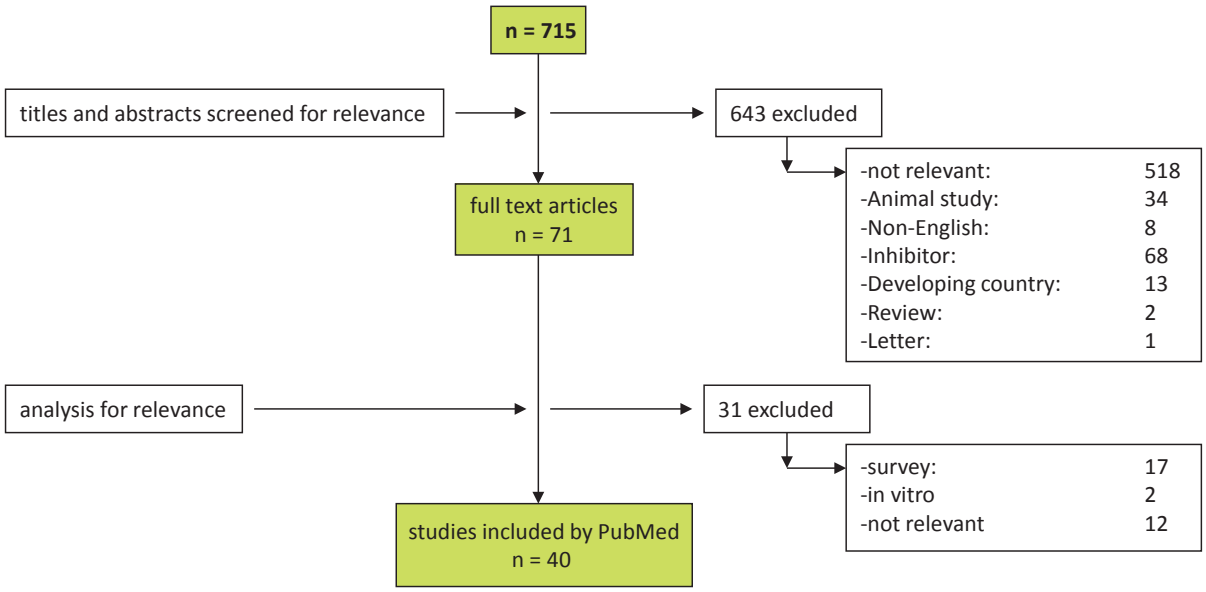
RESULTS

PubMed Search

(2013-02-17)



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Cochrane Classification

Grade	Type of Evidence
I a	at least one systematic review on the basis of methodically high-quality controlled randomized trials (RCTs)
I b	at least one sufficiently large, methodically high-quality RCT
II a	at least one high-quality study without randomization
II b	at least one high-quality study of a different type quasi-experimental study
III	more than one methodically high-quality non-experimental study
IV	expert opinion from clinical experience; expert commissions; descriptive studies

http://www.cochrane.de/de/evidenz-empfehlung

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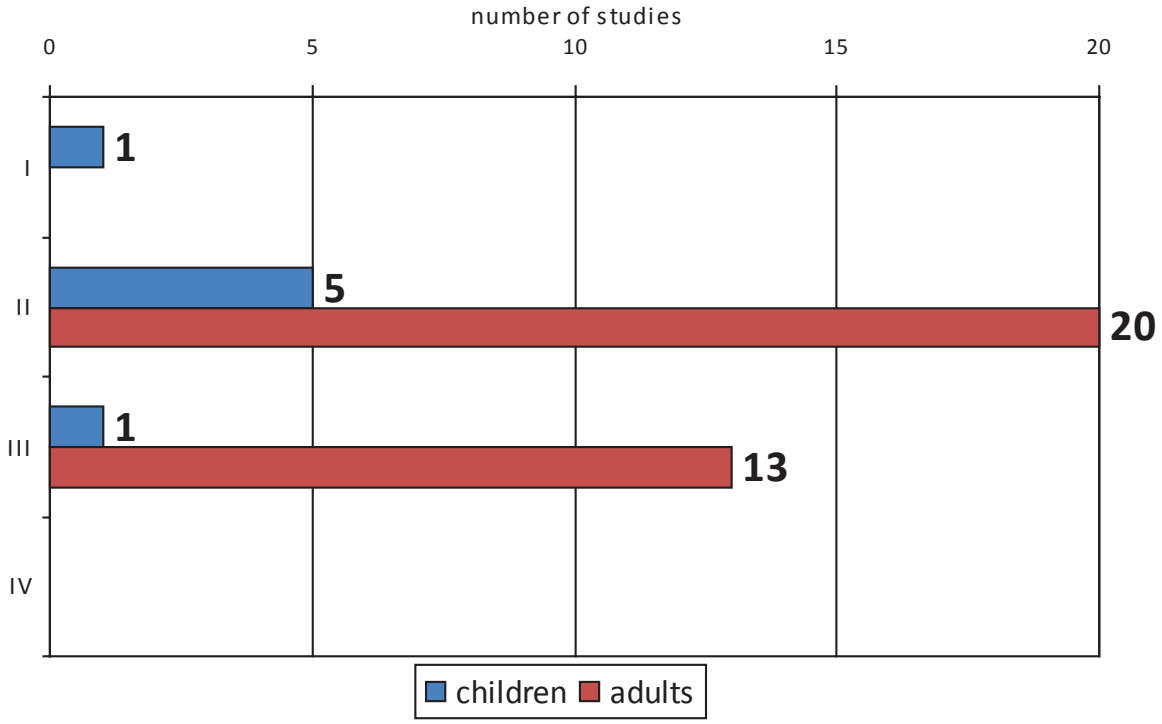
RESULTS

Evidence level of PubMed-publications



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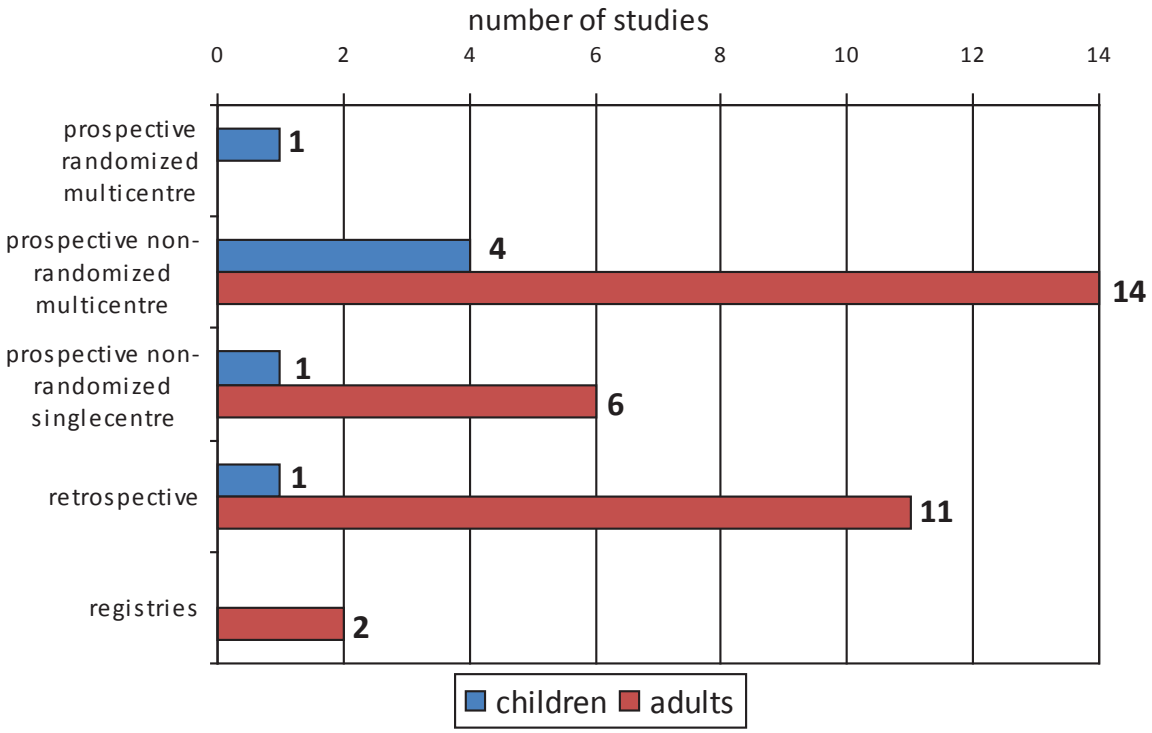
PubMed



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RESULTS

PubMed

Investigated products	Number of studies
Advate	10
Optivate	4
Kogenate	1
Wilate	1
Recombinate	1
N8	1
Haemoctin SDH	1
rFVIIIFc	1

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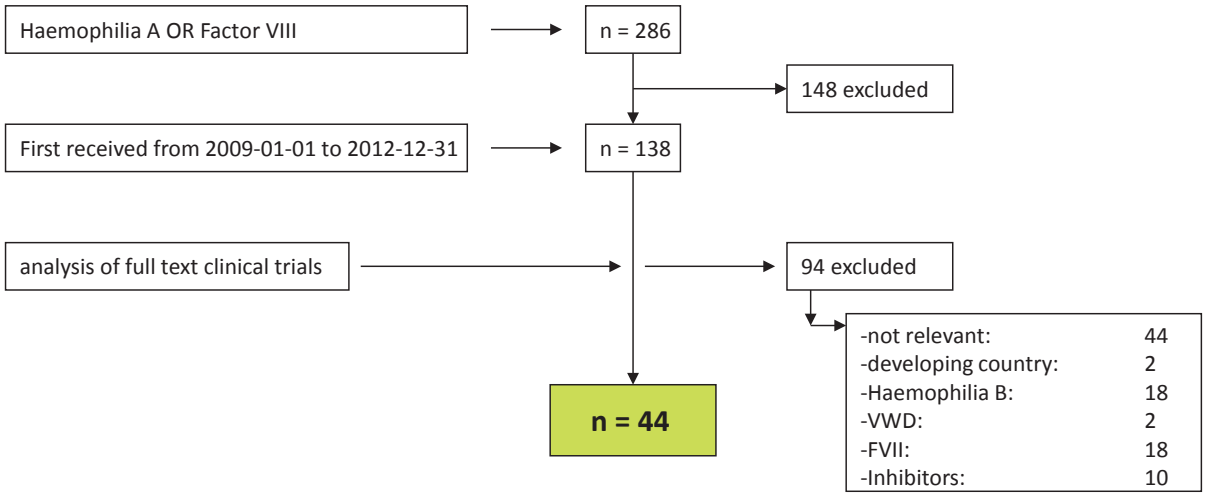
ClinicalTrials.gov Search

(2013-02-17)



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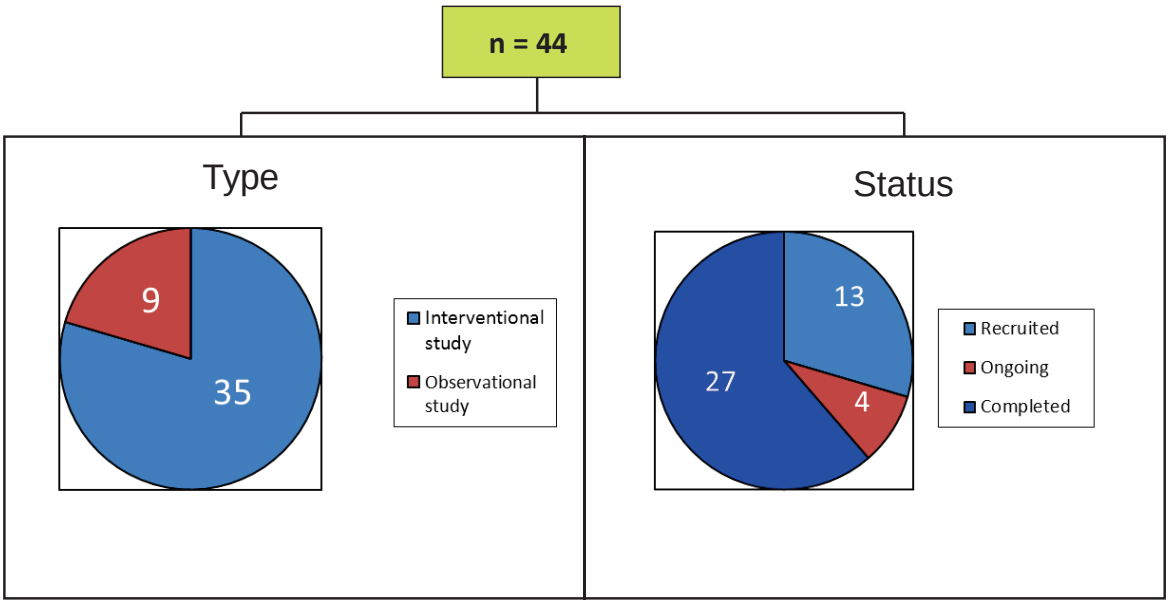
RESULTS

ClinicalTrials.gov Search

(2013-02-17)



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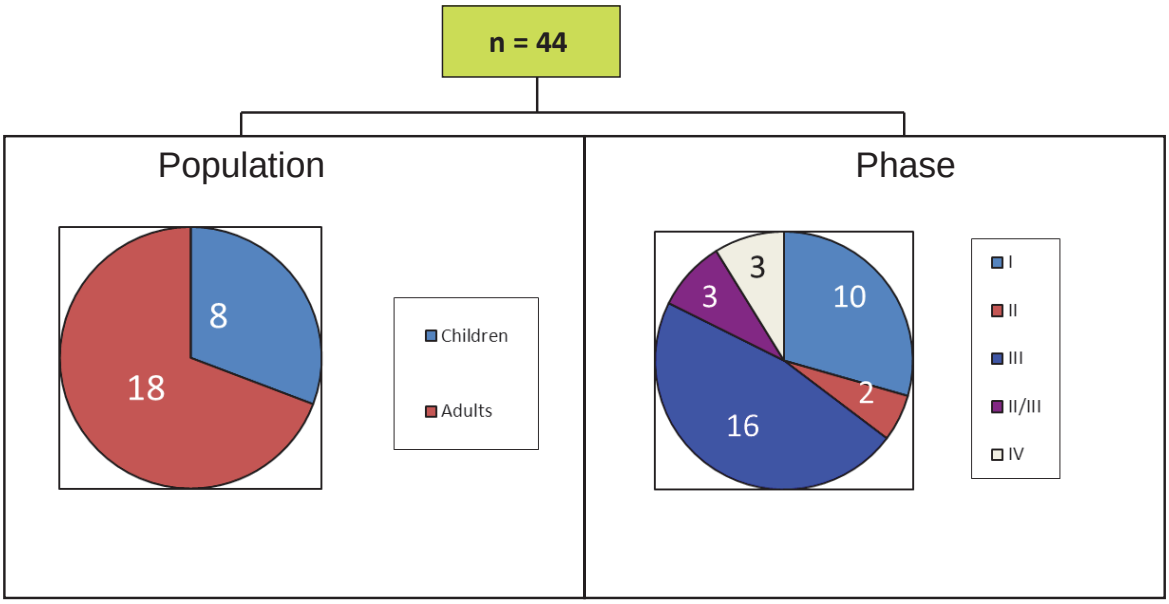
ClinicalTrials.gov Search

(2013-02-17)



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Results for ClinicalTrials.gov

Investigated products

12 recombinant products

rFVIII(N8)	9
Kogenate	7
rFVIIIFc	4
Human-cl rh FVIII	3
Advate, PEGylated rFVIII(BAX 855), rPorcineFVIII(OBI-1), BDDrFVIII(Xyntha), rFVIII(BAY 81-8973), rFVIII(Greengene)	each with 2
PEGylated rFVIII(Bay 94-9027)	1
Helixate	1

1 plasma-derived product

Biostate	1

Conclusion

Expected additional clinical and patient relevant benefit associated with innovative clotting factor concentrates and innovative therapeutical approaches compared to standard haemophilia treatment?

Therapeutical approaches

- Majority of studies : not randomised
  - (18 multicentre + 7 singlecentre)
- Evidence of cochrane levels (Grade I: 1, Grade II: 25, Grade III: 14)
- Most studies (11) focusing on investigation of prophylaxis compared with on-demand therapy
  - bleeding score and patterns
  - joint scores
  - orthopedic outcome
  - quality of life.
- Some studies (7) investigation of early prophylaxis versus standard prophylaxis regime

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Conclusion

Expected additional clinical and patient relevant benefit associated with innovative clotting factor concentrates and innovative therapeutical approaches compared to standard haemophilia treatment?

Innovative clotting factor concentrates

- 1 clinical study published (Pubmed)
- 11 clinical trial retrieved in Clingov
- - introduction of long-acting factors:
  - Prolonged half-lives – expected less administration
  - Convenient prophylaxis – reduced patient burden
- Published studies too limited to conclude on benefit of innovative products at present

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Status quo of new therapy modalities

- Limited Number of studies
  - 4
- Evidence level of studies
  -Grade II (prospective, non-randomized multicentre)
- Focus on personalized prophylactic regimen compared to standard prophylaxis
  dosage regimen adapted to
  - Individual bleeding pattern
  - Factor VIII plasma level
  - life style
- No clinical studies on gene therapy in Hemophilia A, many non-clinical studies

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Research in haemophilia: clinical trials for market authorization, investigator initiated trials and registries.

- Published results of 2 registries retrieved (Medical Committee of the Swiss Hemophilia Society)
- More publications about findings of registries desirable

- 44 clinical trials retrieved (ClinGov)

- 6/44 investigator initiated trials, mainly about quality of life and prophylaxis compared to on-demand

- 38/44 clinical trials for market authorization, mainly about new clotting factor concentrates like B-domain deleted rec FVIII, Fusion Proteins, PEGylated rec FVIII (GCP trials)

HAEMOPHILIA A
TRENDS IN TREATMENT OF HAEMOPHILIA A

Results for PubMed 2009-2012

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CLINICAL USE OF COAGULATION FACTORS & IMMUNOGLOBULINS MEETING (KREUTH III)

SYSTEMATIC LITERATURE RESEARCH: HAEMOPHILIA B

26-27 April 2013, Wildbad Kreuth, Germany

Authors:

Karin Berger
Dorothee Schopohl
Wolfgang Schramm

TOPICS TO BE DISCUSSED AT THE WILDBAD KREUTH III MEETING

1. Expected additional clinical and patient relevant benefit associated with innovative clotting factor concentrates and innovative therapeutical approaches compared to standard haemophilia treatment
2. Research in haemophilia: difference between clinical trials for market authorization, investigator initiated trials and registries
3. Status quo of new therapies (patient tailored, low dose prophylaxis, gene therapy)
4. Access and requirements for reimbursement of clotting factor concentrates at present and in the future in Europe

WORKSHOP DISCUSSIONS SHOULD LEAD TO...

- Critical appraisal of status quo and identification of gaps in clinical and outcomes research in haemophilia
- Identification of future needs and to dos in haemophilia treatment and research

A systematic literature research and analysis based on methods recommended by HTA bodies like the Swedish Council for Health Technology Assessment and the Institute for Quality and Efficiency in Health Care (IQWIG, Germany) has been initiated.

The results summarized in this document should serve as background information for the upcoming meeting in Wilbad Kreuth, April 26., 27.

SYSTEMATIC LITERATURE RESEARCH HAEMOPHILIA B TREATMENT

- Databases used for search:
  - Embase (Ovid interface
  - Medline (Ovid interface)
  - ClinicalTrials.gov
- Retrieved literature (Haem B) is screened subsequently by
  - Title
  - Abstract
  - Full text
- Selected journal articles and conference abstracts are allocated to the 4 overall discussion topics

SYSTEMATIC LITERATURE RESEARCH

Inclusion criteria

- Haemophilia B (HB)
- Factor IX
- Time frame 01.01.2009 - 22.03.2013
- English Language
- Study
- Registry
- Developed country
- Original article
- Conference abstract

Exclusion criteria

- Review
- Case reports
- Comment, editorial, letter, note
- Mixed studies of haemophilia A and B patients (HA/HB) without HB specific aspects
- Animal study, *in vitro* study, healthy volunteers
- Genetics without correlation to HB disease characteristics
- Non English publication

EVALUATION OF LITERATURE EVIDENCE LEVELS

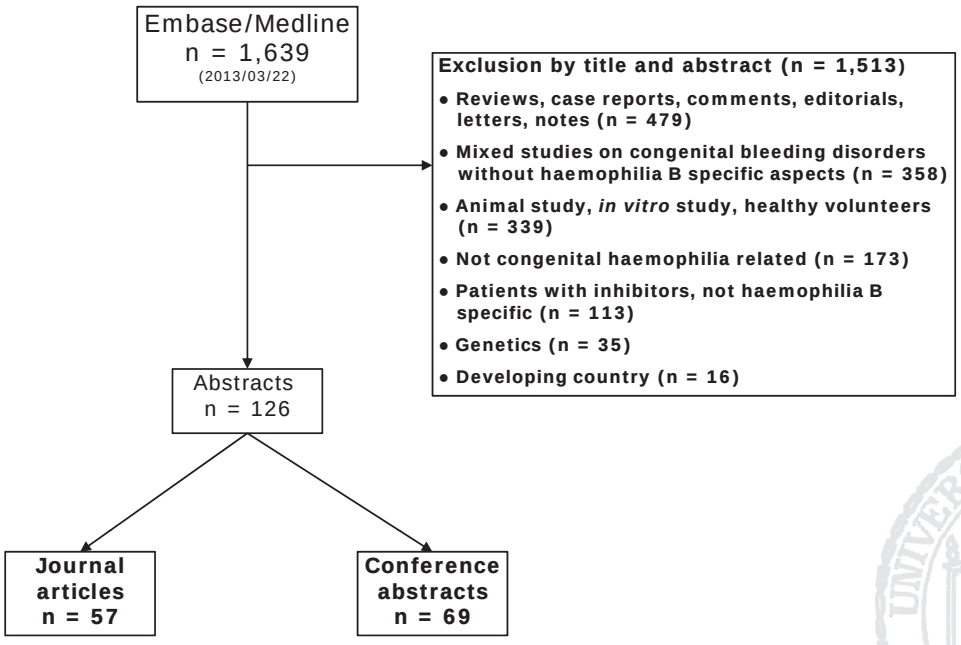
- Studies are rated by evidence levels (Guidelines prior to 2010 used the classification of evidence and grading of recommendations as devised by the US Agency for Health Care Policy and Research (AHCPR). Guidelines published from 2010 onwards have used the 'GRADE' nomenclature.)
  - The British Committee for Standards in Haematology (BCSH)
  - Grading of Recommendations Assessment, Development, and Evaluation (GRADE)

EMBASE AND MEDLINE SEARCH: 1,639 HITS

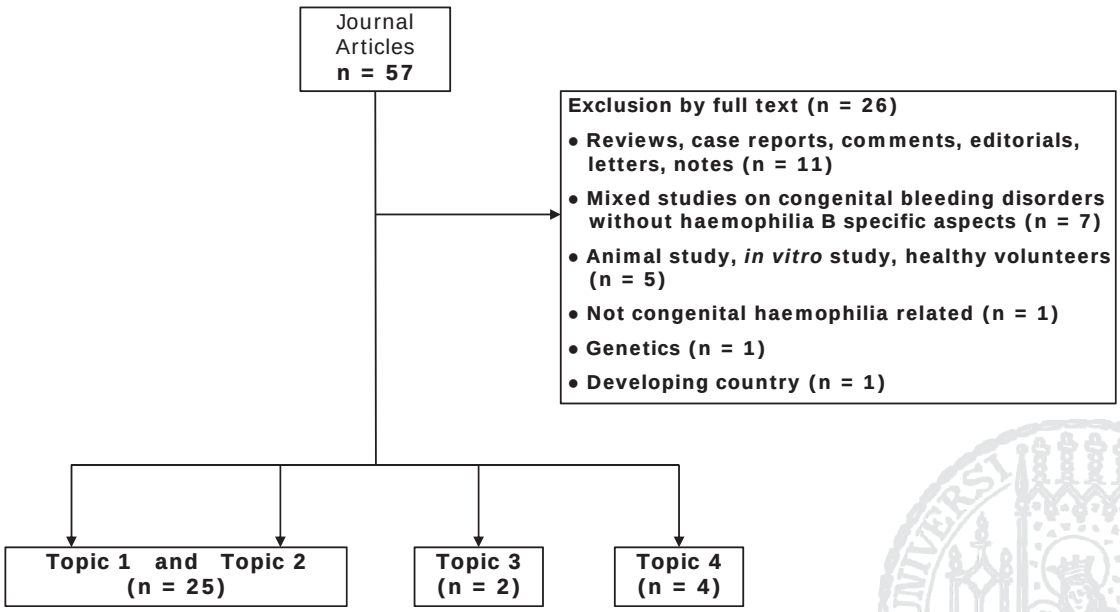
	Search Terms	Results
1	Hemophilia B.mp.	8,848
2	Haemophilia B.mp	1,676
3	Factor IX.mp	9,675
4	1 or 2 or 3	14,908
5	limit 4 to yr=„2009-Current“	2,812
6	limit 5 to english language	2,711
7	limit 6 to human	2,131
8	limit 7 to humans	2,131
9	remove duplicates from 8	**1,639**

Databases: Embase <1974 to 2013 March 22>, Ovid MEDLINE(R) <1946 to March Week 2 2013>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <March 22, 2013>

57 JOURNAL ARTICLES AND 69 CONFERENCE ABSTRACTS WERE SELECTED ACCORDING TO TITLE AND ABSTRACT SCREENING



INCLUSION OF 31 JOURNAL ARTICLES AFTER FULL TEXT SCREENING



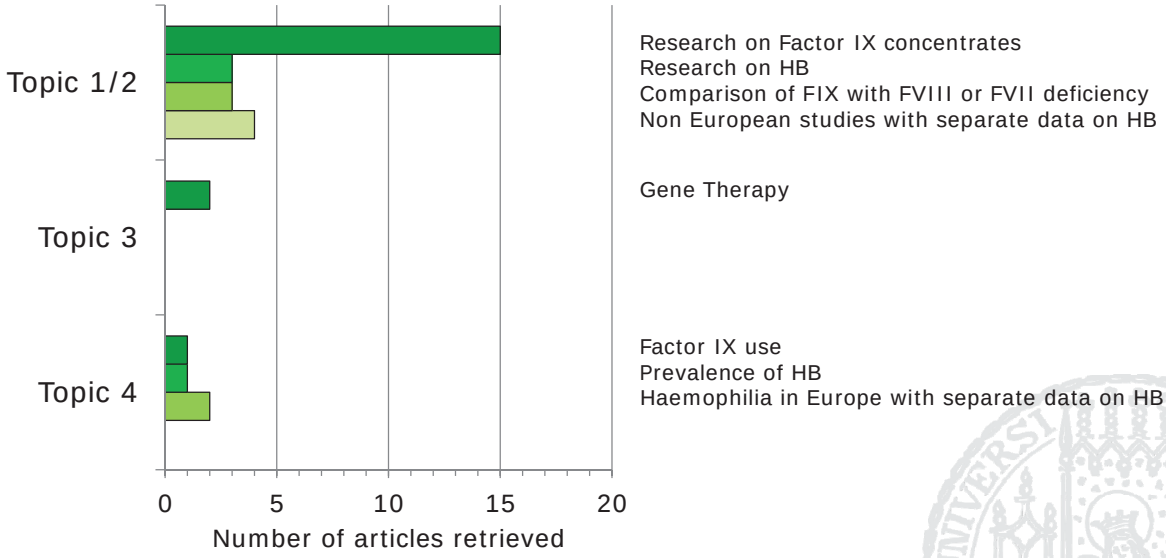
31 (54.4%) OF 57 JOURNAL ARTICLES WERE RELEVANT

- Exclusion by full text: 26 (45.6%)
- Inclusion of 31 journal articles (54.4%)
  - Topic 1 and 2: **25 (80.6%)**
  - Topic 3: **2 (6.5%)**
  - Topic 4: **4 (12.9%)**

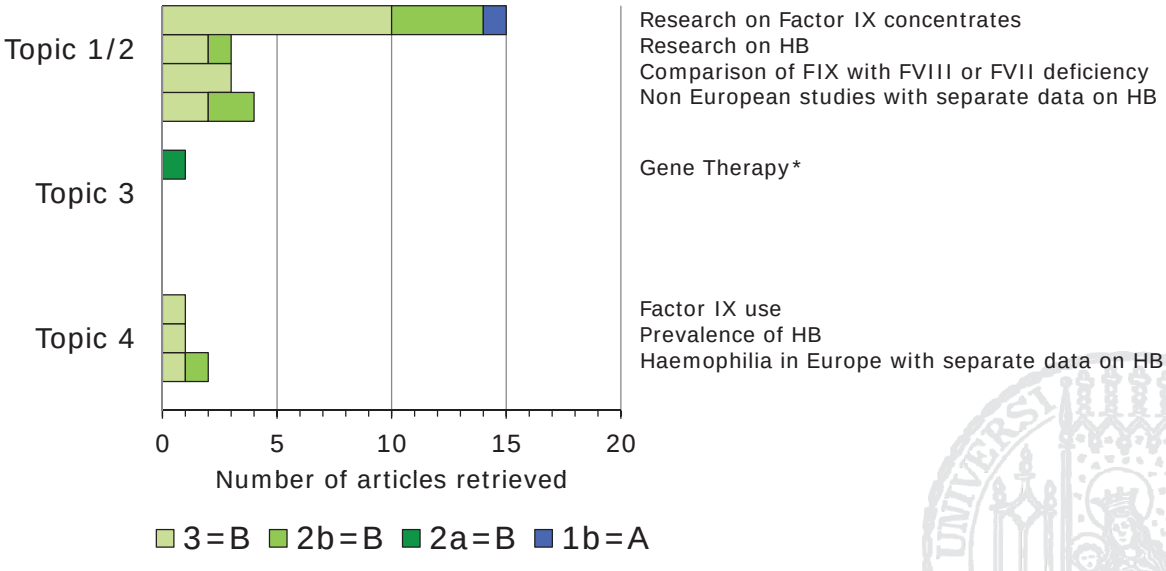
Topic 1. Expected additional clinical and patient relevant benefit associated with innovative clotting factor concentrates and innovative therapeutical approaches compared to standard haemophilia treatment
Topic 2. Research in haemophilia: difference between clinical trials for market authorization, investigator initiated trials and registries
Topic 3. Status quo of new therapies (patient tailored, low dose prophylaxis, gene therapy)
Topic 4. Access and requirements for reimbursement of clotting factor concentrates at present and in the future in Europe

The 32 relevant journal articles are cited in the appendix.

48.4% OF RELEVANT JOURNAL ARTICLES CONCERN RESEARCH ON FACTOR IX CONCENTRATES



OF 30 STUDIES 96.7% HAVE AN EVIDENCE LEVEL **B** (MODERATE,GRADE), RESPECTIVELY 66.7% AN EVIDENCE LEVEL **3** (AHCPR)



*2 publications but only one study

SAFETY, EFFICACY AND/OR PHARMACOKINETICS OF FACTOR IX CONCENTRATES PREDOMINATE

Numbers of journal articles retrieved from the literature research

Topic 1 and 2

- **12** Safety, efficacy and/or pharmacokinetics of different FIX concentrates
- **3** Research on dosing and adverse events concerning FIX concentrates
- **2** Research on HB genetics
- **1** HB specific Registry
- **3** Comparison of FIX deficiency with FVIII or FVII deficiency
- **4** Non European studies on haemophilia with separate data for HB

Topic 3

- **2** Gene therapy

Topic 4

- **1** Factor IX use around the world
- **1** Prevalence of HB around the world
- **2** Studies on haemophilia in Europe with separate data for HB

4 registered trials were retrieved from the published literature, 1 on a new rFIX product and 3 on innovative FIX concentrates

Topic 1. Expected additional clinical and patient relevant benefit associated with innovative clotting factor concentrates and innovative therapeutical approaches compared to standard haemophilia treatment
Topic 2. Research in haemophilia: difference between clinical trials for market authorization, investigator initiated trials and registries

Study	Factor IX / Study design	No. of patients	Dosing	Objectives	Results	Evidence level
Martino-witz et al. (Haemo-philia, 2012)	**IB1001** trenacog alfa (investigational rFIX) randomized, double-blind, non-inferiority, cross-over pharmacokinetic (PK) study	**32** ≥ 12 yrs., ≥40kg, HB with FIX ≤ 2 IU/dL	75 ± 5 IU/kg IB1001 or nonacog alfa	Comparison of PK of IB1001 with nonacog alfa; relationship between PK of IB1001 and degree of sialylation	non-inferiority of IB1001 to nonacog alfa and no clinically meaningful PK differences between IB1001 and nonacog alfa; No clinically meaningful impact of sialylation levels.	**1b, A**
Santa-gostino et al. (Blood, 2012)	**rIX-FP** (FIX fusion protein with human albumin) First-in-human prospective, multicenter, open-label, dose-escalation study	**25** HB with FIX ≤ 2 IU/dl	25, 50 and 75 IU/kg	Safety (primary) Pharmacokinetics (Secondary) after single i.v. dose of 50 IU/kg rIX-FP	No inhibitors, no antibodies, no thrombosis; After 50IU/kg rIX-FP: Prolonged half-life more than 5 x; Baseline-corrected FIX activity after 14 days: ≈ 5 IU/dL.	**2b, B**
Shapiro et al. (Blood, 2012)	**rFIXFc** (FIX fusion protein with human IgG1 Fc domain) First-in-human prospective, multicenter, open-label, dose-escalation study	**14** HB with FIX ≤ 2 IU/dl	6 dose levels, in sequence: 1, 5, 12.5, 25, 50, 100 IU/kg	Safety (primary) Pharmacokinetics (Secondary) after single i.v. doses of 12.5 to 100 IU/kg rFIXFc	No inhibitors, no antibodies, no thrombosis; After 50 IU/kg rFIXFc: Prolonged half-life approximately 3 x; After 7 days the mean activity was on average 2.47 ± 0.911 IU/dL.	**2b. B**
Negrier et al. (Blood, 2011)	**N9-GP** (FIX activated peptide glycoPEGylated by a 40-kDa polyethylene glycol molecule) First-in-human prospective, multicenter, open-label, dose-escalation study	**15** HB with FIX ≤ 2 IU/dl	25, 50, and 100 U/kg	Safety (primary) Pharmacokinetics (Secondary) adjusted to a single dose of 50 U/kg of N9-GP	No inhibitors; 1 serious hypersensitivity reaction; After 50 U/kg N9-GP: Prolonged half-life more than 5 x; Estimated 22.5 and 16.2 days until 1% and 3% FIX activity.	**2b, B**

1 registered trial (2 publications) related to gene therapy

Topic 3. Status quo of new therapies (patient tailored, low dose prophylaxis, gene therapy)

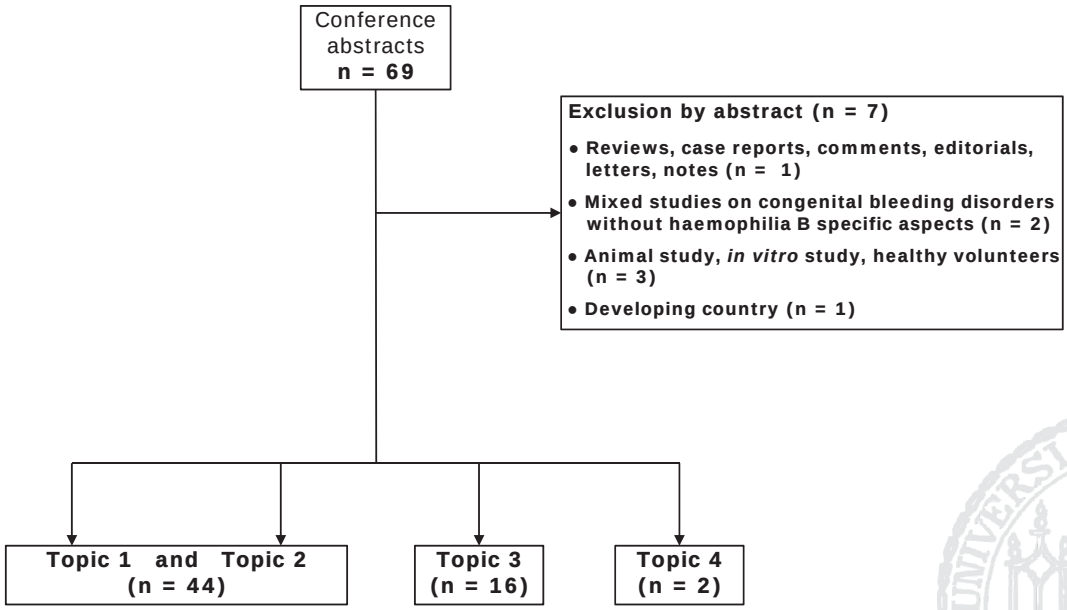
Study	Study design	No. of patients	Dosing	Objectives	Results	Evidence level
Nathwani A. C. et al. (NEJ, 2011)	Experimental type: peripheral vein infusion of a serotype-8-pseudotyped, self-complementary adenovirus-associated virus (AAV) vector expressing a codon-optimized human factor IX transgene (scAAV2/8-LP1-hFIXco)	6 patients with severe HB (FIX activity <1% of normal)	3 cohorts of 2 pts each: high ($2x10^{12}$ vector genomes [vg] per kg), intermediate ($6x10^{11}$ vg per kg) and low dose ($2x10^{11}$ vg per kg) of vector; without immunosuppressive therapy	FIX expression: Efficacy defined as persistence of biologically active FIX at 3% or more of normal levels.	4 pts. could discontinue prophylaxis, 2 pts. increased injection interval; low dose: FIX activity 2% of normal for >15 and >11 weeks; intermediate dose: FIX activity 3 and 4% of normal for >9 and >8 weeks; high dose: FIX activity 8 and 12% of normal for >6 and >5 weeks.	**2a, B**
Tuddenham E. (Haemo-philia, 2012)	See above	30	high ($2x10^{12}$ vector genomes per kg)	Trial halted in March 2011 due to adverse event of liver inflammation; reopening of trial in March 2012 with 7th HB pt. at high dose level. Treatment of possible immune response with prednisolone.		

2 studies with haemophilia B specific data from Europe and 2 FIX and haemophilia B world-wide analyses were retrieved

Topic 4. Access and requirements for reimbursement of clotting factor concentrates at present and in the future in Europe

Study	Study design	Countries	Number of patients	Objective	Evidence level
Stonebraker, J. S. et al. (Haemophilia, 2012)	Descriptive data collection on prevalence of haemophilia B (per 100 000 male population)	105 countries from the World Federation of Hemophilia annual global surveys.		The objectives of this article were to study the reported prevalence of haemophilia B (HB) on a country-by-country basis and to analyse whether the prevalence of HB varied by national economy.	**3, B**
Stonebraker, J. S. et al., (Haemophilia, 2011)	Descriptive data collection on FIX use	90 countries		The objectives of this article were to study the reported factor IX (FIX) use on a country-by-country basis and address the question, whether the reported FIX use varies by national economies.	**3, B**
Tagliaferri, A. et al. (Haemophilia, 2010)	retrospective cohort study	Italy	443 patients with haemophilia, who had died: HA 347; HB 97;	The aim of this study was to investigate mortality, causes of deaths, life expectancy and co-morbidities in Italian persons with haemophilia separately for HA and HB.	**3, B**
Aznar, J. A. et al. (Haemophilia, 2009)	cross-sectional, multi-centre epidemiological study	Spain	2400 patients with haemophilia; HA 2081 (86.7%); HB 319 (13.3%);	To determine the prevalence of haemophilia A and B and their complications in Spain, and to characterize the health care network providing support to haemophiliac patients.	**2b, B**

INCLUSION OF 62 CONFERENCE ABSTRACTS AFTER FURTHER ANALYSIS



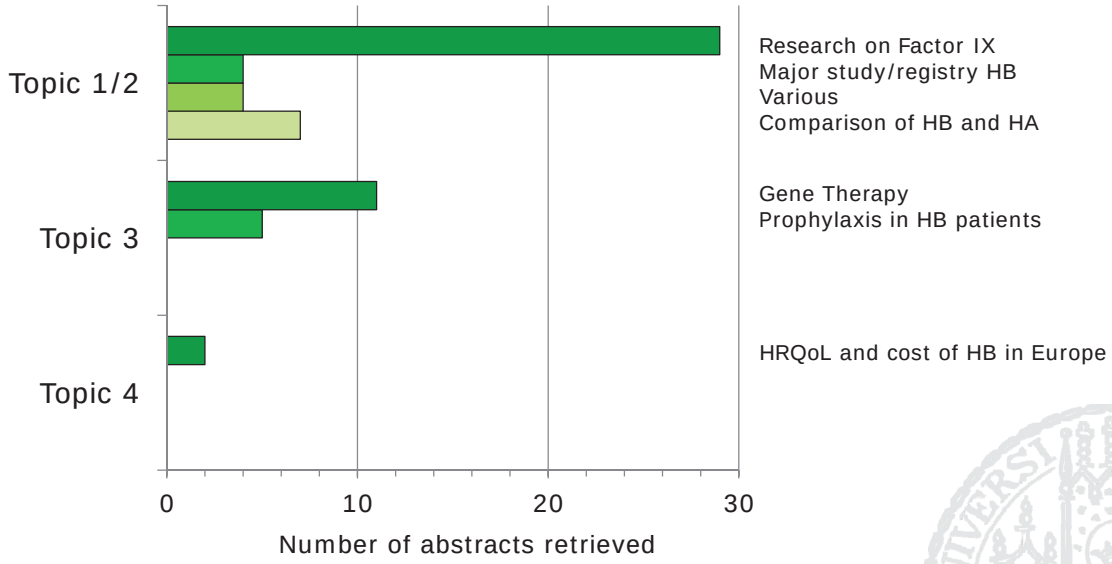
62 (89.9%) OF 69 CONFERENCE ABSTRACTS WERE RELEVANT

- Exclusion by text, second step: 7 (10.1%)
- Inclusion of 62 conference abstracts (89.9%)
  - Topic 1 and 2: **44 (71.0%)**
  - Topic 3: **16 (25.8%)**
  - Topic 4: **2 (3.2%)**

Topic 1. Expected additional clinical and patient relevant benefit associated with innovative clotting factor concentrates and innovative therapeutical approaches compared to standard haemophilia treatment
Topic 2. Research in haemophilia: difference between clinical trials for market authorization, investigator initiated trials and registries
Topic 3. Status quo of new therapies (patient tailored, low dose prophylaxis, gene therapy)
Topic 4. Access and requirements for reimbursement of clotting factor concentrates at present and in the future in Europe

The 62 relevant conference abstracts are cited in the appendix.

46.8% OF RELEVANT CONFERENCE ABSTRACTS CONCERN RESEARCH ON FACTOR IX CONCENTRATES



ALMOST HALF OF THE PUBLISHED STUDIES FOCUS ON SAFETY, EFFICACY AND/OR PHARMACOKINETICS OF FACTOR IX CONCENTRATES

Numbers of conference abstracts retrieved from the literature research

Topic 1 and 2

- **29** safety, efficacy and/or pharmacokinetics of different FIX concentrates
- **2** The hemophilia utilization group study part Vb (HUGS VB)
- **2** The International Factor IX Treatment Network Survey
- **4** HB specific genetics, utility, lack of seasonal variation in bleeding and pain
- **7** Comparison of HB and HA

Topic 3

- **11** Gene therapy
- **5** Studies on prophylaxis in HB

Topic 4

- **2** The EQOFIX study (health-related quality of life and annual direct medical cost of patients with haemophilia B in France)

One international initiative to collect information on haemophilia B patients: the International Factor IX Treatment Network

Study	Berntorp et al. (2011) Haemophilia, EAHAD; Shapiro et al. (2011) Haemophilia, HTRS/NASCOLA;
Design	Survey among haemophilia treatment centers worldwide; start December 2009; extension over 5 years;
Objectives	To characterize the population under care, and to develop a FIX investigators network.
No. Of patients	2617 patients currently under care in North America, Europe, Latin America, and the Middle East;
Results	<12 years: 23%; 12 to 18 years: 16%; 19 to 50 years: 45%; >50 years: 16%; Mild (0.05-0.40 IU/mL) 38%; moderate (0.01-<0.05 IU/mL) 31%; severe (<0.01 IU/mL) 31%; Treatment: plasma-derived products 34%, with recombinant products 66%; On demand: 86%; prophylaxis: 14% (1 dose/week 13%, 2 doses/week 68%, 2-3 doses/week <1%, 3 doses/week 17%, >3 doses/week 2%) History of inhibitors: 66 patients; Median percentage of patients with F9 gene mutation typing: 30%;

One study on HRQOL of haemophilia B patients in Europe: the EQOFIX study

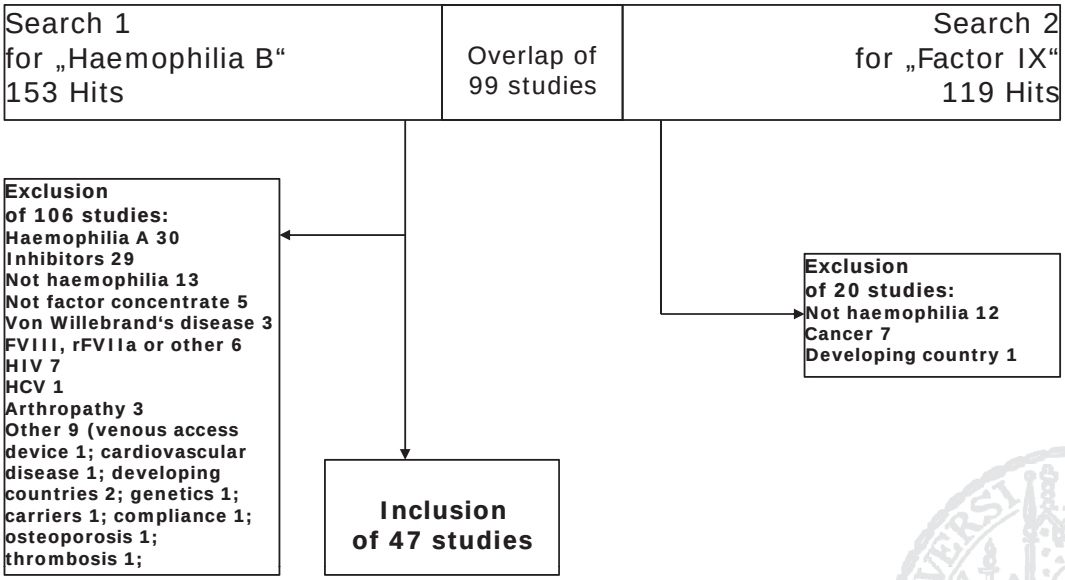
Study	Polack et al. (2012) Value in Health, ISPOR; Polack et al. (2011) Journal of Thrombosis and Haemostasis, ISTH;
Design	Prospective cohort study, 1 year follow-up
Objectives	To evaluate in a representative French HB population the impact of health-related quality of life (HRQOL) and to estimate the costs associated with its management.
No. Of patients	155 patients with HB (severe and moderate); 25% coverage rate of French severe and moderate HB pop.; Children: 51 (40 severe, 11 moderate); Adults: 104 (74 severe, 30 moderate);
Instruments	Generic: Children: Kidscreen; Adults: SF-36; Specific: QUAL-HEMO;
Results	Treatment: 30.4% prophylaxis, 60.4% on-demand; Adults with severe HB reported significantly poorer HRQOL than patients with moderate HB mainly on physical components. No HRQOL difference among children. Average annual direct cost : €95,619 (SD €83,142); Costs are 3.3 times higher in severe vs. moderate HB (p<0.001). Substitutive therapy accounted for 90% of costs, followed by hospitalizations with 6.5% of total.
Conclusions	**Prophylaxis allows for avoiding haemorrhagic events and costs remain in an acceptable cost-effectiveness range.**

INCLUSION OF 47 STUDIES FROM ClinicalTrials.gov

	Search Strategy	Results
1	„Haemophilia B“ or „Hemophilia B“	153
2	„Factor IX“	119
3	Duplicates of Search 1 and 2	99
4	Exclusion	126
5	Inclusion	47

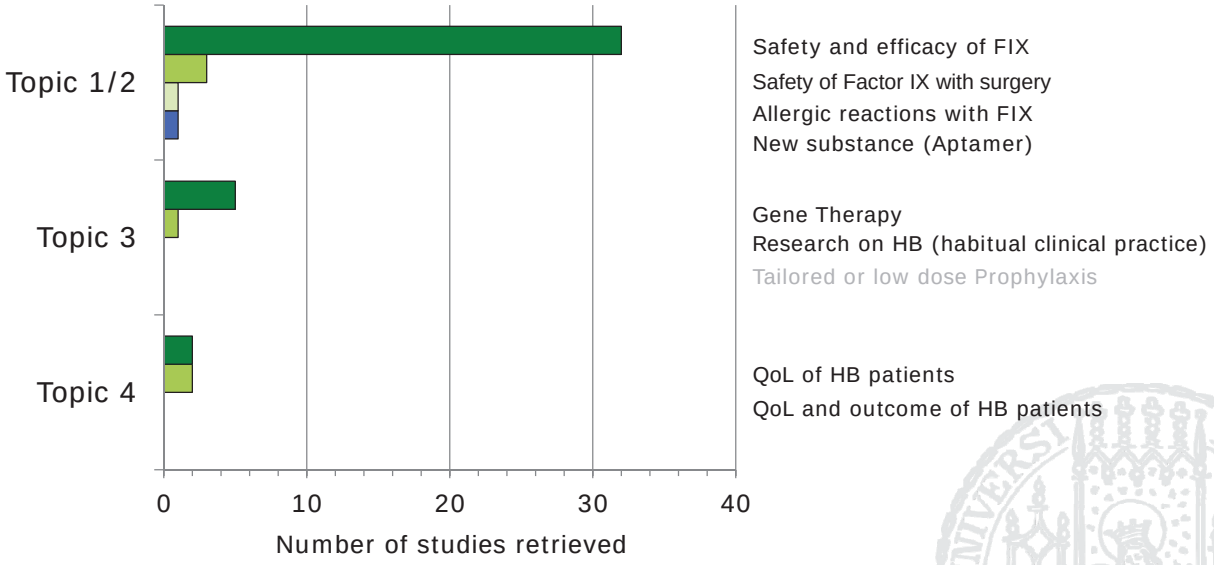
Database: ClinicalTrials.gov searched 2013 February 05

SEARCH: ClinicalTrials.gov



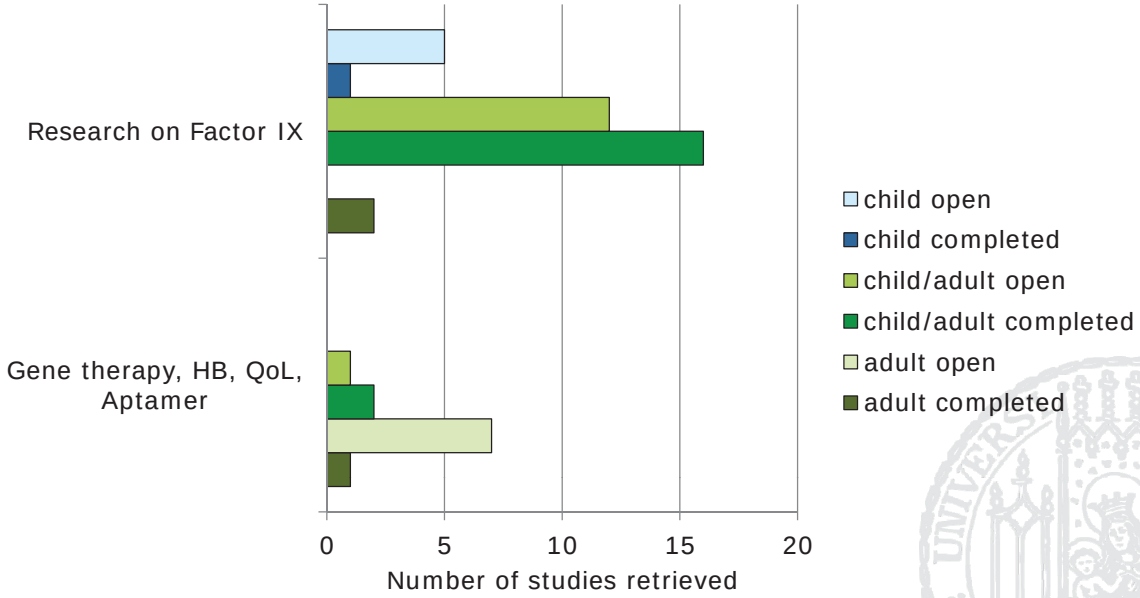
The 47 relevant studies are cited in the Appendix.

76.6% OF RELEVANT STUDIES WERE RELATED TO SAFETY AND/OR EFFICACY AND/OR PHARMACOKINETICS OF FACTOR IX CONCENTRATES.

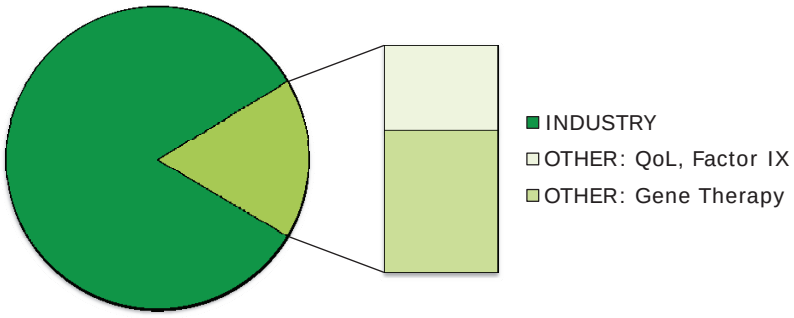


65.9% OF STUDIES INCLUDE CHILDREN AND ADULTS, 12.8% INCLUDE CHILDREN ONLY AND 21.3% ADULTS ONLY

53.2% OF STUDIES WERE STILL RECRUITING AND 46.8% WERE COMPLETED



8 studies (17%) were not industry sponsored, including all 5 gene therapy studies, half of the 4 Qol studies and one phase I/II study of monoclonal FIX concentrate



Topic 1 and 2

Author	Title	Citation	Year	Evidence level*
Martinowitz U., Shapiro A., Quon D.V. et al.	Pharmacokinetic properties of IB1001, an investigational recombinant factor IX, in patients with haemophilia B: Repeat pharmacokinetic evaluation and sialylation analysis.	Haemophilia. 18 (6) (pp 881-887)	2012	1b, A
Santagostino E., Negrier C., Klamroth R. et al.	Safety and pharmacokinetics of a novel recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP) in hemophilia B patients.	Blood. 120 (12) (pp 2405-2411)	2012	2b, B
Shapiro A.D., Ragni M.V., Valentino L.A. et al.	Recombinant factor IX-Fc fusion protein (rFIXFc) demonstrates safety and prolonged activity in a phase 1/2a study in hemophilia B patients.	Blood. 119 (3) (pp 666-672)	2012	2b, B
Berntorp E., Keeling D., Makris M. et al.	A prospective registry of European haemophilia B patients receiving nonacog alfa, recombinant human factor IX, for usual use.	Haemophilia. 18 (4) (pp 503-509)	2012	3, B
Serban M., Skotnicki A.B., Colovic M. et al.	Clinical efficacy, safety and pharmacokinetic properties of the plasma-derived factor IX concentrate Haemonine in previously treated patients with severe haemophilia B.	Haemophilia. 18 (2) (pp 175-181)	2012	3, B
Negrier C., Knobe K., Tiede A. et al.	Enhanced pharmacokinetic properties of a glycoPEGylated recombinant factor IX: A first human dose trial in patients with hemophilia B.	Blood. 118 (10) (pp 2695-2701)	2011	2b, B

*Evidence levels rated according to US Agency for Health Care Policy and Research (AHCPR), as well as British Committee for Standards in Haematology (BCSH) using GRADE (Grading of Recommendations Assessment, Development and Evaluation)

Topic 1 and 2 (continued 1)

Author	Title	Citation	Year	Evidence level*
Quon D.V.K. and Logan L.	Safety and efficacy of plasma-derived coagulation factor IX concentrate (AlphaNine SD) in patients with haemophilia B undergoing surgical intervention: A single institution retrospective analysis.	Haemophilia. 17 (1) (pp e196-e201)	2011	3, B
Mauser-Bunschoten E.P., Kleine Budde I., Lopaciuk S. et al.	An ultrapure plasma-derived monoclonal antibody-purified factor IX concentrate (Nonafact), results of phase III and IV clinical studies.	Haemophilia. 17 (3) (pp 439-445)	2011	3, B
Lissitchkov T., Matysiak M., Zavilska K. et al.	A clinical study assessing the pharmacokinetics, efficacy and safety of AlphaNine, a high-purity factor IX concentrate, in patients with severe haemophilia B.	Haemophilia. 17 (4) (pp 590-596)	2011	2b, B
Lissitchkov T., Matysiak M., Zawilska K. et al.	An open clinical study assessing the efficacy and safety of Factor IX Grifols, a high-purity Factor IX concentrate, in patients with severe haemophilia B.	Haemophilia. 16 (2) (pp 240-246)	2010	3, B
Monahan P.E., Liesner R., Sullivan S.T. et al.	Safety and efficacy of investigator-prescribed BeneFIX prophylaxis in children less than 6 years of age with severe haemophilia B.	Haemophilia. 16 (3) (pp 460-468)	2010	3, B
Aznar J.A., Cabrera N., Matysiak M. et al.	Pharmacokinetic study of a high-purity factor IX concentrate (Factor IX Grifols) with a 6-month follow up in previously treated patients with severe haemophilia B.	Haemophilia. 15 (6) (pp 1243-1248)	2009	3, B

*Evidence levels rated according to US Agency for Health Care Policy and Research (AHCPR), as well as British Committee for Standards in Haematology (BCSH) using GRADE (Grading of Recommendations Assessment, Development and Evaluation)

Topic 1 and 2 (continued 2)

Author	Title	Citation	Year	Evidence level*
Uprichard J., Adamidou D., Goddard N.J. et al.	Factor IX replacement to cover total knee replacement surgery in haemophilia B: A single-centre experience, 2000-2010.	Haemophilia. 18 (1) (pp 46-49)	2012	3, B
Rocca A., Pizzinelli S., Oliovecchio E. et al.	Replacement therapy with recombinant factor IX. A multicentre evaluation of current dosing practices in Italy.	Blood Transfusion. 9 (1) (pp 60-69)	2011	3, B
Recht M., Pollmann H., Tagliaferri A. et al.	A retrospective study to describe the incidence of moderate to severe allergic reactions to factor IX in subjects with haemophilia B.	Haemophilia. 17 (3) (pp 494-499)	2011	3, B
Hamasaki-Katagiri N., Salari R., Simhadri V.L. et al.	Analysis of F9 point mutations and their correlation to severity of haemophilia B disease.	Haemophilia. 18 (6) (pp 933-940)	2012	3, B
Chavali S., Ghosh S. and Bharadwaj D.	Hemophilia B is a quasi-quantitative condition with certain mutations showing phenotypic plasticity.	Genomics. 94 (6) (pp 433-437)	2009	3, B
Chitlur M., Warrier I., Rajpurkar M. et al.	Inhibitors in factor IX deficiency a report of the ISTH-SSC international FIX inhibitor registry (1997-2006).	Haemophilia. 15 (5) (pp 1027-1031)	2009	2b, B

*Evidence levels rated according to US Agency for Health Care Policy and Research (AHCPR), as well as British Committee for Standards in Haematology (BCSH) using GRADE (Grading of Recommendations Assessment, Development and Evaluation)

Topic 1 and 2 (continued 3)

Author	Title	Citation	Year	Evidence level*
Nagel K., Walker I., Decker K. et al.	Comparing bleed frequency and factor concentrate use between haemophilia A and B patients.	Haemophilia. 17 (6) (pp 872-874)	2011	3, B
Tagariello G., Iorio A., Santagostino E. et al.	Comparison of the rates of joint arthroplasty in patients with severe factor VIII and IX deficiency: an index of different clinical severity of the 2 coagulation disorders.	Blood. 114 (4) (pp 779-784)	2009	3, B
Bernardi F., Dolce A., Pinotti M. et al.	Major differences in bleeding symptoms between factor VII deficiency and hemophilia B.	Journal of Thrombosis and Haemostasis. 7 (5) (pp 774-779)	2009	3, B
Zappa S., Mcdaniel M., Marandola J. et al.	Treatment trends for haemophilia A and haemophilia B in the United States: Results from the 2010 practice patterns survey.	Haemophilia. 18 (3) (pp e140-e153)	2012	2b, B
Guh S., Grosse S.D., McAlister S. et al.	Healthcare expenditures for males with haemophilia and employer-sponsored insurance in the United States, 2008.	Haemophilia. 18 (2) (pp 268-275)	2012	3, B
Monahan PE, Baker JR, Riske B et al.	Physical functioning in boys with hemophilia in the U.S.	American Journal of Preventive Medicine. 41(6 Suppl 4):S360-8,	2011	3, B
Taki M. and Shirahata A.	Current situation of regular replacement therapy (prophylaxis) for haemophilia in Japan.	Haemophilia. 15 (1) (pp 78-82)	2009	2b, B

*Evidence levels rated according to US Agency for Health Care Policy and Research (AHCPR), as well as British Committee for Standards in Haematology (BCSH) using GRADE (Grading of Recommendations Assessment, Development and Evaluation)

Topic 3

Author	Title	Citation	Year	Evidence level*
Tuddenham E.	Gene therapy for haemophilia B.	Haemophilia. 18 (SUPPL.4) (pp 13-17)	2012	2a, B
Nathwani A.C., Tuddenham E.G.D., Rangarajan S. et al.	Adenovirus-associated virus vector-mediated gene transfer in hemophilia B.	New England Journal of Medicine. 365 (25) (pp 2357-2365)	2011	

Topic 4

Author	Title	Citation	Year	Evidence level*
Stonebraker J.S., Bolton-Maggs P.H.B., Brooker M. et al.	A study of reported factor IX use around the world.	Haemophilia. 17 (3) (pp 446-455)	2011	3, B
Stonebraker J.S., Bolton-Maggs P.H.B., Michael Soucie J. et al.	A study of variations in the reported haemophilia B prevalence around the world.	Haemophilia. 18 (3) (pp e91-e94)	2012	3, B
Tagliaferri A, Rivolta GF, Iorio A et al.	Mortality and causes of death in Italian persons with haemophilia, 1990-2007.	Haemophilia. 16(3):437-46,	2010	3, B
Aznar J.A., Lucia F., Abad-Franch L. et al.	Haemophilia in Spain.	Haemophilia. 15 (3) (pp 665-675)	2009	2b, B

*Evidence levels rated according to US Agency for Health Care Policy and Research (AHCPR), as well as British Committee for Standards in Haematology (BCSH) using GRADE (Grading of Recommendations Assessment, Development and Evaluation)

29 Conference Abstracts: : Research on Factor IX [Topic 1 and 2]		
Powell J.	Safety, efficacy, and improved pharmacokinetics (PK) demonstrated in a phase 3 clinical trial of extended half-life recombinant FC fusion factor IX (B-LONG).	Haemophilia. Conference: 6th Annual Congress of the European Association for Haemophilia and Allied Disorders Warsaw Poland. Conference Publication: (var.pagings). 19 (pp 76-77), 2013. Date of Publication: February 2013.
Diao L.	Population pharmacokinetic analysis of a longacting recombinant factor IX-FC fusion protein (RFIXFC) in patients with severe haemophilia B.	Haemophilia. Conference: 6th Annual Congress of the European Association for Haemophilia and Allied Disorders Warsaw Poland. Conference Publication: (var.pagings). 19 (pp 33), 2013. Date of Publication: February 2013.
Kulkarni R.	Clinical study program to evaluate long-lasting recombinant factor VIII and IX FC fusion factors for paediatric use.	Haemophilia. Conference: 6th Annual Congress of the European Association for Haemophilia and Allied Disorders Warsaw Poland.Conference Publication: (var.pagings). 19 (pp 32), 2013. Date of Publication: February 2013.
Martinowitz U.	Efficacy, PK and safety results of a phase I/II clinical trial of recombinant fusion protein linking coagulation factor ix with albumin (rIX-FP) in previously treated patients with haemophilia b (prolong-9FP).	Blood. Conference: 54th Annual Meeting of the American Society of Hematology, ASH 2012 Atlanta, GA United States. Conference Publication: (var.pagings). 120 (21) , 2012. Date of Publication: 16 Nov 2012.
Windyga J.	Pharmacokinetics, efficacy and safety of BAX326, a novel recombinant factor IX: A prospective, controlled, multicenter study in previously treated patients with severe (FIX level < 1%) or moderately severe (FIX level <= 2%) hemophilia B.	Blood. Conference: 54th Annual Meeting of the American Society of Hematology, ASH 2012 Atlanta, GA United States. Conference Publication: (var.pagings). 120 (21) , 2012. Date of Publication: 16 Nov 2012.
Gomperts E.D.	IB1001, an investigational recombinant factor IX, pharmacokinetics in pediatric patients with hemophilia B.	Blood. Conference: 54th Annual Meeting of the American Society of Hematology, ASH 2012 Atlanta, GA United States. Conference Publication: (var.pagings). 120 (21) , 2012. Date of Publication: 16 Nov 2012.
Laws H.-J.	Non-interventional trial to assess the safety and efficacy of recombinant factor IX: Interim analysis of patients < 6 years.	Hamostaseologie. Conference: 56. Jahrestagung der Gesellschaft fur Thrombose- und Hamostase - Forschung e. V., GTH St. Gallen Switzerland. Conference Publication: (var.pagings). 32 (1) (pp A45), 2012. Date of Publication: 2012.
Horn C.	Functional characterization of recombinant factor IX albumin fusion protein.	Hamostaseologie. Conference: 56. Jahrestagung der Gesellschaft fur Thrombose- und Hamostase - Forschung e. V., GTH St. Gallen Switzerland. Conference Publication: (var.pagings). 32 (1) (pp A45), 2012. Date of Publication: 2012.
Santagostino E.	Results of a phase I international clinical trial of recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP) in patients with hemophilia B (PROLONG-9FP).	Hamostaseologie. Conference: 56. Jahrestagung der Gesellschaft fur Thrombose- und Hamostase - Forschung e. V., GTH St. Gallen Switzerland. Conference Publication: (var.pagings). 32 (1) (pp A12), 2012. Date of Publication: 2012.
Rendo P.	One-year assessment of coagulation markers and monitoring for thrombotic events in patients with hemophilia B treated with nonacog alfa.	Haemophilia. Conference: 30th International Congress of the World Federation of Hemophilia Paris France. Conference Publication: (var.pagings). 18 (pp 30), 2012. Date of Publication: July 2012.

29 Conference Abstracts: Research on Factor IX (continued 1) [Topic 1 and 2]		
Lubetsky A.	Safety and pharmacokinetic results of a phase I/II clinical trial of recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP) in previously treated patients with hemophilia B (PROLONG-9FP).	Haemophilia. Conference: 30th International Congress of the World Federation of Hemophilia Paris France. Conference Publication: (var.pagings). 18 (pp 24), 2012. Date of Publication: July 2012.
Hardewig J.	Four-year interim results of a non-interventional trial to assess the safety and efficacy of treatment with recombinant factor IX, BeneFIX.	Haemophilia. Conference: 30th International Congress of the World Federation of Hemophilia Paris France. Conference Publication: (var.pagings). 18 (pp 24), 2012. Date of Publication: July 2012.
Rothschild C.	Interim results (2-year) of a French non-interventional study to assess the long-term safety and efficacy of BeneFIX.	Haemophilia. Conference: 30th International Congress of the World Federation of Hemophilia Paris France. Conference Publication: (var.pagings). 18 (pp 23-24), 2012. Date of Publication: July 2012.
Santagostino E.	Results of a phase I international clinical trial of recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP) in patients with hemophilia B (PROLONG-9FP).	Haemophilia. Conference: 30th International Congress of the World Federation of Hemophilia Paris France. Conference Publication: (var.pagings). 18 (pp 22), 2012. Date of Publication: July 2012.
Suzuki T. .	Evaluation of the safety, efficacy of recombinant factor ix (nonacog alfa) in japanese patients with hemophilia B-interim result of post marketing surveillance study-.	Blood. Conference: 54th Annual Meeting of the American Society of Hematology, ASH 2012 Atlanta, GA United States.Conference Publication: (var.pagings). 120 (21) , 2012. Date of Publication: 16 Nov 2012.
Uprichard J.	Factor IX replacement to cover total knee replacement surgery in haemophilia B: 10 years experience in a single centre.	Haemophilia. Conference: 4th Annual Congress of the European Association for Haemophilia and Allied Disorders, EAHAD 2011 Geneva Switzerland. Conference Publication: (var.pagings). 17 (2) (pp 360), 2011. Date of Publication: March 2011.
Laws H.J.	Non-interventional trial to assess the safety and efficacy of recombinant factor IX: Interim analysis of patients < 6 years.	Hamostaseologie. Conference: 55th Annual Meeting of the Gesellschaft fur Thrombose- und Hamostaseforschung, GTH 2011 Wiesbaden Germany.Conference Publication: (var.pagings). 31 (1) (pp A38), 2011. Date of Publication: 2011.
Martinowitz U.	Pharmacokinetic behavior of IB1001, an investigational recombinant factor IX, in patients with hemophilia B: Repeat pharmacokinetic study and subgroup analysis.	Blood. Conference: 53rd Annual Meeting of the American Society of Hematology, ASH 2011 San Diego, CA United States. Conference Publication: (var.pagings). 118 (21) , 2011. Date of Publication: 18 Nov 2011.
Yamashita A.	Comparison of in vivo recovery of recombinant factor IX and plasma derived factor IX in previously treated JPNese hemophilia B patients.	Journal of Thrombosis and Haemostasis. Conference: 23rd Congress of the International Society on Thrombosis and Haemostasis 57th Annual SSC Meeting Kyoto Japan. Conference Publication: (var.pagings). 9 (pp 577-578), 2011. Date of Publication: July 2011.
Alamelu J.	Pharmacokinetic and dynamic properties of recombinant vs. plasma derived fix in patients with haemophilia B: A prospective cross-over study.	Journal of Thrombosis and Haemostasis. Conference: 23rd Congress of the International Society on Thrombosis and Haemostasis 57th Annual SSC Meeting Kyoto Japan. Conference Publication: (var.pagings). 9 (pp 465), 2011. Date of Publication: July 2011.

29 Conference Abstracts: Research on Factor IX (continued 2) [Topic 1 and 2]		
Chambost H.	Five-year post-marketing surveillance of haemophilia B patient receiving a factor IX concentrate: Final results.	Journal of Thrombosis and Haemostasis. Conference: 23rd Congress of the International Society on Thrombosis and Haemostasis 57th Annual SSC Meeting Kyoto Japan. Conference Publication: (var.pagings). 9 (pp 371), 2011. Date of Publication: July 2011.
Renchi Y.	Evaluation of the safety and efficacy of recombinant factor IX (nonacog alfa) in minimally treated and previously treated Chinese patients with hemophilia B.	Journal of Thrombosis and Haemostasis. Conference: 23rd Congress of the International Society on Thrombosis and Haemostasis 57th Annual SSC Meeting Kyoto Japan. Conference Publication: (var.pagings). 9 (pp 356), 2011. Date of Publication: July 2011.
Negrier C.	Safety and pharmacokinetic properties of glycopegylated recombinant factor IX: A first human dose trial in patients with haemophilia B.	Journal of Thrombosis and Haemostasis. Conference: 23rd Congress of the International Society on Thrombosis and Haemostasis 57th Annual SSC Meeting Kyoto Japan. Conference Publication: (var.pagings). 9 (pp 283-284), 2011. Date of Publication: July 2011.
Luk A.	Clinical trial for long-lasting recombinant factor IX-FC (rFIXFc) in subjects with haemophilia B (B-LONG).	Haemophilia. Conference: 4th Annual Congress of the European Association for Haemophilia and Allied Disorders, EAHAD 2011 Geneva Switzerland. Conference Publication: (var.pagings). 17 (2) (pp 355), 2011. Date of Publication: March 2011.
Westfeld M.	Non-interventional trial to assess the safety and efficacy of treatment with recombinant factor IX: Interim analysis after two years of study duration.	Hamostaseologie. Conference: 54. Jahrestagung der Gesellschaft fur Thrombose- und Hamostaseforschung and Symposium van de Nederlandse Vereniging voor Trombose en Hemostase Nurnberg Germany. Conference Publication: (var.pagings). 30 (1) (pp A63), 2010. Date of Publication: 2010.
Feddern J.	Pharmacokinetic characteristics of a high purity plasma-derived FIX concentrate (Octanine F) in paediatric and adult haemophilia B patients - An overview of the clinical trial data.	Hamostaseologie. Conference: 54. Jahrestagung der Gesellschaft fur Thrombose- und Hamostaseforschung and Symposium van de Nederlandse Vereniging voor Trombose en Hemostase Nurnberg Germany. Conference Publication: (var.pagings). 30 (1) (pp A53), 2010. Date of Publication: 2010.
Rendo P.	Safety of recombinant human factor IX, nonacog alfa, for usual use in pediatric patients: Results from a prospective registry of european hemophilia B patients.	Blood. Conference: 52nd Annual Meeting of the American Society of Hematology, ASH 2010 Orlando, FL United States. Conference Publication: (var.pagings). 116 (21) , 2010. Date of Publication: 19 Nov 2010.
Rendo P.	Safety of BeneFIX (nonacog alfa, recombinant human factor IX) for usual use in pediatric patients: Results from a prospective registry of European hemophilia B patients.	Pediatric Blood and Cancer. Conference: 23rd Annual Meeting of the American Society of Pediatric Hematology/Oncology, ASPHO 2010 Montreal, QC Canada.Conference Publication: (var.pagings). 54 (6) (pp 811), 2010. Date of Publication: June 2010.
Shapiro A.D.	Safety and prolonged biological activity following a single administration of a recombinant molecular fusion of native human coagulation factor IX and the Fc region of immunoglobulin G (IgG) (rFIXFc) to subjects with hemophilia B.	Haemophilia. Conference: 29th International Congress of the World Federation of Hemophilia Buenos Aires Argentina. Conference Publication: (var.pagings). 16 (pp 30), 2010. Date of Publication: July 2010.

2 Conference Abstracts: The hemophilia utilitzation group study part Vb (HUGS VB) [Topic 1 and 2]		
Lou M.	Indirect costs among persons with hemophilia B: The hemophilia utilization group study part Vb (HUGS Vb).	Haemophilia. Conference: 30th International Congress of the World Federation of Hemophilia Paris France. Conference Publication: (var.pagings). 18 (pp 68-69), 2012. Date of Publication: July 2012.
Poon J.L.	The hemophilia utilization group study (HUGS-VB): Health-related quality of life in hemophilia B.	Value in Health. Conference: 16th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, ISPOR 2011 Baltimore, MD United States. Conference Publication: (var.pagings). 14 (3) (pp A210), 2011. Date of Publication: May 2011.
2 Conference Abstracts: The International Factor IX Treatment Network Survey [Topic 1 and 2]		
Berntorp E.	The international factor IX treatment network survey.	Haemophilia. Conference: 4th Annual Congress of the European Association for Haemophilia and Allied Disorders, EAHAD 2011 Geneva Switzerland. Conference Publication: (var.pagings). 17 (2) (pp 367), 2011. Date of Publication: March 2011.
Shapiro A.D.	The international factor IX treatment network survey.	Haemophilia. Conference: HTRS/NASCOLA Scientific Symposium 2010 Chicago, IL United States. Conference Publication: (var.pagings). 17 (3) (pp 563), 2011. Date of Publication: May 2011.
2 Conference Abstracts: HB specific genetics [Topic 1 and 2]		
Guillerm E.	Spectrum of mutations in 345 unrelated hemophilia B patients.	Haemophilia. Conference: 30th International Congress of the World Federation of Hemophilia Paris France. Conference Publication: (var.pagings). 18 (pp 108), 2012. Date of Publication: July 2012.
Tagariello G.	Update of Italian hemophilia B (HB) mutation database: Suggestions for genetic counselling in patients and related females.	Haemophilia. Conference: 30th International Congress of the World Federation of Hemophilia Paris France. Conference Publication: (var.pagings). 18 (pp 46), 2012. Date of Publication: July 2012.
2 Conference Abstracts: Various [Topic 1 and 2]		
Shafer F.E.	Lack of seasonal variation in bleeding and patient-assessed pain patterns in patients with hemophilia b receiving on-demand therapy.	Blood. Conference: 54th Annual Meeting of the American Society of Hematology, ASH 2012 Atlanta, GA United States. Conference Publication: (var.pagings). 120 (21) , 2012. Date of Publication: 16 Nov 2012.
Lou M.	Utilizing a paper standard gamble instrument to assess health utility in patients with hemophilia B.	Value in Health. Conference: 16th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, ISPOR 2011 Baltimore, MD United States. Conference Publication: (var.pagings). 14 (3) (pp A208), 2011. Date of Publication: May 2011.

7 Conference Abstracts: Comparison of HB and HA [Topic 1 and 2]		
Clausen N.	Similar bleeding phenotype in young children with haemophilia A or B: A cohort study.	Haemophilia. Conference: 6th Annual Congress of the European Association for Haemophilia and Allied Disorders Warsaw Poland. Conference Publication: (var.pagings). 19 (pp 38-39), 2013. Date of Publication: February 2013.
Siegmund B.	Haemophilia A versus Haemophilia B: Are there relevant clinical differences?.	Hamostaseologie. Conference: 56. Jahrestagung der Gesellschaft fur Thrombose- und Hamostase - Forschung e. V., GTH St. Gallen Switzerland. Conference Publication: (var.pagings). 32 (1) (pp A37), 2012. Date of Publication: 2012.
Johnson K.A.	Health care utilization and cost of care: Insights from the hemophilia utilization group study (HUGS).	Haemophilia. Conference: 30th International Congress of the World Federation of Hemophilia Paris France. Conference Publication: (var.pagings). 18 (pp 175), 2012. Date of Publication: July 2012.
Siegmund B.	Differences in the bleeding phenotypes of hemophilia A and B.	Haemophilia. Conference: 30th International Congress of the World Federation of Hemophilia Paris France. Conference Publication: (var.pagings). 18 (pp 141), 2012. Date of Publication: July 2012.
Tardy-Poncet B.	Difference in tissue factor pathway inhibitor (TFPI) levels between hemophilia A and B patients.	Journal of Thrombosis and Haemostasis. Conference: 23rd Congress of the International Society on Thrombosis and Haemostasis 57th Annual SSC Meeting Kyoto Japan. Conference Publication: (var.pagings). 9 (pp 922), 2011. Date of Publication: July 2011.
Kelly D.	Prevalence of hip arthropathy in hemophilia A and B: An analysis of the UDC database.	Haemophilia. Conference: HTRS/NASCOLA Scientific Symposium 2010 Chicago, IL United States. Conference Publication: (var.pagings). 17 (3) (pp 556-557), 2011. Date of Publication: May 2011.
Escuriola Ettingshausen C.	Long-term prophylaxis in children and adolescents with haemophilia B.	Hamostaseologie. Conference: 54. Jahrestagung der Gesellschaft fur Thrombose- und Hamostaseforschung and Symposium van de Nederlandse Vereniging voor Trombose en Hemostase Nurnberg Germany. Conference Publication: (var.pagings). 30 (1) (pp A58), 2010. Date of Publication: 2010.

11 Conference Abstracts: Gene therapy [Topic 3]		
Davidoff A.	Stable factor IX activity following AAV-mediated gene transfer in patients with severe hemophilia B.	Blood. Conference: 54th Annual Meeting of the American Society of Hematology, ASH 2012 Atlanta, GA United States. Conference Publication: (var.pagings). 120 (21) , 2012. Date of Publication: 16 Nov 2012.
Tuddenham E.	Gene therapy for severe hemophilia B.	Haemophilia. Conference: 30th International Congress of the World Federation of Hemophilia Paris France. Conference Publication: (var.pagings). 18 (pp 107), 2012. Date of Publication: July 2012.
Wellman J.A.	Results from the long-term follow-up of severe hemophilia B subjects previously enrolled in a clinical study of AAV2-FIX gene transfer to the liver.	Molecular Therapy. Conference: 15th Annual Meeting of the American Society of Gene and Cell Therapy, ASGCT 2012 Philadelphia, PA United States. Conference Publication: (var.pagings). 20 (pp S28-S29), 2012. Date of Publication: May 2012.
Nathwani A.C.	Adeno-Associated Viral Vector Mediated Gene Transfer for Hemophilia B.	Blood. Conference: 53rd Annual Meeting of the American Society of Hematology, ASH 2011 San Diego, CA United States. Conference Publication: (var.pagings). 118 (21) , 2011. Date of Publication: 18 Nov 2011.
Nathwani A.	A phase I/II clinical trial entailing peripheral vein administration of a novel self complementary adeno-associated viral vector encoding human FIX for haemophilia B gene therapy.	Human Gene Therapy. Conference: European Society of Gene and Cell Therapy British Society for Gene Therapy Collaborative Congress 2011 Brighton United Kingdom.Conference Publication: (var.pagings). 22 (10) (pp A20), 2011. Date of Publication: October 2011.
Tuddenham E.G.	Gene therapy in haemophilia B: Interim report of a clinical trial using an AAV8 vector.	Hamostaseologie. Conference: 55th Annual Meeting of the Gesellschaft fur Thrombose- und Hamostaseforschung, GTH 2011 Wiesbaden Germany. Conference Publication: (var.pagings). 31 (1) (pp A32), 2011. Date of Publication: 2011.
Mingozzi F.	Dose-dependent activation of capsid-specific T cells after AAV serotype 8 vector administration in a clinical study for hemophilia B.	Journal of Thrombosis and Haemostasis. Conference: 23rd Congress of the International Society on Thrombosis and Haemostasis 57th Annual SSC Meeting Kyoto Japan. Conference Publication: (var.pagings). 9 (pp 761-762), 2011. Date of Publication: July 2011.
Nathwani A.C.	A phase i/ii clinical trial entailing peripheral vein administration of a novel self complementary adeno-associated viral vector encoding human fix for haemophilia b gene therapy.	Human Gene Therapy. Conference: 10th Annual Congress of the French Society of Cell and Gene Therapy, SFTCG 2011 Nantes France. Conference Publication: (var.pagings). 22 (6) (pp A7-A8), 2011. Date of Publication: June 2011.
Basner-Tschakarjan E.	Dose-dependent activation of capsid-specific T cells after AAV serotype 8 vector administration in a clinical study for hemophilia B.	Molecular Therapy. Conference: 14th Annual Meeting of the American Society of Gene and Cell Therapy Seattle, WA United States. Conference Publication: (var.pagings). 19 (pp S230), 2011. Date of Publication: May 2011.
Nathwani A.	Early clinical trial results following administration of a low dose of a novel self complementary adeno-associated viral vector encoding human factor IX in two subjects with severe hemophilia B.	Blood. Conference: 52nd Annual Meeting of the American Society of Hematology, ASH 2010 Orlando, FL United States. Conference Publication: (var.pagings). 116 (21) , 2010. Date of Publication: 19 Nov 2010.
Nathwani A.C.	Early clinical trial results following administration of a low dose of a novel self complementary adenohyphen;associated viral vector encoding human factor ix in two subjects with severe Haemophilia B.	Human Gene Therapy. Conference: 18th Annual Congress of the European Society of Gene and Cell Therapy, ESGCT 2010 Milan Italy.Conference Publication: (var.pagings). 21 (10) (pp 1362), 2010. Date of Publication: October 2010.

5 Conference Abstracts: Prophylaxis in HB [Topic 3]		
Rendo P.	Evaluation of two secondary prophylaxis regimens of recombinant factor IX (r-fix) in moderately severe to severe (fix <=2%) hemophilia B patients.	Haemophilia. Conference: 6th Annual Congress of the European Association for Haemophilia and Allied Disorders Warsaw Poland. Conference Publication: (var.pagings). 19 (pp 20), 2013. Date of Publication: February 2013.
Rendo P.	Evaluation of two secondary prophylaxis regimens of recombinant factor ix(r-ix) in moderately severe to severe(fix <=2%) hemophilia b patients.	Blood. Conference: 54th Annual Meeting of the American Society of Hematology, ASH 2012 Atlanta, GA United States.Conference Publication: (var.pagings). 120 (21) , 2012. Date of Publication: 16 Nov 2012.
Korth-Bradley J.M.	Pharmacokinetic/pharmacodynamic assessment of reformulated recombinant coagulation factor IX in adults and children with severe hemophilia B.	Blood. Conference: 53rd Annual Meeting of the American Society of Hematology, ASH 2011 San Diego, CA United States. Conference Publication: (var.pagings). 118 (21) , 2011. Date of Publication: 18 Nov 2011.
Plyusch O.	High dosage prophylactic treatment of severe patients with haemophilia B.	Journal of Thrombosis and Haemostasis. Conference: 23rd Congress of the International Society on Thrombosis and Haemostasis 57th Annual SSC Meeting Kyoto Japan. Conference Publication: (var.pagings). 9 (pp 673), 2011. Date of Publication: July 2011.
Valentino L.A.	A multicenter, open-label study to compare on-demand treatment with two prophylaxis regimens of recombinant coagulation factor IX in subjects with hemophilia B.	Journal of Thrombosis and Haemostasis. Conference: 23rd Congress of the International Society on Thrombosis and Haemostasis 57th Annual SSC Meeting Kyoto Japan. Conference Publication: (var.pagings). 9 (pp 357), 2011. Date of Publication: July 2011.
2 Conference Abstracts: The EQOFIX study [Topic 4]		
Polack B.	Health-related quality of life and annual direct medical cost of patients with haemophilia B in France: The eqofix study.	Value in Health. Conference: ISPOR 15th Annual European Congress Berlin Germany. Conference Publication: (var.pagings). 15 (7) (pp A515-A516), 2012. Date of Publication: November 2012.
Polack B.	Medico-economic and quality of life study of replacement therapy for haemophilia B in FRA: The Eqofix study.	Journal of Thrombosis and Haemostasis. Conference: 23rd Congress of the International Society on Thrombosis and Haemostasis 57th Annual SSC Meeting Kyoto Japan. Conference Publication: (var.pagings). 9 (pp 467), 2011. Date of Publication: July 2011.

COMPLETED STUDIES

Patients enrolled		Title of study	Topic	Recruitment
Age	**No.**			
c/a/s	14	Study Evaluating BENEFIX in Previously Treated Patients With Hemophilia B	S, Surgery	Completed
c/a/s	11	Post Marketing Surveillance To Observe Safety and Efficacy Of BeneFIX In Patients With Hemophilia B	S, E	Completed
c	20	Study Evaluating rFIX; BeneFIX in Severe Hemophilia B	S, E	Completed
c/a/s	35	Study Evaluating On-Demand Treatment With BeneFIX In Chinese Subjects	S, E	Completed
c/a/s	12	Post Marketing Study in Haemophilia B Patients Using Nonafact® (Human Coagulation Factor IX)	S, E	Completed
c/a	86	Pivotal Study (Pharmacokinetics, Efficacy, Safety) of BAX 326 (rFIX) in Hemophilia B Patients	S, E, PK	Completed
c/a	17	A Safety and Efficacy Study of a Recombinant Factor IX in Patients With Severe Hemophilia B	S, E, PK	Completed
c/a/s	218	Prospective Registry of European Hemophilia B Patients Receiving BeneFIX® for Usual Use	S	Completed
c/a/s	20	Study Evaluating Allergic Reactions To Benefix In Hemophilia B Patients	Allergic reactions	Completed
c/a/s	166	Study to Describe the Allergic Reactions to Factor IX in Patients With Hemophilia B	S, Allergic reactions	Completed
c/a/s	105	Study of Recombinant Factor IX Fc Fusion Protein (rFIXFc) in Subjects With Hemophilia B	S, E, PK	Completed

Abbreviations: c = children; a = adults; s = senior; S = safety; E = efficacy; PK = pharmacokinetics;

COMPLETED STUDIES (CONTINUED)

Patients enrolled		Title of study	Topic	Recruitment
Age	No.			
c/a/s	3 ?	Phase I/II Study of Monoclonal Factor IX Concentrate for Factor IX Deficiency	S, E	Completed
c/a/s	1 ?	Study Evaluating BeneFIX in Patients With Haemophilia B, Previously Treated With Plasma Derived Factor IX	E	Completed
c/a/s	23	Study Evaluating rFIX; BeneFIX® in Hemophilia B	S, E	Completed
c/a/s	?	Study Evaluating of Recombinant Human Factor IX (BeneFIX) and a New Formulation of BeneFIX (rFIX-R) in Moderate to Severe Hemophilia B	S, E	Completed
c/a	25	Safety and Pharmacokinetic Study of a Recombinant Coagulation Factor IX Albumin Fusion Protein in Subjects With Hemophilia B	S, PK	Completed (published)
a	18	Safety of 40K Pegylated Recombinant Factor IX in Non-Bleeding Patients With Haemophilia B	S, PK	Completed (published)
a/s	10	Phase I/IIa Study of FIXFc in Hemophilia B Patients	S, PK	Completed (published)
c/a	57	IMMUNINE Pre-Treatment Study	S, E	Completed
c/a/s	52	Study Evaluating Approach to Treatment of Haemophilia A and B in Spain	clinical practice	Completed
c/a	50	Study Comparing On-Demand Treatment With Two Prophylaxis Regimens Of BeneFIX In Patients With Severe Hemophilia B	QOL, SF-36	Completed
a/s	1370	Survey Evaluating the Psychosocial Effects of Living With Haemophilia	QOL, outcome	Completed

Abbreviations: c = children; a = adults; s = senior; S = safety; E = efficacy; PK = pharmacokinetics;

NOT COMPLETED STUDIES

Patients enrolled		Title of study	Topic	Recruitment
Age	No.			
a/s	60	Socialization of Adult Men With Congenital Hemophilia A or B	HRQOL	Recruiting
c/a	110	Comparing the Burden of Illness of Hemophilia in the Developing and the Developed World	CHO-KLAT	Not yet recruiting
c/a	24	Study To Compare On-Demand Treatment To A Prophylaxis Regimen Of BeneFIX In Subjects With Moderately Severe to Severe Hemophilia B	E	Recruiting
c	22	Study of Recombinant Factor IX Product, IB1001, in Previously Treated Pediatric Subjects With Hemophilia B	S, E, PK	Active, not recruiting
c/a/s	120	Long-Term Safety and Efficacy of Recombinant Human Coagulation Factor IX Fusion Protein (rFIXFc) in the Prevention and Treatment of Bleeding Episodes in Previously Treated Subjects With Hemophilia B	S, E	Recruiting
c/a	60	A Safety and Efficacy Study of a Recombinant Fusion Protein Linking Coagulation Factor IX With Albumin (rIX-FP) in Patients With Hemophilia B	S, E, PK	Recruiting
c	24	A Safety, Efficacy and Pharmacokinetics Study of a Recombinant Fusion Protein Linking Coagulation Factor IX With Albumin (rIX-FP) in Children With Hemophilia B	S, E, PK	Recruiting
c/a/s	60	Post Marketing Observational Study of Reformulated BeneFIX	S, E	Recruiting
c/a	300	BeneFIX Drug Use Results Survey [All-Case Surveillance]	E	Active, not recruiting
c	26	Study of Recombinant Coagulation Factor IX Fc Fusion Protein, BIIB 029, in Pediatric PTP Subjects With Hemophilia B.	S, E	Recruiting

Abbreviations: c = children; a = adults; s = seniors; S = safety; E = efficacy; PK = pharmacokinetics;

NOT COMPLETED STUDIES (CONTINUED 1)

Patients enrolled		Title of study	Topic	Recruitment
Age	No.			
c/a/s	77	Study of Recombinant Factor IX Product, IB1001, in Subjects With Hemophilia B	E	Active, not recruiting
c/a/s	74	Safety and Efficacy of NNC-0156-0000-0009 in Haemophilia B Patients	S, E	Active, not recruiting
c/a/s	100	Registry For Patients Treated With BeneFix In Usual Care Setting In Germany	S, E	Recruiting
c/a	30	BAX 326 Surgery Study	S, Surgery	Recruiting
c/a	100	BAX 326 (rFIX) Continuation Study	S, E	Recruiting
c	24	Safety, Efficacy and Pharmacokinetics of NNC-0156-0000-0009 in Previously Treated Children With Haemophilia B	S, E, PK	Recruiting
c	24	BAX 326 Pediatric Study	S, E, PK	Active, not recruiting
c/a/s	12	Efficacy and Safety of NNC-0156-0000-0009 During Surgical Procedures in Subjects With Haemophilia B	S, E Surgery	Recruitiing
c/a/s	70	Safety and Efficacy of NNC-0156-0000-0009 After Long-Term Exposure in Patients With Haemophilia B: An Extension to Trials NN7999-3747 and NN7999-3773	S, E	Recruiting
a/s	26	First-in-Human and Proof-of-Mechanism Study of ARC19499 Administered to Hemophilia Patients	PK of Aptamer	No yet recruiting

Abbreviations: c = children; a = adults; s = seniors; S = safety; E = efficacy; PK = pharmacokinetics;

NOT COMPLETED STUDIES (CONTINUED 2)

Patients enrolled		Title of study	Topic	Recruitment
Age	No.			
a/s	15	Safety of a New Type of Treatment Called Gene Transfer for the Treatment of Severe Hemophilia B	Gene therapy	Terminated
a/s	9	Gene Transfer for Subjects With Hemophilia B Factor IX Deficiency	Gene therapy	Active, not recruiting
a/s	15	Hemophilia B Gene Therapy - CCMT at CHOP	Gene therapy	Recruiting
a/s	16	Open-Label Single Ascending Dose of Adeno-associated Virus Serotype 8 Factor IX Gene Therapy in Adults With Hemophilia B	Gene therapy	Recruiting
a/s	18	Dose-Escalation Study Of A Self Complementary Adeno-Associated Viral Vector For Gene Transfer in Hemophilia B	Gene therapy	Recruiting

Abbreviations: c = children; a = adults; s = seniors; S = safety; E = efficacy; PK = pharmacokinetics;

Bibliographic list of publications related to a therapeutic role of IVIg

The recent guidelines from Australia (AU*; National Blood authority, 2nd Edition, 2012*) and Great Britain (UK; *Dept of Health, 2nd Edition 2008, updated 2012*) provided the basis for this bibliographic list. Chapter 5 of the Australian guidelines was used as template to rank conditions for which IVIg/SCIg has an established, emerging or no therapeutic role. The colour of references refers to their source:

Purple = AU BLACK = UK Brown: additional references

* References found in both guidelines from other sources

AU: Chapter 5: Conditions for which IVIg has an established therapeutic role

AU: Acquired hypogammaglobulinaemia secondary to haematological malignancies (CLL, NHL, MM, other relevant malignancies, post HSCT)

UK: Hemato-Oncology (p38-40)

Biotext 2004, 'Summary data on conditions and papers', in A systematic literature review and report on the efficacy of intravenous immunoglobulin therapy and its risks, commissioned by the National Blood Authority on behalf of all Australian Governments. Available from: http://www.nba.gov.au/pubs/pdf/report-lit-rev.pdf.

*Cordonnier, C, Chevret, S, Legrand, M, et al 2003, 'Should immunoglobulin therapy be used in allogeneic stem cell transplantation? A randomised, double-blind dose effect, placebo-controlled, multicentre trial', Annals of Internal Medicine, vol. 139, pp. 8–18.

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UK: Chronic inflammatory demyelinating Polyradiculoneuropathy (Neurology) P. 41

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UK: Guillain-Barré syndrome (Neurology) P. 42

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UK: ITP., adult and children (Hematology) P. 35 , 37

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AU: Inflammatory myopathies

UK: Inflammatory myopathies P.42

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AU: Kawasaki disease

UK: Kawasaki disease (Immunology) P. 30

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AU: Lambert–Eaton myasthenic syndrome

UK: Lambert-Eaton myasthenic syndrome (Neurology) P. 43

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AU: Multifocal motor neuropathy

UK: Multifocal motor neuropathy (Neurology) P. 43

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AU: Myasthenia gravis

UK: Myasthenia gravis (Neurology) P. 43

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AU: Neonatal haemochromatosis

UK: Not existing in the DH Guidelines

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AU: Primary immunodeficiency diseases

UK: Primary immunodeficiencies (Immunology) P. 28

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AU: Stiff person syndrome

UK: Stiff person syndrome (Neurology) P. 46

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AU: Chapter 6: Conditions for which IVIg has an emerging therapeutic role

AU: Acute disseminated encephalomyelitis (ADEM)

UK: Acute disseminated encephalomyelitis (Neurology, grey indications) P. 46

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AU: Anti-neutrophil cytoplasmic antibody (ANCA)-positive systemic necrotising vasculitis

UK: ANCA pos vasculitis P.61 Rheumatology (grey indication)

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AU: Autoimmune haemolytic anaemia (AIHA)

UK: Autoimmune haemolytic anaemia (Haematology) P. 33

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Hilgartner MW, Bussel J. Use of intravenous gamma globulin for the treatment of autoimmune neutropenia of childhood and autoimmunehemolytic anemia. Am J Med 1987;83:25–9.

AU: Bullous pemphigoid , Pemphigus foliaceus (PF) and Pemphigus vulgaris (PV)

AU: Cicatricial pemphigoid (CP) or mucous membrane pemphigoid (MMP)

UK: Immunobullous diseases Dermatology P.49

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AU: Evans syndrome - autoimmune haemolytic anaemia (AIHA) with immune thrombocytopenia

UK: Evans' syndrome (Haematology) and autoimmune Neutropenia. P. 33

Darabi, K, Abdel-Wahab, O & Dzik, WH 2006, 'Current usage of intravenous immunoglobulin and the rationale behind it: the Massachusetts General Hospital data and review of the literature', Transfusion, vol. 46, no. 5, pp. 741–53.
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AU: Foeto-maternal/neonatal alloimmune thrombocytopenia (FMAIT/NAIT)

UK: Alloimmune thrombocytopenia (Paediatrics) P. 52

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AU: Haemophagocytic syndrome

UK: Haemophagocytic lymphohistiocytosis/haemophagocytic syndrome (Haematology) P. 34 + 39

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UK: Idiopathic thrombocytopenia purpura <16 years (Paediatrics) P. 43

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AU: IgM paraproteinaemic neuropathy

UK: IgM-, IgA- or IgG- Paraprotein-associated demyelinating neuropathy (Neurlogy) P. 45

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AU: Kidney transplantation

UK: Treatment of acute antibodymediated rejection and steroidresistant rejection following solidorgan transplantation . P. 65 (Grey indication)

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UK: Not mentionened

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AU: Opsoclonus myoclonus ataxia (OMA)

UK: Neuromyotonus, Neurology P.47 (grey indication)

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AU: Post-transfusion purpura (PTP)

UK: Post-transfusion purpura (Haematology) P. 36 . Post-transfusion hyperhemolysis in Sickle cell anemia (Haematology) P.37 (grey indication

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AU: Secondary hypogammaglobulinaemia (including iatrogenic immunodeficiency)

UK: Low serum IgG following HSCT or thymoma and iatrogenic causes (Immunodeficiency) P.29, P.31 (Update 2012)

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AU: Specific antibody deficiency (including IgG subclasses)

UK: Specific antibody deficiency (Immunology, update 2012) P.31

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AU: Toxic epidermal necrolysis (TEN; Lyell syndrome)/Stevens–Johnson syndrome (SJS)

UK: Toxic epidermal necrolysis and Stevens–Johnson syndrome (Dermatology) P. 50

*Prins, C, Vittorio, C, Padilla, RS, et al 2003, 'Effect of high-dose intravenous immunoglobulin therapy in Stevens-Johnson syndrome: a retrospective, multicentre study', Dermatology, vol. 207, no. 1, pp. 96–9.

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AU: Toxic shock syndrome (TSS)

UK: Staphylococcal toxic shock syndrome (Infectious diseases) P. 62 ; Toxin-related infections P.54

*Darenberg, J, Ihendyane, N, Sjoelin, J, et al 2003, 'Intravenous immunoglobulin G therapy for streptococcal toxic shock syndrome: a European randomised double-blind placebo-controlled trial', Clinical Infectious Diseases, vol. 37, pp. 333–40.
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AU: Chapter 7: Conditions for which IVIg is used in exceptional circumstances only

AU: Acute leukaemia in children (Evidence 2a)

UK: Not mentioned

Orange, JS, Hossny, EM, Weiler, CR, et al 2006, 'Use of intravenous immunoglobulin in human disease: A review of primary evidence by members of the Primary Immuno-deficiency Committee of the American Academy of Allergy, Asthma and Immunology. J Allergy Clin Immunol 117:S525-53

AU: Autoimmune congenital heart block (evidence 4a)

UK: Not mentioned

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AU: Autoimmune neutropenia

UK: Autoimmune neutropenia (Haematology) P. 37

Anderson, D, Ali, K, Blanchette, V, et al 2007, 'Guidelines on the use of intravenous immune globulin for hematologic conditions', Transfusion Medicine Reviews, vol. 21, no. 2, suppl. 1, pp. S9–56.

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AU: Autoimmune uveitis

UK: not mentioned

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Orange, JS, Hossny, EM, Weiler, CR, et al 2006, 'Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology', Journal of Allergy and Clinical Immunology, vol. 117, no. 4, pp. S525–53.

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AU: Catastrophic antiphospholipid syndrome

UK: Catastrophic antiphospholipid syndrome, Rheumatology, P.60 (grey indication) and Cerebral infarction with antiphospholipi antibodies (Neurology) p.47 (grey indication)

Asherson, RA, Cervera, R, de Groot, PG, Erkan, D, Boffa, M-C, Piette, J-C, et al 2003, 'Catastrophic antiphospholipid syndrome: international consensus statement on classification criteria and treatment guidelines', Lupus, vol. 12, pp. 530–34.

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AU: Coagulation factor inhibitors

UK: Acquired haemophilia (Hematology) P. 32. Acquired von Willebrand disease (Hematology) P.36 (grey indication)

Hay, CR, Brown, S, Collins, PW, et al 2006, 'The diagnosis and management of factor VIII and IX inhibitors: a guideline from the United Kingdom Haemophilia Centre Doctors Organisation', British Journal of Haematology, vol. 133, no. 6, pp. 591–605.

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AU: Devic disease

UK: Not mentioned

Lennon, VA, Wingerchuk, DM, Kryzer, TJ, et al 2004, 'A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis', Lancet, vol. 364, no. 9451, pp. 2106–12.

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AU: Childhood Epilepsy (blue indication, 2a)

UK: Intractable childhood epilepsy (Neurology) P.47 (grey indication); UK: Rasmussen syndrome (Neurology) P.46

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AU: Graves ophthalmopathy

UK: not mentioned

Tagami, T, Tanaka, K, Sugawa, H, et al 1996, 'High-dose intravenous steroid pulse therapy in thyroid associated ophthalmopathy', Endocrinology Journal, vol. 43, no. 6, pp. 689–99.

AU: Haemolytic disease of the newborn

UK: Haemolytic disease of the fetus and newborn (isoimmune haemolytic jaundice in neonates) (Haematology) P. 34 + (Paediatrics) P. 53

*Gottstein, R & Cooke, RW 2003, 'Systematic review of intravenous immunoglobulin in haemolytic disease of the newborn', Archives of Disease in Childhood – Fetal Neonatal Edition, vol. 88, no. 1, pp. F6–10.

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AU: Hashimoto encephalopathy

UK: not mentioned

Jacob, S & Rajabally, YA 2005, 'Hashimoto's encephalopathy: steroid resistance and response to intravenous immunoglobulins', Journal of Neurology, Neurosurgery and Psychiatry, vol. 76, no. 3, pp. 455–6.

AU: HIV in children

UK: not mentioned

Orange, JS, Hossny, EM, Weiler, CR, et al 2006, 'Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology', Journal of Allergy and Clinical Immunology, vol. 117, no. 4, pp. S525–53.

AU: Myocarditis in children

UK: Not mentioned

Drucker, NA, Colan, SD, Lewis, AB, et al 1994, 'Gamma-globulin treatment of acute myocarditis in the pediatric population', Circulation, vol. 89, pp. 252–7.

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AU: Limbic encephalitis, nonparaneoplastic; Potassium channel antibody-associated encephalopathy

UK: Mentioned under Potassium channel antibodyassociated, non-neoplastic limbic encephalitis (Neurology) P. 48

*Vincent, A, Buckley, C, Schott, JM, et al 2004, 'Potassium channel antibody-associated encephalopathy: a potentially immunotherapy-responsive form of limbic encephalitis', Brain, vol. 127, pt 3, pp. 701–12.

Hudson, LA, et al 2008, 'Reduplicative paramnesia in Morvan's syndrome', Journal of the Neurological Sciences, vol. 267, no. 1–2, pp. 154–7.

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AU: Paediatric autoimmune neuropsychiatric disorder associated with streptococcal infections

UK: Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) (Neurology) P. 48 + (Paediatrics) P. 57

*Perlmutter, SJ, Leitman, SF, Garvey, MA, et al 1999, 'Therapeutic plasma exchange and intravenous immunoglobulin for obsessive-compulsive disorder and tic disorders in childhood', Lancet, vol. 354, no. 9185, pp. 1153–8.

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AU: Paraneoplastic syndromes: subacute sensory neuropathy, cerebellar degeneration, limbic encephalitis

UK: Paraneoplastic disorders , POEMS (Neurology) P.48; POEMS (Hematology) P.40

Bataller, L, Galiano, R, Garcia-Escrig, M, Martinez, B, Sevilla, T, Blasco, R, et al 2010, 'Reversible paraneoplastic limbic encephalitis associated with antibodies to the AMPA receptor', *Neurology*, vol. 74, no. 3, pp. 265–7.

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AU: Pure red cell aplasia

UK: Acquired red cell aplasia (Hematology) P.36 (grey indication)

Anderson, D, Ali, K, Blanchette, V, et al 2007, 'Guidelines on the use of intravenous immune globulin for hematologic conditions', Transfusion Medicine Reviews, vol. 21, no. 2, suppl. 1, pp. S9–56.

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Linardaki GD, Boki KA, Fertakis A, Tzioufas AG. Pure red cell aplasia as presentation of SLE: antibodies to erythropoietin. Scand J Rheumatol 1999;28:189–91.

AU: Pyoderma gangrenosum

UK: Pyoderma gangrenosum (Dermatology) P. 51 (grey indication)

Cummins, DL, Anhalt, GJ, Monahan, T & Meyerle, JH 2007, 'Treatment of pyoderma gangrenosum with intravenous immunoglobulin', British Journal of Dermatology, vol. 157, no. 6, pp. 1235–39.

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AU: Scleromyxedema

UK: Not mentioned

Kulczycki, A, Nelson, M, Eisen, A, et al 2003, 'Scleromyxedema: treatment of cutaneous and systemic manifestations with high-dose intravenous immunoglobulin', British Journal of Dermatology, vol. 149, no. 6, pp. 1276–81.

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AU: Sjogren's syndrome

UK: Not mentioned

Smith, A, Jackson, M, Wang, F, et al 2005, 'Neutralisation of muscarinic receptor autoantibodies by intravenous immunoglobulin in Sjogren's syndrome', Human Immunology, vol. 66, no. 4, pp. 411–6.

AU: Solid organ transplantation

UK: Antibody incompatible transplantation ; Treatment of acute antibodymediated rejection and steroidresistant rejection following solid organ transplantation (Transplantation) p. 65 (grey indication)

*Jordan, SC, Vo, A, Bunnapradist, S, et al 2003, 'Intravenous immune globulin treatment inhibits cross match positivity and allows for successful transplantation of incompatible organs in living-donor and cadaver recipients', Transplantation, vol. 76, no. 4, pp. 631–6.

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AU: Susac syndrome

UK: CNS Vasculitis P.47 and Vasculitic neuropathy P.48 (Neurology (grey indications)

Aubart-Cohen, F, Klein, I, Alexandra, J, et al 2007, 'Long-term outcome in Susac syndrome', Medicine (Baltimore), vol. 86, no. 2, pp. 93–102.

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AU: Systemic capillary leak syndrome (SCLS) and Sepsis (grey indications)

UK: Systemic vasculitis (Rheumatology)P.61; severe invasive Streptococcal group A disease P.62, Staphylococcal septic shock syndrome P.62, necrotizing Staühylococcal sepsis P.63 (Infections)

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AU: Chapter 8: Conditions for which IVIg use is not supported

AU: Acute optic neuritis

UK: Not mentioned

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UK: Atopic dermatitis/eczema (Dermatology) P. 50 (not beneficial)

none

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AU: Haemolytic uraemic syndrome

UK: Haemolytic uraemic syndrome (Haematology) P. 37

none

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none

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UK: Not mentioned

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AU: Systemic lupus erythematosus

UK: Systemic lupus erythematosus (Rheumatology) P. 61 (grey indication)

none

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UK: Not mentioned: Alzheimer's disease

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AU: Conditions for which IVIg is not supported (tables copied from 2012 guidelines)

Acute optic neuritis IVIg is not supported in this setting. There is anecdotal evidence for use in Devic disease but not optic neuritis. **Reference** Roed, HG, Langkilde, A, Sellebjerg, F, et al 2005, 'A double-blind randomised trial of intravenous immunoglobulin treatment in acute optic neuritis', *Neurology*, vol. 64, pp. 804–10.	2b
Acute rheumatic fever	2b
Adrenoleukodystrophy	4b
Amegakaryocytic thrombocytopenia	4b
Antiphospholipid syndrome (non-obstetric)	4b
Aplastic anaemia/pancytopenia	4b
Asthma	2c
Atopic dermatitis/eczema — adult	2b
Autism	4b
Autologous haemopoietic stem cell transplantation Use of IVIg in autologous stem cell transplant recipients is not supported unless the patient has established humoral deficiency (see Secondary hypogammaglobulinaemia).	2c

UK : Conditions for which IVIg is not supported (tables copied from 2012 guidelines)

- Immunodeficiency secondary to paediatric HIV infection
- Autologous BMT
- Adrenoleukodystrophy
- Alzheimer's disease
- Amyotrophic lateral sclerosis
- Chronic fatigue syndrome
- Critical illness neuropathy
- Multiple sclerosis
- Rheumatoid arthritis
- Neonatal sepsis (prevention or treatment)
- Sepsis in the intensive care unit not related to specific toxins or C. difficile
- Asthma
- Graves' ophthalmopathy
- IVF failure
- Recurrent spontaneous pregnancy loss

Behçet's disease	4b
Cardiac surgery with bypass — prophylaxis	2a
IVIg is not supported in this setting; preferable alternative treatments are available.	
Congestive cardiac failure	2a
IVIg is not supported in this setting; preferable alternative treatments are available.	
Crohn's disease	4b
Diamond Blackfan syndrome	4b
Female infertility	4a
Glomerulonephritis — IgA nephritis	2b
Haemolytic uraemic syndrome	4b
Henoch–Schonlein purpura	4b
HIV/AIDS — adult	2b
(see Secondary hypogammaglobulinaemia and/or ITP in adults)	
Idiopathic dilated cardiomyopathy	2b
Linear IgA disease	4b
Lupus cerebritis	4a
IVIg is not supported as preferable alternative treatments are available.	
Lupus nephritis	2a
IVIg is not supported in this setting; preferable alternative treatments are available.	
Motor neuron disease/amyotrophic lateral sclerosis	4b
Note: IVIg is sometimes used when the diagnosis of motor neuron disease has not yet been established and an alternative diagnosis of multifocal motor neuropathy has not been ruled out.	
Myalgic encephalomyelitis	2c

UK: Conditions for which IVIg is not supported 2008

Immunodeficiency secondary to paediatric HIV infection
Autologous BMT
Adrenoleukodystrophy
Alzheimer's disease
Amyotrophic lateral sclerosis
Chronic fatigue syndrome
Critical illness neuropathy
Multiple sclerosis
Rheumatoid arthritis
Neonatal sepsis (prevention or treatment)
Sepsis in the intensive care unit not related to specific toxins or C. difficile
Asthma
Graves' ophthalmopathy
IVF failure
Recurrent spontaneous pregnancy loss

Narcolepsy/cataplexy
Nephrotic syndrome
IVIg is not supported in this setting; preferable alternativ treatments are available.
Obsessive compulsive disorders
IVIg is not supported in this setting (see PANDAS).
Polyneuropathy of critical illness
Recurrent foetal loss (with or without antiphospholipid syndrome)
Reference
Empson, M, Lassere, M, Craig, J, et al 2005, 'Prevention of recurrent miscarriage for women with antiphospholipi antibody or lupus anticoagulant (Cochrane Review)', in *The Cochrane Library*, Issue 2, John Wiley & Sons, Ltd, Chichester, UK.
Rheumatoid arthritis
IVIg is not supported in this setting; preferable alternativ treatments are available.
Sepsis
Adult and paediatric treatment or prevention If IgG levels are low, the use of IVIg should be considered under PID and/or secondary hypogammaglobulinaemia (including iatrogenic immunodeficiency).
Neonatal prevention IVIg is not supported. Therapy with intravenous immune globulin had no effect on the outcomes of suspected or p neonatal sepsis (Brockelhurst et al 2011).

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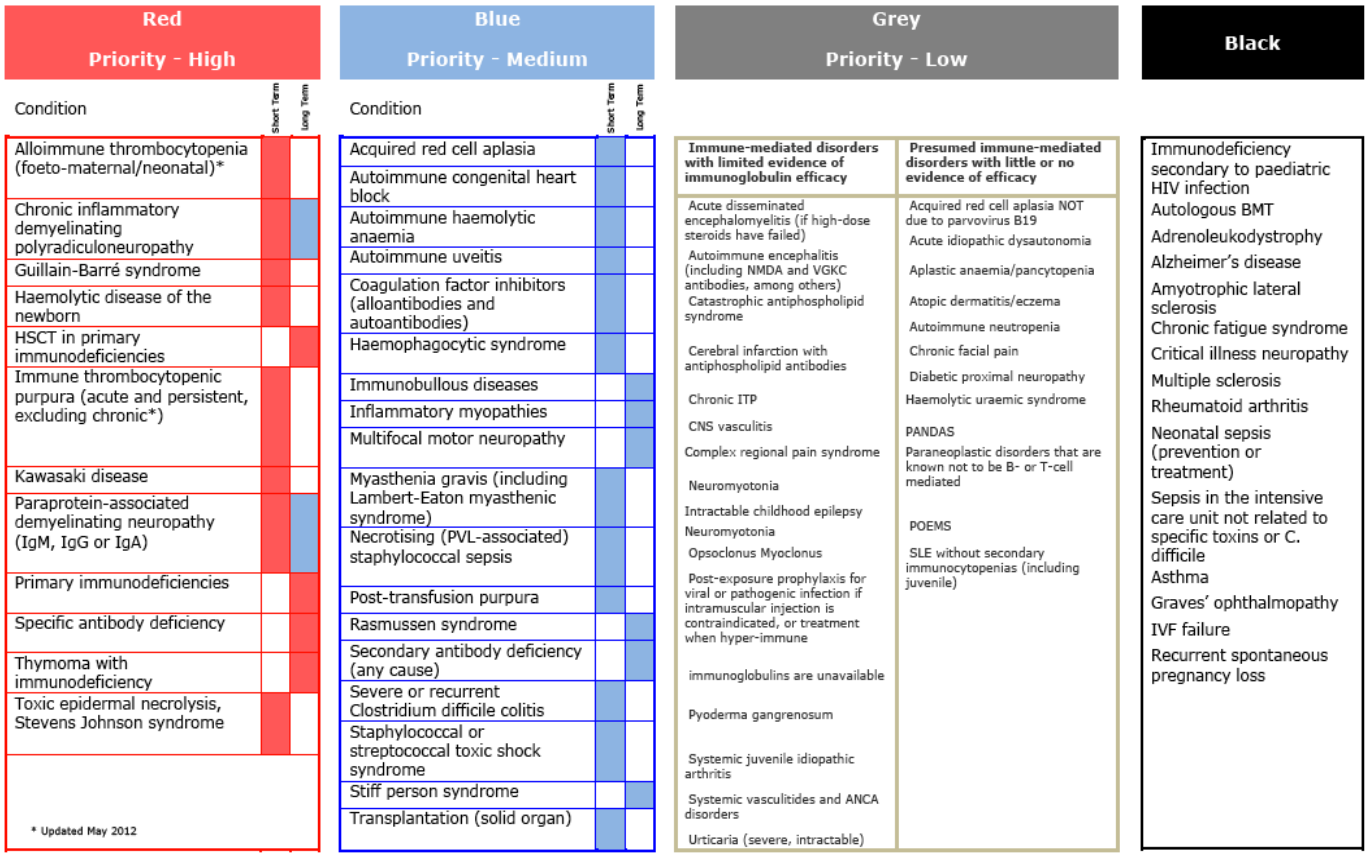
Concluding remark to the bibliographic list

Although the Australian and British guidelines show good concordance for the established indications they differ considerably for emerging and exceptional indications as well as for the non-indications.

UK Poster: Demand Management Plan



Red — Priority - High

Condition	Short Term	Long Term
Alloimmune thrombocytopenia (foeto-maternal/neonatal)*	■	
Chronic inflammatory demyelinating polyradiculoneuropathy	■	■
Guillain-Barré syndrome	■	
Haemolytic disease of the newborn	■	
HSCT in primary immunodeficiencies		■
Immune thrombocytopenic purpura (acute and persistent, excluding chronic*)	■	
Kawasaki disease	■	
Paraprotein-associated demyelinating neuropathy (IgM, IgG or IgA)	■	■
Primary immunodeficiencies		■
Specific antibody deficiency		■
Thymoma with immunodeficiency		■
Toxic epidermal necrolysis, Stevens Johnson syndrome	■	

* Updated May 2012

Blue — Priority - Medium

Condition	Short Term	Long Term
Acquired red cell aplasia	■	
Autoimmune congenital heart block	■	
Autoimmune haemolytic anaemia	■	
Autoimmune uveitis	■	
Coagulation factor inhibitors (alloantibodies and autoantibodies)	■	
Haemophagocytic syndrome	■	
Immunobullous diseases		■
Inflammatory myopathies		■
Multifocal motor neuropathy		■
Myasthenia gravis (including Lambert-Eaton myasthenic syndrome)	■	
Necrotising (PVL-associated) staphylococcal sepsis	■	
Post-transfusion purpura	■	
Rasmussen syndrome		■
Secondary antibody deficiency (any cause)		■
Severe or recurrent Clostridium difficile colitis	■	
Staphylococcal or streptococcal toxic shock syndrome	■	
Stiff person syndrome		■
Transplantation (solid organ)	■	

Grey — Priority - Low

Immune-mediated disorders with limited evidence of immunoglobulin efficacy	Presumed immune-mediated disorders with little or no evidence of efficacy
Acute disseminated encephalomyelitis (if high-dose steroids have failed)	Acquired red cell aplasia NOT due to parvovirus B19
Autoimmune encephalitis (including NMDA and VGKC antibodies, among others)	Acute idiopathic dysautonomia
Catastrophic antiphospholipid syndrome	Aplastic anaemia/pancytopenia
Cerebral infarction with antiphospholipid antibodies	Atopic dermatitis/eczema
Chronic ITP	Autoimmune neutropenia
CNS vasculitis	Chronic facial pain
Complex regional pain syndrome	Diabetic proximal neuropathy
Neuromyotonia	Haemolytic uraemic syndrome
Intractable childhood epilepsy	PANDAS
Neuromyotonia	Paraneoplastic disorders that are known not to be B- or T-cell mediated
Opsoclonus Myoclonus	POEMS
Post-exposure prophylaxis for viral or pathogenic infection if intramuscular injection is contraindicated, or treatment when hyper-immune immunoglobulins are unavailable	SLE without secondary immunocytopenias (including juvenile)
Pyoderma gangrenosum	
Systemic juvenile idiopathic arthritis	
Systemic vasculitides and ANCA disorders	
Urticaria (severe, intractable)	

Black

- Immunodeficiency secondary to paediatric HIV infection
- Autologous BMT
- Adrenoleukodystrophy
- Alzheimer's disease
- Amyotrophic lateral sclerosis
- Chronic fatigue syndrome
- Critical illness neuropathy
- Multiple sclerosis
- Rheumatoid arthritis
- Neonatal sepsis (prevention or treatment)
- Sepsis in the intensive care unit not related to specific toxins or C. difficile
- Asthma
- Graves' ophthalmopathy
- IVF failure
- Recurrent spontaneous pregnancy loss

References to immunomodulatory effects of IVIg in experimental models (P. Späth)

Schwab I, Nimmerjahn F (2013) Intravenous immunoglobulin therapy: How does IgG modulate the immune system? Nat.Rev.Immunol. 13:176-189

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Leontyev D, Katsman Y, Branch DR (2012) Mouse background and IVIG dosage are critical in establishing the role of inhibitory Fc© receptor for the amelioration of experimental ITP. Blood 119:5261-5264

Leontyev D, Katsman Y, MA XZ, Miescher S, Käsermann F, Branch DR (2012) Sialylation-independent mechanism involved in the amelioration of murine immune thrombocytopenia using intravenous gammaglobulin. Transfusion (Paris). 52:1799-1805

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Anumula KR (2012) Quantitative glycan profiling of normal human plasma derived immunoglobulin and its fragments Fab and Fc. J.Immunol.Meth. 382:167-176

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Session Summaries

SESSION 1: General information on the clinical use of clotting factors and immunoglobulins

Moderator: Karl-Heinz Buchheit
Rapporteurs: Rainer Seitz & Harvey Klein

Plasma fractionation for the preparation of medicinal proteins began in the 1940s, with the goal of providing a concentrate of albumin suitable for treating haemorrhagic shock on the battlefield. For several years thereafter, albumin production was the driving force behind commercial fractionation. By the 1970s, the first generation of commercial clotting factor concentrates became available and represented both a major advancement in the treatment of haemophilia and an additional commercial incentive to expand plasma collection and fractionation. The risk of transmission of hepatitis viruses, not seen with the pasteurised albumin products, was reluctantly tolerated as the price for improved haemophilia care. However, the recognition of HIV transmission by clotting factor concentrates in the early 1980s and the infection and death of more than 90% of patients with severe haemophilia in the US drew attention to the safety hazards of new plasma products and reduced the demand for all plasma fractions. By 1985, methods to reduce the risk of viral transmission were introduced into the production of clotting factor concentrates and products of higher purity and potency began to appear. Recombinant clotting factors were introduced in the early 1990s and have gone through several generations of modifications.

By 1973, commercialisation of another plasma fraction that concentrated IgG led to a major advancement in the treatment of congenital immunodeficiency disorders. Intramuscular (IM) immunoglobulin injections replaced plasma infusions as the accepted treatment for these uncommon disorders. By the 1980s, several intravascular preparations (IVIg) had been developed and began to replace the earlier IM preparations, which did not produce effective treatment levels. These products were also administered by the sub-cutaneous route and, by the late 1990s, specific preparations for the sub-cutaneous route reached the European market. A major development that impacted the entire fractionation industry was the discovery in 1981 that IVIg administration has immunomodulatory properties. From the initial indication for use in immune thrombocytopenic purpura (ITP), IVIg has been administered to an ever-increasing number of patients with inflammatory and auto-immune disorders. Production of IVIg now drives an expanding plasma fractionation industry yet, on occasion, demand still out-strips supply.

Rationale for the meeting: The Wildbad Kreuth Initiative

Several European initiatives from 1989 to 2009 have dealt with the issues of self-sufficiency and optimal use of blood and blood products. The first Wildbad Kreuth conference in 1999 addressed, along with other issues, the optimal use of the then available plasma products in the treatment of haemophilia. Among the specific recommendations were: 1) establishment of patient registries; 2) development of a network of Comprehensive Care Centres, and 3) the general recommendation of prophylactic care for children with severe disease. These recommendations were updated at the Wildbad Kreuth Initiative II in 2009, and new recommendations were added on best practices, home treatment, cost-effectiveness, genetic counselling and equitable treatment across EU member states. The recommendations from Kreuth I & II are widely recognised as having had an impact in improving haemophilia care across the EU.

Nevertheless, great variability in patient care practices and availability of the different concentrates persists across member states, as highlighted by the presentation of B. O'Mahoney in Session 2. The differences in per capita use of Factor VIII are particularly striking. In addition, since Kreuth I, a variety of plasma-derived and recombinant clotting factors have become available. Several new and innovative products are in different stages of development. Some of these are expected to reach the market soon. Furthermore, neither Kreuth I nor Kreuth II dealt with self-sufficiency and appropriate use of immunoglobulin preparations; a growing concern for immunodeficiency patients. Kreuth III was designed to appraise the status quo of clotting factor and immunoglobulin concentrates, and to identify gaps and future needs in treatment, supply and research.

Haemophilia Treatment

Treatment of haemophilia has evolved from the early episodic treatment that was necessitated by the scarcity of concentrate and its high cost, to the eventual prophylactic use that has become standard care for children. Recommendations based on the available evidence in 1999 were proposed at Kreuth I. Data remain scarce on the factor levels required for different bleeding events and therapeutic interventions, as well as the duration of treatment. There is still controversy regarding the optimal preparations for individual patients and clinical circumstances; although the use of recombinant products for previously untreated patients (PUPs) is widely acknowledged. Comprehensive care and treatment centres differ dramatically in availability and quality across Europe. The optimal management of inhibitors has not been adequately studied, nor has the issue of prophylaxis for adults. The costs of concentrate and especially of recombinant factors prove prohibitive for many countries and two-thirds of patients with haemophilia worldwide have limited access to treatment. P. Robert showed in his presentation that the Factor VIII demand in Europe has increased 3.1-fold in the period between 1996 and 2003. Yet demand is expected to continue growing - driven by demographics, improved health services, lobbying by patient groups and product awareness among patients and physicians.

There is no doubt that widespread availability of safe treatment has dramatically improved life expectancy and quality of life. However, when haemophilia treatment in Europe has been evaluated, e.g. by the ESCHQol study and a survey of 35 countries under the auspices of the European Haemophilia Consortium (EHC), disparities and gaps were still identified. Novel products, e.g. molecules modified in order to prolong their half-lives, will be ready for market access in the near future. Such products appear to hold promise to improve therapy, but their safety needs to be evaluated and their incremental cost will be an important issue. P. Giangrande emphasized that improving patient quality of life should drive treatment decisions, not economics. Nevertheless, he predicted greater emphasis on the cost-effectiveness of therapy, and a trend towards fewer but larger dedicated treatment centres.

Use of Immunoglobulins

Regarding immunoglobulin concentrates, it is now clear that preparations differ significantly, at least in adverse event profiles, if not in composition and action. The treatment levels for patients with primary immunodeficiency remain controversial, and the majority of patients remain undiagnosed and untreated. In addition to the licensed indications, the number of auto-immune and inflammatory disorders being treated "off-label" continues to grow, and at least a dozen of these are considered "high priority". This is shown in H.H. Peter's presentation, which reviewed interesting findings on the role of Fc. However, the in vivo mechanism(s) are still incompletely understood and there are no markers that predict which patients and which

disorders are most likely to respond to immunomodulatory therapy. Since expanding indications are combined with the additional use of these preparations for secondary immunodeficiency states, the requirements for IVIg in Europe and worldwide have now become the driving force behind plasma collection and fractionation, as demonstrated in the overview presented by P. Robert. Despite the dramatic increase in plasma collection, shortages have been experienced in many countries. Concerns about shortages have led to prioritisation strategies, such as the Demand Management Plan developed in the UK by the Department of Health in London.

Regulatory Issues

While it is widely acknowledged that patients have a right to access safe and affordable medicines - the right product in the right dose at the right time for the right indication, by the right route of administration – several regulatory issues affect the safety, availability and affordability of plasma-derived and recombinant medicinal products. There are a number of European Regulators involved in these issues, in addition to the national regulatory authorities (NRAs) of the individual member states. In the European Medicines Agency (EMA), the central scientific group is the Committee on Human Medicinal Products (CHMP), which is comprised of experts delegated by the EU member states. CHMP is assisted by scientific groups, such as the Blood Product Working Party (BPWP). Recently, the Paediatric Committee (PDCO) (for the special needs of children) and the Pharmacovigilance Risk Assessment Committee (PRAC) have become involved, both installed at the EMA by specific legislation. A variety of safe and efficacious immunoglobulin products have been authorised, but off-label use, new indications and product supply remain important regulatory concerns. Similarly, in the area of bleeding disorders, a variety of different safe and efficacious plasma-derived and recombinant products have already been authorised. However, the therapeutic modalities (e.g. continuous infusion, immune tolerance induction (ITI)), the licensing of novel products such as those with prolonged half-lives, the nature of the required trials and questions of safety (particularly immunogenicity, which may take years to appreciate in this relatively small patient population), remain problems for regulatory discussion. Both physicians and patients have expressed concerns that enhanced requirements for trials in the updated guidelines and the new instrument of ‘paediatric investigation plans’ will inhibit or prevent important new products from reaching the market. The potency assays for factors VIII and IX are an additional concern, particularly for recombinant products, which yield different values when calibrated with the International Standard. Another major problem involves the designation of products as “orphan medicinal products”. On the one hand, such designation may be needed to provide the necessary incentives for a manufacturer to invest in improved biologics. On the other hand, this precludes member states from granting or extending marketing authorisation for a period of 10 years for similar medicinal products with the same therapeutic indication. Granting market exclusivity can create a monopoly that has the effect of limiting access to, and raising the costs of, novel products for haemophilia treatment. Finally, the classical regulatory criteria for market authorisation are quality, efficacy and safety. In recent years, healthcare providers increasingly ask about the evidence for incremental benefit of any new medicine over existing ones, and ask for health technology assessment to take into account the medical, economic, social and ethical implications for the population or the individual patient. In Germany, for example, reimbursement for a new medicine is determined by the Federal Joint Committee (G-BA) by assessing its incremental benefit as documented by the applicant in a dossier on the basis of clinical data.

Outcome of the EDQM surveys

During the preparation of the symposium, questionnaires on the current status of treatment were sent to all invited participants, representing 43 countries. Thirty-five delegates responded to the survey on clotting factor concentrates. The survey showed that there is substantial use of plasma-derived concentrates, but 21 respondents indicated that they “always” used recombinant products, and 11 “rarely” used plasma-derived concentrates. The availability of prophylaxis was reported by 88.6% (31) of respondents, predominantly for children. Home treatment and supervision by Comprehensive Care Centres is common, but by no means the rule. Registries exist in 25 countries.

Contributions to the immunoglobulin survey were provided by 34 delegates. The pattern of available products varies considerably; the products are purchased through national tenders in 36.4% of countries. For immunoglobulins too, home treatment and supervision by Comprehensive Care Centres are common (>51% of patients in 13/20 responding countries), but are not widely established. The evaluation of the responses confirmed that there is substantial off-label use in various indications.

SESSION 2: Clotting Factors

Moderators & Rapporteurs: Wolfgang Schramm & Rainer Seitz

The purpose of this session was to provide an overview of the current status of haemophilia treatment from the perspective of clinicians, patients and regulators, and to set the scene for the discussions in Working Group 1.

Haemophilia care has much improved in the past decades, but there are still access issues and unmet patient needs, as pointed out by B. O'Mahony who spoke on behalf of the European Haemophilia Consortium (EHC). The recommendations from the previous Kreuth meetings were helpful in lobbying for improvements; particularly the recommendations to aim at a minimum consumption of 2 IU of factor VIII per capita and to also consider prophylaxis in adults. However, a survey of 35 countries published in 2012 revealed that 12/35 European countries still remain below 2 IU of factor VIII per capita, and 5/35 remain below 1 IU per capita. Factor VIII consumption is clearly related to GDP, but there is an upward trend in most countries, even in some countries where general health expenditure has declined. A matter of concern is that the concept of Comprehensive Care Centres (CCC) is only partially implemented in some countries. Patients are concerned that requirements for clinical studies to obtain marketing authorisation would possibly delay access to novel products in Europe, and consider that a proactive dialogue is needed with industry to set price expectations at a realistic level.

The life expectancy of haemophilia patients under optimal treatment is far better than that of patients with other monogenic disorders like cystic fibrosis or thalassaemia, as was pointed out by P.M. Mannucci. Thus, framing the future of haemophilia care in the third millennium means building on strengths. Goals include greater and wider availability of coagulation factors and reducing allo-antibodies (inhibitors) in previously untreated patients (PUP). Longer-acting products, i.e. engineered factor VIII, factor IX and factor VIIa concentrates, aim at potential benefits, such as extended protection from bleeding and reduced infusion frequency (which might help to avoid central catheter implantation for venous access). Possible difficulties include increased costs and potential neo-antigenicity. P.M. Mannucci reviewed the current stage of clinical development of longer-acting factor VIII, factor IX and factor VIIa products; for factor IX in particular, there is apparently a significant prolongation of half-life. He voiced his concern that the requirements of regulatory agencies for the design and conduct of clinical trials have recently been enhanced and may be exceedingly demanding. He mentioned the possibility of gene therapy in the future; progress is being made in this regard, particularly for haemophilia B.

An overview of the strategies to produce recombinant factors with prolonged half-lives was provided by F. Peyvandi. Currently, PEGylation, PEGylated liposomes, fusion proteins with albumin or Fc fragments, and proteins with modified amino acid sequences are being evaluated.

In comparison to unmodified factors, the half-lives are increased 3- to 5-fold for factor IX, 1.5- to 1.8-fold for factor VIII, and 3- to 5-fold for factor VIIa. For haemophilia B patients, one weekly injection could be sufficient. Several additional or alternative strategies are currently being elaborated, including tissue factor pathway inhibitor (TFPI) inhibitors, inhibition of activated protein C or anti-thrombin by aptamers or RNAi silencing, and a bi-specific antibody (ACE910) against activated factor IX and factor X. Preliminary clinical data

with a TFPI inhibitor has shown an excessive increase in TFPI, leading to increased bleeding. The bi-specific antibody ACE910 binds factors IXa and X in a way that mimics the factor VIII-mediated formation of the tenase complex and could be an elegant by-passing agent for controlling the bleeding in patients with factor VIII inhibitors; clinical studies are just commencing. F. Peyvandi also addressed challenges in the evaluation of the potency and safety of novel products. The potency measurement of novel products may be highly dependent on the choice of assay methods and reagents, and units assigned in vitro may correlate differently with the clinical activity of the new products, particularly if the modification has changed their pharmacokinetic profile. Recently, the FVIII/FIX sub-committee of the Scientific and Standardisation Committee (SSC) of the International Society on Thrombosis and Haemostasis (ISTH) published recommendations, including an algorithm. The determination of potency has important implications for clinical trials; not only for choosing the dose, but also for monitoring post-infusion levels in patients. Suitable assays should be validated and standardised, particularly for by-passing agents and alternative treatment strategies. Clinically, the most important risk in haemophilia treatment is inhibitor formation, for which the Nijmegen-modified Bethesda assay is currently the gold standard. It will be necessary to explore the performance of this assay and possibly also alternative methods, particularly for novel strategies. Current SSC sub-committee projects deal with laboratory assessment and standardisation and clinical trial design in haemophilia. Concerning the clinical evaluation of products, F. Peyvandi advocated further harmonisation of the regulatory requirements set by the FDA and EMA.

The adherence to the 10 principles of haemophilia care (Haemophilia 2008; 14:361–374) recently published by the European Association for Haemophilia and Associated Disorders (EHAD) was discussed by C. Hermans, taking into account two recent surveys. Central organisations of haemophilia care (mostly physicians' treatment boards) are present in 11/14 (79%) of the European countries surveyed, and national registries exist in 8/14 (57%) of the countries. All 14 countries surveyed had designated Comprehensive Care Centres (CCC); the total patient number per centre ranged from 55 to 1,317. Forty or more adults with severe haemophilia were cared for by 81% of centres, but only 47% of centres cared for 40 or more children with severe haemophilia, and the extent of services provided by CCC was variable.

Concern had been expressed by B. O'Mahony, P.M. Mannucci and F. Peyvandi about enhanced regulatory requirements for clinical studies of factor VIII and IX products. A. Hilger explained that the clinical evaluation of medicinal products according to Directive 2001/20/EC needs to be compliant with Good Clinical Practice (GCP). She reiterated the history of the guidance on clinical investigation and the core summary of product characteristics (SmPC) of recombinant and plasma-derived FVIII and FIX, from the first version from 1996 to the current version adopted in July 2011. She compared the requirements for evaluation of efficacy and safety of the previous guideline with the current guideline.

Addressing the risk of induction of inhibitors will mean accepting that the evidence from pre-licensing studies will be limited and that further data from larger GCP post-marketing studies will be required. An important impact came from the Paediatric Regulation (EC) No 1901/2006, which led to the requirement of including more children (particularly PUP) in studies, especially for novel products. A. Hilger pointed out that the current guideline is an example of the new concept of adaptive marketing authorisation, with a step-wise approach composed of pre- and post-licensing data that balances the minimum data needed against patient availability and ensures evaluation of the products both in adults and in children (who are the most vulnerable patients).

In the final presentation of session 2, M. Makris highlighted the role of registries. He addressed three types of registries: 1) national, regional or local patient registers, 2) study-associated registries, and 3) specific adverse event registries. The UK Haemophilia Centre Doctors Organisation (UKHCDO) was founded in 1968, and virtually all UK patients with bleeding disorders and their treatments have been registered with it from birth to death since its foundation. The registry provides, for example, detailed figures of product usage and information about the occurrence of inhibitors. The RODIN registry (N Engl J Med 2013; 368:231-239) collected detailed information from 29 haemophilia centres about 574 recruited PUP with 177 observed inhibitors (32.4%). One controversial result was the higher incidence of inhibitors under a second-generation recombinant factor VIII product. The European Haemophilia Safety Surveillance (EUHASS) project is a registry that collects specific information on adverse events, which is funded by the European Union (in the framework of the Public Health Programme), as well as by industry. Data compiled for the period 1 October 2008 – 30 September 2011 from 74 haemophilia centres in 26 European countries represent 29,692 patients. So far, no significant difference in inhibitor induction has been found between plasma-derived and recombinant products.

SESSION 3: Immunoglobulins

Moderators & Rapporteurs: Hans-Hartmut Peter, Isabella Quinti & Carrock Sewell

The purpose of this session was to provide an overview of the ever-increasing spectrum of indications for intravenous and sub-cutaneous immunoglobulins (IVIg, SCIg) in primary and secondary immunodeficiency (H Chapel, HH Peter) and in immunomodulatory indications, notably in neurology (I van Schaik). The benefits of the UK's Immunoglobulin Demand Management Plan and National Immunoglobulin Database were demonstrated (WAC Sewell) and the European regulatory perspective was underlined (J Kerr). In order to ensure access and a sufficient supply of IVIg and SCIg for the well-established indications in primary immunodeficiency (PID), the information generated by patient registries in Europe (notably the ESID Registry) was highlighted as being of the utmost importance (B. Grimbacher). Similarly, continued dialogue with patient organisations will help to increase awareness of undiagnosed patients and address unmet needs for patients who might benefit from immunoglobulin therapies (J Drabwell). A presentation on "Innovative products and new developments" had to be cancelled as the speaker (L Hammarström) was unavailable.

Patients with primary immunodeficiencies are very concerned; a point underlined since the International Patients' Organisation for Primary Immunodeficiencies (IPOPI) carried out a major survey of 300 patients and carers from over 20 countries. Even in Europe, where access to healthcare is generally good, access to specialist immunology expertise remains patchy, with some countries having almost no clinicians in this field. This has a significant impact on patients' lives, with evidence from the Immune Deficiency Foundation 2008 survey that only 16% of patients with an undiagnosed primary immunodeficiency enjoy good health, compared to 66% of those diagnosed and treated. Primary immunodeficiencies are considered 'rare' but, in fact, are as common as many other recognised medical conditions, with over 200 types, collectively affecting between 1-5 people per 1000 population. The bulk of primary immunodeficiency disorders affect antibody production and most of these disorders require treatment with immunoglobulin therapy. Indeed, for many of the disorders, immunoglobulin therapy is the only effective form of treatment, meaning that primary immunodeficiency patients have an absolute need for secure and reliable supplies of immunoglobulins as there are no alternative therapies available. In countries without the expertise to administer and monitor immunoglobulin therapy effectively, many patients have received sub-optimal doses and breakthrough infections (and, hence, long-term damage). Several modes of treatment exist, such as intravenous and sub-cutaneous therapies, each of which can be administered in a range of settings, such as in a hospital or at home. The range and types of product continue to improve, but all patients cannot yet access them, and the IPOPI survey has shown there can still be significant impairment in quality of life. Understanding the immunoglobulin supply chain and market is therefore essential for the effective treatment of many Europeans; changes to this market, such as altering the licensed indications for immunoglobulin therapy, could have very significant effects on the stability and security of supplies for those patients who have an absolute requirement for this treatment. The destabilising effect of the 'threat' of Alzheimer's disease (and other conditions) from being treated with immunoglobulin therapy remains a very significant concern for patients, who would otherwise die without regular and sufficient supplies of immunoglobulin.

The discussion about which indications are on- and off-label (licensed or unlicensed) appears to vary across the EU. Significant regulatory issues remain regarding licensing of individual

products for each disease, in an area where many clinicians feel there is a ‘class effect’. The regulatory status of each product is particularly significant in those countries with an insurance-based healthcare system, as funding for immunoglobulin then depends on insurers rather than on government mandate. Demands on the immunoglobulin supply continue to increase. In the UK, there are now 12 highest priority (red) conditions, 18 medium priority (blue) conditions and 27 low priority (grey) conditions; not of all of which are within the product license, but for which there is some evidence of efficacy. Over 100 tonnes of immunoglobulin are now prescribed each year around the world. Indications continue to increase as evidence accrues; although, it should be noted that accumulating evidence has also led to the removal of some indications for immunoglobulin therapy.

One of the reasons that immunoglobulin therapy is used for so many different conditions is the fact that it does not work through a single mechanism of action; a wide range of mechanisms have now been discovered, some of which are more relevant for immuno-modulatory indications. It is becoming clear that the relevant mechanisms depend on the dose used, as well as the disease being treated. Interest is increasing in the status of the various glycoforms of IgG, which can play a role (in animal models at least) in the immunosuppressive and anti-inflammatory actions of immunoglobulin. As understanding of these processes grows, synthetic Fc products may be developed and, if effective, they may replace some immunomodulatory indications for immunoglobulin therapy, thereby relieving pressure on the world’s immunoglobulin supply. Interest is also increasing in modulating the expression of various Fc-receptors for immunoglobulin (including the neonatal FcRn receptor) as modulation of these key receptors may play a role in altering the amount of immunoglobulin product needed to produce a given effect.

From an EU regulatory perspective, the clinical investigation guidelines for intravenous (IVIg; EMA/CHMP/BPWP/94033/2007 rev. 2,) and sub-cutaneous (SCIg; EMA/CHMP/BPWP/410415/2011 rev 1) immunoglobulins form the basis for the optimal use of immunoglobulins. They are the template for the clinical trials which, once performed and submitted to the regulatory authorities, permit assessment of the efficacy and safety of the various products. In the case of a positive assessment, the product is granted a Marketing Authorisation for selected indications. The clinical investigation guidelines should be viewed within a broader collection of additional guidelines (covering diagnosis, therapeutics, European monographs and health technology assessment) to obtain an overview of what “optimal use” actually implies.

The IVIg clinical investigation guideline has been recently revised (in 2011) and the revision of the SCIg guideline is currently on-going. Following a consultation with all relevant stakeholders (patient organisations, physicians and industry), the revision process endeavours to reflect the state-of-the-art in treatment strategies, relevant models for immunomodulation (if possible, in order to achieve regulatory harmonisation with other authorities, e.g. the FDA), and a pragmatic approach towards off-label indications. On the basis of various clinical trials with different products, some former off-label indications have become “established indications” (i.e. accepted as being treatable by all intravenous products) and, in other cases, former off-label indications have been granted to individual companies on the basis of studies with their product. Further work is required to address how much clinical evidence is needed for other off-label uses to become “established indications” and, given the increasing demand for these products, whether indication priority rankings (as for example in the UK) would be helpful should immunoglobulins be in short supply.

The best-established indications for immunoglobulin therapy are primary immunodeficiencies (PID), which can be classified into predominant T cell deficiencies, complex combined immunodeficiencies and predominant antibody deficiencies (PAD). The predominant T cell deficiencies comprise a spectrum of severe congenital T cell defects (severe combined immunodeficiencies, SCID), with very poor prognoses unless treated with haematopoietic stem cell transplantation (HSCT). Sub-groups of milder T cell deficiencies exhibit T cell receptor (TCR) signalling defects or complex combined immunodeficiency (e.g. MHC-II deficiency, Di George syndrome, Wiskott-Aldrich syndrome, Ataxia telangiectasia, etc.), which often but not always require HSCT. All predominant T cell deficiencies also suffer from antibody deficiency due to impaired T cell help for B cells. Therefore, the patients require IVIg replacement therapy in the peri- and post-HSCT phases until re-population and functional recovery of the B cell compartment is completed.

The largest domain of IVIg/SCIg therapy relates to predominant antibody deficiencies (PAD), which represent approximately 60-65% of all PIDs. Ten per cent of these patients lack B cells and exhibit either the X-linked or the autosomal-recessive forms of agammaglobulinaemia, while 90% of patients fall into the group of pan-hypogammaglobulinaemias, of which the great majority fulfil the diagnostic criteria of a common variable immunodeficiency (CVID; www.esid.org). A minority of patients correspond to class-switch recombination defects (hyper-IgM syndromes), Good's syndrome or seIective IgG-subclass deficiencies, with or without IgA deficiency. While life-long IVIg or SCIg replacement therapy is mandatory and life-saving for most PAD sub-types, IVIg substitution is not recommended in isolated selective IgA deficiency and transient hypogammaglobulinaemia during infancy. In specific polysaccharide antibody deficiency (SPAD) with normal Ig serum concentrations, IVIg should only be considered after unsuccessful pneumococcal vaccination attempts. Recently, considerable progress has been made in defining CVID sub-sets with respect to prognoses, biomarkers and monogenetic defects. CVID patients who suffer from infections have a very good prognosis only when they are regularly IVIg-substituted to trough levels above 7g/l (95% survival in a 40-year follow-up), while patients with additional complications such as gastro-intestinal manifestations, lympho-proliferation, sarcoid-like granulomas , auto-immune phenomena or development of malignancies attain only a 42% survival rate. In some of these patients, a late-onset combined immunodeficiency (LOCID) with impaired T cell function has been diagnosed and HSCT has occasionally been performed. Biomarkers with some prognostic value have been increasingly validated; poor prognosis indicators are low B cell counts, totally absent $CD27^{+}$ switched memory B cells, elevated $CD21^{low}$ B cells and low $CD4^{+}CD45RA^{+}$ naïve T helper cells. To date, at least 12 different monogenic defects have been associated with CVID, but over 90% of cases remain genetically unexplained.

Immunoglobulin replacement therapy remains a treatment option in many cases of secondary immunodeficiency following prolonged treatment with immunosuppressive drugs (valproate, carbamazepine, rituximab, cyclophosphamide, methotrexate, etc.) or associated with chronic lymphoid leukaemia (CLL) and non-Hodgkin's lymphoma. In these cases, prophylactic antibiotic treatment or vaccination with pneumococcal and haemophilus polysaccharide vaccines should be tried first before embarking on long-term immunoglobulin replacement therapy.

Immunomodulatory immunoglobulin therapies have an established, on-label therapeutic role for Guillain–Barré syndrome (GBS), idiopathic thrombocytopenia purpura (ITP) and Kawasaki disease. Furthermore, some products have been authorised in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP; 2 products) and in multi-focal motor

neuropathy with conduction block (MMN) (1 product). Approximately 66% of all immunoglobulin use is on-label for five diseases (2010/2011 NHS database report). The remainder (one-third) is used off-label for over 50 different diseases. For certain off-label indications, there is a relatively broad consensus in the medical community that immunoglobulin is efficacious (dermatomyositis/polymyositis, myasthenia gravis (during exacerbations), Lambert Eaton myasthenic syndrome, neonatal haemochromatosis and stiff person syndrome). For many other indications, there is reasonable evidence for a therapeutic role, but further research is necessary. The largest areas of IVIg use (according to the 2010/2011 NHS database report) are in the field of neurology (41% - mainly CIDP (48%) and MMN (23%)) and immunology (29% - PID 87%), followed by paediatrics (11% - mainly ITP ~70%).

One of the interesting questions when addressing on/off-label use is whether or not immunoglobulins can be seen as generic or if labelling should be individualised. In a Cochrane systematic review of immunoglobulins (of five different brands) in placebo-controlled CIDP trials, efficacy showed the same positive trends for IVIg, with an absolute risk difference of 32% (95% CI = 21-43%). In a smaller head-to-head trial in 27 CIDP patients, the data demonstrated equal clinical efficacy between a freeze-dried and a liquid IVIg preparation for maintenance treatment of CIDP. In clinical practice, the effect is often considered to be a generic class effect, but the different products may have different side-effect profiles. Again, further research is needed to answer this question.

A further issue pertaining to immunomodulation is the route of administration. While this has hitherto been the domain of intravenous application, the sub-cutaneous route is interesting for a number of reasons: with lower peaks and higher trough levels, the IgG concentration is more constant. Due to self-administration in the home setting, reduced hospitalisation and need for healthcare personnel (with resulting cost-reductions), as well as the lack of need for venous access, the quality of life is improved and the patient's autonomy is increased. For the most part, there are fewer and less severe systemic side-effects. The main drawbacks concern the volumes to be administered sub-cutaneously, the localised side-effects and the frequency of administration. A number of small studies have been published in the last few years looking at SCIg in CIDP and MMN, with larger trials currently underway.

With the increase in immunoglobulin use for both on- and off-label indications and the possibility of its use in Alzheimer's disease (AD) (note of rapporteur: the negative study results of the large AD trial had not yet been released), an important issue is how to prioritise these indications. A good example of such prioritisation can be seen in the UK Demand Management Plan.

Currently operating in England, the Demand Management Plan requires that clinicians prescribing immunoglobulin therapies should register their proposed use on a national database and have their prescriptions approved by local panels, which consider each request on the basis of national guidelines and the current availability of immunoglobulin products. Each individual infusion of immunoglobulin is centrally logged, providing an important public health function in the event of immunoglobulin contamination and allowing national oversight of immunoglobulin use. This is invaluable in planning and purchasing products, as well as in giving invaluable insight into epidemiology and efficacy.

With increasing budget restraints and the rise in Health Technology Assessment (HTA), the cost-effectiveness of immunoglobulins in some immunomodulatory disorders will have to be addressed, (as was done by Blackwell *et al* in Canada for CIDP). Cost is also related to

optimal dosing. For example, when maintaining a clinically-stable situation in CIDP during maintenance treatment, the dosing regimen varies between 0.4–1.2 g/kg body weight every 2–6 weeks. A recent study (*J Neurol Neurosurg Psychiatry* 2013; 84:859-861) showed that the total dosage per infusion required to reach a stable clinical state in CIDP did not correlate with age, sex, body weight, lean body mass, muscle strength, disability or sensory dysfunction, but may be due to differences in FcRn-mediated IVIg metabolism. In order to establish a more tailored form of immunomodulatory therapy with immunoglobulin, it is essential for future research to identify biomarkers for disease activity and for predicting responsiveness.

The ESID registry was started in 2004 with 154 patients documented by 19 centres; as of April 2013, it has recorded 18,259 patients documented by 117 European centres and the accrual rate continues to increase steadily. Nevertheless, due to under-reporting, PID prevalence throughout Europe still varies considerably between areas; ranging from <0.5 (Eastern Europe) to >3.0 (France, Spain). By comparison, the US and Canadian registry (USIDnet) recorded 3,025 patients by 2012, the Latin American registry (LASID) had 4,179 and the Australian and New Zealand registry (ASCIA) had 1,207 (latest figures from 2007).
The data from the ESID registry reveal several important findings. The gender and age distributions clearly show a peak of recorded cases of PID at 10-15 years, with a significant male preponderance until the age of 30, which did not totally disappear when X-linked PID cases were removed from the analysis. Predominant antibody deficiencies (PAD) were by far the leading category, with 56.1% of cases, followed by other well-defined PIDs (Di George, WAS, AT, etc., 14.9%), phagocytic disorders (8.4%), predominant T cell deficiencies (7.8%), complement defects (4.1%), auto-immune dysregulation syndromes (4.0%), auto-inflammatory syndromes (2.1%), defects in innate immunity (1.0%) and unclassified cases (1.5%). Comparison of immunoglobulins/kg bodyweight dosages for patients in different European countries ranks the Czech Republic (320 mg/kg) and Germany (400 mg/kg) at the low extreme, while Greece (650 mg/kg) leads the field, followed by Holland (650 mg/kg), UK and Ireland (630 mg/kg), France (600 mg/kg), Sweden (560 mg/kg) and Turkey (540 mg/kg). The ESID sub-registry on common variable immunodeficiency (CVID), the most common form of PAD, lists 2,012 patients. The median diagnostic delay lies between 2.8 and 4.0 years, without significant improvement over the last 20 years. The figures look better for agammaglobulinaemia: for 762 patients registered, the median diagnostic delay ranges between 0.8 and 1.3 years, with a small but significant improvement over the last 20 years. The CVID phenotype analysis confirms previous findings from other large cohorts. Serious infectious episodes and days in hospital are significantly decreased in CVID patients with increasing serum IgG trough levels. The data suggest that trough levels above 7.0 g/l serum IgG should be targeted. In conclusion, the ESID registry is a most valuable tool, not only to study prevalence and distribution of genotypes and phenotypes of PID throughout Europe, but also for decision-making by health authorities and plasma product-producing companies. The ESID registry is largely under-used for scientific purposes and could be employed for future pharmacovigilance and post-licensing studies in Europe. Furthermore, a European Ethics Board to supervise European Disease Registries would be a valuable service.

Recommendations

Working Group 1: Clotting factors

Moderators: P.M. Mannucci & Wolfgang Schramm
Rapporteur: P. Giangrande

Summary of discussions:

Several new factor VIII, IX and VIIa concentrates are under development that are essentially copies of existing products. Although the term "biosimilars" is widely used to describe such products, the working group was not entirely satisfied with this term, although no obvious and universally acceptable alternative was agreed upon. It was recognised that these products are effectively in competition with long-acting products for enrollment of patients in clinical trials. For scientific reasons, the latter are generally more attractive to both patients and physicians engaged in clinical trials. However, the working group felt very strongly that biosimilars should not be ignored in favour of new long-acting products. It was also accepted that no "short cuts" should be taken to license biosimilar products, although there certainly is an expectation that these should be significantly cheaper than current products.

On the basis of current data, the working group was enthusiastic about new long-acting factor concentrates under development, particularly for IX, for which a 5-fold extension of half-life has been achieved. It was felt that these novel agents should be used for the treatment of actual bleeds as well as for prophylaxis. At the same time, the unanimous feeling of the working group was that long-acting products would not completely replace the need for current plasma-derived and recombinant concentrates. The principal perceived advantage of long-acting products is the need for fewer infusions, which would be particularly helpful in children, where the need for venous access devices might be avoided. It was also felt that these novel agents could make it easier to individualise therapy and maintain higher trough levels. Peri-operative management would also be easier if fewer infusions are required. Possible disadvantages include concerns about enhanced immunogenicity, thrombogenicity and allergic reactions. A particular issue, for which more data are required, relates to the potential for accumulation of polyetheylene glycol (PEG) with repeated administration over many years. The adoption of these products will also create practical problems with regards to assignment of potency and laboratory monitoring in patients. New laboratory standards will be required for assays and indeed some products may eventually be marketed in weight rather that international units. The working group called for pharmaceutical companies to work with the medical community to standardise useful assays. It was accepted that these novel products will be more expensive but, if this drawback is assigned too much weight, then wide-scale adoption in clinical practice will be hindered. As guidance for the representatives of pharmaceutical companies present during this part of the discussions, the working group indicated that a 50% price premium would be considered reasonable; although there would be an expectation that the price of current products would also fall simultaneously.

The working group felt very strongly that decisions on whether to adopt any new product should not be based solely on cost, but also quality. Consensus is required on a model for assessing cost-effectiveness, which should incorporate measurements of quality of life as well as historical control data for comparison.

It was restated that prophylaxis for children with severe haemophilia is recognised as the optimum therapy, as was made clear in recommendations from both the preceding 1999 and 2009 Wildbad Kreuth meetings. There was a strong feeling that the option of on-going prophylaxis for adults should also be considered. Another major recommendation that came

out of the 2009 meeting was that the minimum factor VIII level in a country should be 2 IU/capita. The working group voted to raise this figure to 3 IU/capita in light of data from a recent survey, which indicated that the lower threshold is not sufficient to guarantee successful prophylaxis in children.

There was also a consensus that children with inhibitors who have failed immune tolerance induction (ITI) or are not suitable candidates for this therapy should also be offered prophylaxis with by-passing agents. No such agreement was reached in relation to adults with inhibitors, largely because many of these would have already established joint damage. The cost of on-going treatment in adults would also be very high. More research is clearly needed in relation to the principal by-passing agents, FEIBA and NovoSeven. Two areas that the working group felt merited particular attention included development of a validated laboratory test for monitoring therapy as well as comparative head-to-head clinical studies.

The working group reaffirmed that single factor concentrates should be used wherever possible in rare bleeding disorders. It was noted that five new fibrinogen concentrates have recently been developed, as well as concentrates of factors V and X. Orphan drug designation for a factor concentrate should not be used to hinder the development, licensing and marketing of other products for the same condition that have demonstrably different protein modification or enhancement profiles. It was recognised that regulators have to follow legislation and do not have an entirely free hand in this regard. Pharmaceutical companies sometimes exploit the current position by requesting this protected status in order to secure market exclusivity for their products.

High-purity plasma-derived and recombinant von Willebrand factor concentrates will soon become available. Theoretical advantages over combined FVIII-VWF products include avoidance of accumulation of FVIII (which has been infrequently implicated in the development of venous thromboembolism after repeated treatment). The working group felt that these new products do not offer clear advantages over current products in routine clinical use, with the possible exceptions of elective surgery and prophylaxis, particularly in patients with recurrent gastrointestinal haemorrhage associated with angiodysplasia.

Organisation of haemophilia care is a very important issue. The working group approved the on-going work of the EUHANET project and agreed that a certification system for HTCs should be adopted by member states, based on common criteria, in order to improve standardisation of haemophilia care and to provide better access to services.

The working group also felt that a system of peer review external audits should be established in the longer term. In order to optimise the organisation of haemophilia care at a national level, the working group recommended that a formal body (such as a National Haemophilia Council) should be established in each country. This should include the relevant clinicians, national haemophilia patient organisation, health ministry, paying authority and (if appropriate) regulatory authority.

Principal conclusions and recommendations:

1. In order to optimise the organisation of haemophilia care nationally, it is recommended that a formal body be established in each country, including the relevant clinicians, national haemophilia patient organisation, health ministry, paying authority and (if appropriate) regulatory authority.

2. The minimum factor VIII consumption level in a country should be 3 IU/capita.

3. Decisions on whether to adopt a new product should not be based solely on cost.

4. Prophylaxis for children with severe haemophilia is already recognised as the optimum therapy. On-going prophylaxis for individual adults should also be provided when appropriate, based on a clinical decision made by the clinician in consultation with the patient.

5. Children with inhibitors who have failed immune tolerance induction (ITI) therapy, or who are not suitable for this treatment, should be offered prophylaxis with by-passing agents.

6. Single factor concentrates should be used as therapy wherever possible in patients with rare bleeding disorders.

7. Orphan drug designation for a factor concentrate should not be used to hinder the development, licensing and marketing of other products for the same condition that have demonstrably different protein modification or enhancement profiles.

Working Group 2: Immunoglobulins

Moderators: Hans-Hartmut Peter, Jacqueline Kerr
Rapporteurs: Hans-Hartmut Peter, Jacqueline Kerr, Isabella Quinti & Carrock Sewell

Outcome of the immunoglobulin working group discussions:

Following extensive discussion in open sessions (with industry representatives) and closed sessions, the Immunoglobulin Working Group produced the following recommendations. Formulation of these proposals recognises that there is a wide range of different healthcare funding processes across Europe, and the working group felt it was particularly important that insurance companies should jointly consider these proposals as a group, in order to ensure equity of access across the EU.

Recommendation 1: to adopt a process for the management of immunoglobulin demand across the EU in order to ensure adequate supplies for all patients who need immunoglobulin.

There was widespread approval of the UK's Demand Management Program, presented during the meeting, as an appropriate model to emulate**.** Many countries have a similar system in place, and it was agreed that these could be harmonised, using the UK as a model. The aim of the Demand Management Process would be to ensure continuity of supply to all patients who need immunoglobulin, particularly in times of product shortage (whether because of manufacturing issues, contamination incidents, or other reasons).

The process recognises that different diseases have different priorities of treatment, with some conditions having absolute priority as there are no effective alternatives, and a range of relative priorities for others. Conditions that need absolute priority in times of immunoglobulin shortage include: primary immunodeficiencies, Kawasaki disease, Guillian-Barré syndrome and other life-threatening diseases that have not been improved by other medications. As clinical evidence of efficacy changes over time, it is important that the Demand Management Process is reviewed regularly as evidence grows, and there is merit in linking this process to Rare Disease Registries. For off-label indications, local committees can usefully be involved in making decisions, based on expert knowledge, evidence-based guidelines and knowledge of product supply. The working group recommended that a European working group be established to make priority recommendations.

Recommendation 2: for all EU countries to acknowledge that immunoglobulin is a 'WHO Essential Medicine' and to ensure that all patients who need this drug have access to sufficient quantities of immunoglobulin for this to be clinically effective.

The working group was concerned to see evidence from both IPOPI and the ESID Registry of primary immunodeficiency diseases that the availability of immunoglobulin therapies (and in some cases adequate doses of immunoglobulin) is not equal across the EU, and that some patients are experiencing significant harm and reduced life expectancy because of this. The working group discussed the appropriate doses of immunoglobulin and acknowledged that the core summary of product characteristics (SmPC) suggests a starting dose (in primary immunodeficiency) of 0.4 g/kg/month, but emphasised that current evidence suggests that this

dose should be titrated to effect. There was recognition that each patient is different and that co-morbidities such as bronchiectasis, enteropathy and others affect the Effective Dose. There was an understanding that 'dose per kg' may be irrelevant, as evidence indicates that body mass index does not affect serum IgG levels for a given dose of immunoglobulin, and that initial prescribing according to 'ideal body weight' may be valid. It was recognised that the traditional immunomodulatory dose of 2 g/kg/month is not the only possible dose, and that significant savings could be made by finding better target values; more research is clearly needed here. The working group agreed that there is little point in prescribing immunoglobulin if the amount given is not sufficient to produce a sustained clinical benefit, and agreed on the term 'Clinically Effective Level' of IgG, which should be determined for each patient on an individual basis. There was also recognition that 'Clinically Effective Doses' may be different in chronic and acute conditions.

Recommendation 3: that all recognised routes of immunoglobulin administration are made available to patients.

The working group agreed that evidence is accumulating that sub-cutaneous immunoglobulin therapy may work for some neurological diseases as well as for primary immunodeficiency diseases, but is not suitable for all patients. Evidence is accumulating for sub-cutaneous maintenance dose immune-modulatory therapy. It was agreed that sub-cutaneous and intravenous doses in primary immunodeficiency can be similar, but that the dose equivalence for immunodulatory indications is not known. There was complete acceptance that patient choice is paramount in deciding whether replacement therapy should be intravenous or sub-cutaneous.

Recommendation 4: Immunoglobulin products differ from one another.

The working group agreed that immunoglobulins are not generic products, and had an extensive discussion about when they are similar and when they are different. There was agreement that the beneficial clinical effects of differing brands are likely to be similar, but that side-effects may differ from product to product, and even batch to batch. In terms of product choice, there are very few head-to-head studies comparing products and these are usually small scale. Understanding the possible mechanisms for these differences may change this view, particularly in replacement dose treatment of primary immunodeficiencies, and this question should be the subject of more research. Issues such as differences in IgG glycosylation and Fc-receptor polymorphisms may be involved.

Recommendation 5: Better mechanisms are required for Health Technology Assessment of immunoglobulin therapies.

The working group noted that assessment of risk/benefit and price/benefit are currently separate. If a Regulator adopts a different stance, there is a significant risk of 'wasting' several clinical trials. There may be a need for adopting larger (and hence more expensive) trials, and companies should be strongly encouraged to co-operate in undertaking larger joint studies in order to produce more robust data (as in many successful HIV trials). Maximum use should be made of pharmacovigilance registries and post-marketing surveillance.

Recommendation 6: more research is needed on the use of immunoglobulin in treatment of secondary immunodeficiencies.

Immunoglobulin therapy can be used in selected patients with recurrent infections and antibody deficiency secondary to lymphoma, multiple myeloma, chronic lymphocytic leukaemia and chronic immunosuppressive treatment. Patients may be selected on the basis of the levels of serum immunoglobulins and the intensity of individual antibody responses to specific immunisations. However, it is recognised that such assessments are time-consuming in patients who already have a reduced life expectancy. The working group recommended that more studies be carried out to assess patient suitability for immunoglobulin therapy in these conditions, and that the original study data should be re-examined to determine if antibody levels of low specificity are sufficient for patient selection.

Optimal use of clotting factors and immunoglobulins

The EDQM is a directorate of the Council of Europe, an international organisation founded in 1949 that covers almost the entire continent of Europe. The Council of Europe aims to develop common democratic and legal principles based on the European Convention on Human Rights and other reference texts on the protection of individuals.

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