Current and future challenges of the funding of rare diseases: The case of haemophilia

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### Speaker disclosures

<table>
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<tr>
<td>Shareholder</td>
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<td>No relevant conflicts of interest to declare</td>
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Haemophilia

Blood Coagulation Defect
(Factor VIII or IX < 1 %)

Spontaneous bleeding complications
debilitating arthropathy
HAEMOPHILIA : “ROYAL DISEASE”
THE MOST FAMOUS HAEMOPHILIA PATIENT
TSAREVITCH ALEXIS (1904-1918)

4 year-old

8 year-old

10 year-old
This young boy with severe haemophilia can now be treated safely and have a normal life.

Annual cost of his treatment could reach 300,000 euros.

This represents the price to pay (invest) to correct his genetically determined impaired production of coagulation factor VIII or IX.
Haemophilia : Key features of a rare disease with a specific status

• Rare, complex, potentially life-threatening haematological bleeding disease with musculoskeletal complications mainly

• Life-long disease with specific challenges at each period of life

• Requiring self-replacement therapy with major parents’/patient commitment

• Modalities of management and care in constant mutation

• Very expensive disease because of the cost of treatment

Haemophilia in Belgium

- Haemophilia A 800*
- Haemophilia B 200*
- Medical doctors 40,000

Population: 10,600,000 inhabitants
FVIII annual consumption: 80 M units/year

* Association des Hémophiles AH-VH.
Treatment of haemophilia

Replacement or substitutive therapy by regular intravenous infusions of exogenous clotting Factor F8 or F9 to correct clotting factor deficiency in order to treat or prevent bleeding episodes
Ideal treatment of severe hemophilia: prevention / abolition of bleeding episodes by regular self-infusions - prophylaxis

Hemophilia Tx Goals
- Treat/avoid/abolish bleeding complications
- Avoid joint disease
- Avoid side effects
  - Inhibitors
  - Infections
- Achieve the life the patient chooses

Origins of FVIII and FIX concentrates needed to treat patients with haemophilia

Plasma-derived

Blood fractionation
Plasma-derived F8 or F9
(National blood services)
(International companies)

Bio-technology

Synthetic
F8 or F9 concentrates
produced by biotechnology
Short history of factor replacement therapy

1960's

- Plasma concentrates made home infusions possible.

Early 70's

- HBV identified

Mid-late 70's

- Up to 85% haemophilia patients HBV^2
  - 70% of patients have non A non B hepatitis^2

Mid 80's

- 80% of patients HIV^2
  - Heat treated plasma concentrates

Late 80's

- Enhanced viral inactivation
- Expanded donor screening
- Up to 95% of haemophilia patients are HCV^1

References:
Short history of factor replacement therapy

**1960’s**
- HBV identified

**Early 70’s**
- Up to 85% haemophilia patients HBV+
- 70% of patients have non A non B hepatitis

**Mid-late 70’s**
- 80% of patients HIV
- Heat treated plasma concentrates

**Mid 80’s**
- Enhanced viral inactivation
- Expanded donor screening

**Late 80’s**
- Up to 95% of haemophilia patients are HCV+

**Early 90’s**
- 1992: first commercially available recombinant factor

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Evolution of FVIII / FIX Concentrates has mainly been driven by infectious safety

Key NS, Negrier C. Lancet 2007;370:439–48

rFVIII: Recombinant FVIII; rFIX: Recombinant FIX; pdFVIII: Plasma derived FVIII; HBV: Hepatitis B virus; HCV: Hepatitis C virus; S / D: Solvent detergent; NAT: Nucleic acid testing
## Causes of Mortality for Haemophiliacs (2005)

<table>
<thead>
<tr>
<th></th>
<th>Switzerland</th>
<th>Romania</th>
<th>Germany</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS</td>
<td>29.16%</td>
<td>Haemorrhage: 90%</td>
<td>!!AIDS: 14%</td>
</tr>
<tr>
<td>Cancer</td>
<td>20.83%</td>
<td>AIDS: 5%</td>
<td>Hepatic cirrhosis: 14%</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>12.5%</td>
<td>Other: 5%</td>
<td>Cancer: 23%</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>16.66%</td>
<td></td>
<td>Haemorrhage: 10%</td>
</tr>
</tbody>
</table>

Prophylaxis: optimal but costly treatment for haemophilia (up to 300,000 euros/yr/patient)

- Prophylaxis considered optimal therapy for individuals with severe haemophilia A or B
  - World Health Organization (WHO)
  - World Federation of Haemophilia (WFH)

Recommended treatment regimen:
20-30 U/kg 3 x / week
1 unit F8: up to 0.9 euros
Annual cost: between 100,000 up to 300,000 euros/patient/year
FVIII Units by UK Haemophilia Centres
Life Expectancy in Haemophilia

- Availability of safe and effective factor concentrate
- Prophylaxis
- Comprehensive Care

SPECIAL ARTICLE
European Association for Haemophilia and associated disorders (EHAD)

European principles of haemophilia care

B. T. COLVIN,* J. ASTERMARK,† K. FISCHER,‡ A. GRINGERI,§ R. LASSILA,*
W. SCHRAMM,** A. THOMAS†† and J. INGERSLEV‡‡ FOR THE INTER DISCIPLINARY
WORKING GROUP

*Haemophilia* (2008), 14, 361–374
Life-expectancy of patients with haemophilia

Spectrum of age in haemophilia
Number of patients, according to age and severity of haemophilia, treated at the Van Creveldkliniek in 2007 (\( n = 668 \))

EMPLOYMENT OF INDIVIDUALS WITH HAEMOPHILIA IN THE NETHERLANDS

I Varekamp, 1 C Smit, 2, 3 F R Rosendaal, 2 A Brocker-Vriends, 4 E Briët, 2 H van Dijck 3 and T P B M Suurmeijer 1, 4

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2 Department of Haematology, Leiden University Hospital, Building C2R, PO Box 9600, 2300 RC Leiden,
3 Dutch Haemophilia Society (NVHP), Plesmanlaan 125 Room E 125, 1066 CX Amsterdam
and 4 Clinical Genetics Centre, Leiden University Hospital, Building 33, PO Box 9600, 2300 RC Leiden,
The Netherlands

Social participation of patients with hemophilia in the Netherlands

Iris Plug, 1 Marjolein Peters, 2 Eveline P. Mauser-Bunschoten, 9 Arja de Goede-Bolder, 4 Lily Heijnen, 3, 5 Cees Smit, 6
José Willems, 6 Frits R. Rosendaal, 1, 7, 8 and Johanna G. van der Bom 1, 3

1 Department of Clinical Epidemiology, Leiden University Medical Center, Leiden; 2 Academic Medical Center, Emma Children’s Hospital, Amsterdam; 3 University Medical Center Utrecht, Hematology and Van Creveldlinie, Utrecht; 4 Erasmus Medical Center, Sophia Children’s Hospital, Rotterdam; 5 Rehabilitation Center “De Trappenberg,” Huisen; 6 Netherlands Hemophilia Society, Badhoevedorp; 7 Eindhoven Laboratory for Experimental Vascular Medicine, Leiden University Medical Center, Leiden; and 8 Department of Thrombosis and Hemostasis, Leiden University Medical Center, Leiden, the Netherlands

Review Article

Relationship between haemophilia and social status

Katharina Holstein *, Barbara Eifrig, Florian Langer

II. Medizinische Klinik und Poliklinik, Gerinnungsambulanz und Hämostaseezentrum, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany
Level of education and labour force participation in adult haemophilia patients according to prophylactic regimen and compared with the general population

<table>
<thead>
<tr>
<th>Achieved level of education</th>
<th>Netherlands</th>
<th>Sweden</th>
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<tbody>
<tr>
<td><strong>Intermediate-dose, % of n=62</strong>*</td>
<td><strong>General population, %*,†</strong></td>
<td><strong>High-dose, % of n=41</strong>*</td>
</tr>
<tr>
<td>Compulsory/secondary</td>
<td>29</td>
<td>20</td>
</tr>
<tr>
<td>Upper secondary/professional</td>
<td>68</td>
<td>43</td>
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<tr>
<td>University</td>
<td>3</td>
<td>36</td>
</tr>
<tr>
<td>Missing</td>
<td>0</td>
<td>2*</td>
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<table>
<thead>
<tr>
<th>Labour force participation</th>
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<tbody>
<tr>
<td><strong>Active</strong></td>
</tr>
<tr>
<td><strong>Employed</strong></td>
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<tr>
<td><strong>Unemployed</strong></td>
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<tr>
<td><strong>Not active</strong></td>
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<td><strong>Student</strong></td>
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<td><strong>Disability allowance</strong></td>
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<td><strong>Housekeeping</strong></td>
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<td><strong>Missing</strong></td>
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Overall, 96% of patients did not report days lost from work of school because of haemophilia

# FVIII Needed for Appropriate Therapy

<table>
<thead>
<tr>
<th>FVIII IU Per Capita Needed</th>
<th>Expected Outcome</th>
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<tbody>
<tr>
<td>&lt;1</td>
<td>• Shortened life expectancy</td>
</tr>
<tr>
<td>1</td>
<td>• Survival from worse effects</td>
</tr>
<tr>
<td>2 – 4</td>
<td>• Adequate episodic therapy</td>
</tr>
<tr>
<td></td>
<td>• Elective surgery</td>
</tr>
<tr>
<td></td>
<td>• Secondary prophylaxis in target joints</td>
</tr>
<tr>
<td>5 – 7</td>
<td>• Primary prophylaxis</td>
</tr>
<tr>
<td></td>
<td>• Immune tolerance induction (ITI)</td>
</tr>
</tbody>
</table>

Evatt BL. Haemophilia 2002; 8:1.152
Clotting factor consumption to treat haemophilia
Consumption of clotting factor to treat haemophilia in Europe in units per capita (2014)
FVIII use per capita vs GDP (2011 data)

Mean total lifetime costs reached €7.8 million per people with haemophilia, 94.3% being direct costs and 5.7% indirect costs.

Clotting factors accounted for 82.5% of direct costs.
Le TOP 25 des médicaments dans les dépenses soins de santé (2014)

<table>
<thead>
<tr>
<th></th>
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<tr>
<td>1</td>
<td>123.692.491</td>
<td>L04AB04</td>
<td>ADAIRUMAB</td>
<td>11.983</td>
<td>8.584.801</td>
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<td>68.988.006</td>
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<td>50.289.101</td>
<td>A02BC02</td>
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<td>1.083.301</td>
<td>1.875.486</td>
<td>1997</td>
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<td>6</td>
<td>40.211.886</td>
<td>B11D01</td>
<td>RIVAROXABAN</td>
<td>64.599</td>
<td>13.303.050</td>
<td>2009</td>
<td>2013</td>
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<td>7</td>
<td>34.849.772</td>
<td>R03AK06</td>
<td>SALMETEROL ET FLUTICASONE</td>
<td>226.178</td>
<td>-3.789.991</td>
<td>2001</td>
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<td>9</td>
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<td>1997**</td>
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<td>10</td>
<td>31.085.833</td>
<td>R03AK07</td>
<td>FORMOTEROL ET BUDUCONIDE</td>
<td>255.043</td>
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<td>11</td>
<td>30.800.703</td>
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<td>ESCLITOLIPRAM</td>
<td>317.814</td>
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<td>12</td>
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<td>M02BX04</td>
<td>DENOSUMAB</td>
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<td>9.478.029</td>
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<td>14</td>
<td>28.945.844</td>
<td>C13AA05</td>
<td>ATORVASTATINE</td>
<td>411.638</td>
<td>-29.242.041</td>
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<td>16</td>
<td>25.643.893</td>
<td>N05AX21</td>
<td>DULOXETINE</td>
<td>105.156</td>
<td>1.844.673</td>
<td>2006</td>
<td>2012</td>
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<td>B01AB05</td>
<td>ENOXAPARINE</td>
<td>257.128</td>
<td>535.175</td>
<td>1999</td>
<td>2010</td>
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<td>A10AE04</td>
<td>INSULINE GLARGINE</td>
<td>64.477</td>
<td>1.866.046</td>
<td>2008</td>
<td>2012</td>
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<td>20</td>
<td>23.101.382</td>
<td>J01CR02</td>
<td>AMOXICLUNE ET INHIBITEURS D'ENZYME</td>
<td>1.481.244</td>
<td>-1.171.105</td>
<td>1996</td>
<td>1997**</td>
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<td>21</td>
<td>22.786.579</td>
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<td>METFORMINE</td>
<td>816.129</td>
<td>1980</td>
<td>2013</td>
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<td>22</td>
<td>22.111.420</td>
<td>C01DX03</td>
<td>MOXIDOMINE</td>
<td>109.701</td>
<td>-1.514.192</td>
<td>1981</td>
<td>1997**</td>
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<td>23</td>
<td>21.341.308</td>
<td>J05AR03</td>
<td>TENOFOVIR DISOPROXIL ET EMTRICABINE</td>
<td>4.043</td>
<td>743.915</td>
<td>2009</td>
<td>2012</td>
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**R05**

| TOTAL TOP 25 | 913.069.466 | 1.346.013.235 | - | - | - | - |

* 1990 ou avant
** 1997 est la première année pour laquelle des données sont disponibles dans Pharmar.net; l’apparition dans le TOP 25 de ce principe actif est probablement antérieure.

Source : IMAMI – Pharmar.net
Cost of Recombinant-FVIII unit highly variable around the world

Lowest cost: < 0.3 euro/unit

Highest cost: > 1.0 euro/unit

- The cost of each FVIII unit is influenced by:
  - Health care system
  - Competition between pharma companies
  - Local resources
The cost of severe haemophilia in Europe: the CHESS study

Jamie O'Hara¹, David Hughes¹, Charlotte Camp¹, Tom Burke², Liz Carroll³ and Daniel-Anibal García Diego⁴

Fig. 1 Distribution of per-patient costs (EUR). Total per-patient costs are shown for each of the five countries as well as a study average split by CFRT, other direct medical costs, and indirect costs.

O'Hara et al. Orphanet Journal of Rare Diseases (2017) 12:106
DOI 10.1186/s13023-017-0660-y
STRATEGIES TO REDUCE THE COST OF HAEMOPHILIA REPLACEMENT THERAPY

• Tender process
• Competition between original products
• Reduction of reimbursement by third payer
• Development of low-cost biosimilars (unknown impact)
Tender and Procurement Systems for Factor Concentrates in Europe

Tender
Alternative
Both

Brian O Mahony 2015
## Impact of Tender and Procurement Systems on prices of Factor VIII and IX Concentrates in Europe (cost per Unit in Euro)

<table>
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<th>Alternative Process</th>
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<td></td>
<td>n</td>
<td>Median (€)</td>
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<tr>
<td>Recombinant FVIII*</td>
<td>12</td>
<td>0.56</td>
</tr>
<tr>
<td>Plasma-Derived FVIII</td>
<td>15</td>
<td>0.40</td>
</tr>
<tr>
<td>Recombinant FIX</td>
<td>6</td>
<td>0.73</td>
</tr>
<tr>
<td>Plasma-Derived FIX*</td>
<td>15</td>
<td>0.40</td>
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</tbody>
</table>

Brian O Mahony 2015
How we choose factor VIII to treat hemophilia

Pier Mannuccio Mannucci,¹ Maria Elisa Mancuso,² and Elena Santagostino²

¹Scientific Direction, and ²Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Department of Medicine and Medical Specialties, Istituto di Ricovero e Cura a Carattere Scientifico Ca' Granda Maggiore Policlinico Hospital Foundation, Milan, Italy

In high-income countries, the large availability of coagulation factors for replacement therapy of patients with hemophilia A has raised the life expectancy of these lifelong bleeders to that of males from the general population. The practicing clinician is offered a multitude of choices among several commercial brands of factor VIII extracted from human plasma or engineered from mammalian cell cultures by means of recombinant DNA technology. This article has the goal to offer our opinions on how to choose among the different products, that we consider interchangeable relevant to their clinical efficacy in the control of bleeding and safety from pathogen transmission. Hence, the main determinants of our choices are price and the risk of occurrence of factor VIII inhibitory antibodies. With this as background, we present the rationale underlying the choices for different categories of patients with severe hemophilia A: previously untreated patients, multiply treated patients, and patients undergoing immune tolerance induction with large doses of factor VIII to eradicate inhibitors. Mention is also made to the possible strategies that should be implemented to make available coagulation factors for replacement therapy in developing countries. (Blood. 2012;119(18):4108-4114)

according to a composite product score, thus retaining in the United Kingdom the existing plurality of products, mitigating the risk of supply interruption, maintaining some degree of prescription freedom, and minimizing the number of patients who had to switch FVIII brand. The net result of the program is that the price of recombinant FVIII did decrease stepwise by approximately 50%. Most importantly, as a result of the implementation of this national procurement scheme and the resulting savings, the Department of Health has not cut the budget that it does allocate to hemophilia, notwithstanding the current economic constraints. We are aware that it may not be
Purchasing factor concentrates in the 21st century through competitive tendering

- The UK system of procurement is described. This system, following EU procurement rules, evaluated products technically and by price. The price of bioequivalent products was determined by reverse e-auction. Considerable cost reductions were achieved whilst retaining all suppliers and maintaining a degree of prescribing freedom. Elements of this system could be more widely applied.

# NEW TREATMENT OPTIONS FOR HAEMOPHILIA AND IMPACT ON COST

<table>
<thead>
<tr>
<th>Treatment Options</th>
<th>Description</th>
<th>Cost Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified Longer Acting F8 and F9</td>
<td></td>
<td>$\text{COST} = \text{or} \times 1.5$</td>
</tr>
<tr>
<td>Non-Substitutive Therapies (in development)</td>
<td></td>
<td>COST UNKNOWN</td>
</tr>
<tr>
<td>Gene Therapy</td>
<td></td>
<td>$\text{COST} \ ? \ &gt; 1 \text{ million euro/patient}$ \ \text{LEASING} ?</td>
</tr>
<tr>
<td>ACE 9-10 Anti-TFPI Fitusiran</td>
<td></td>
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</tr>
</tbody>
</table>
Gene therapy requires an innovative economic model for success in modern healthcare

- Patients with inherited disorders individually impose a much heavier financial burden on the healthcare system compared to the average person.

- Gene therapy has the potential to achieve substantial savings.

- Over the last 20 years, greater than $4.3 billion have been spent on development of gene therapy technology and return on this investment is still awaited.

- A pay-for-performance system has been proposed with yearly-capped annuity paid to the pharmaceutical company.

- Criteria of cost-effectiveness and not only cost-saving will probably be used.

Inherit Metab Dis DOI 10.1007/s10545-017-0053
THE MAJOR ROLE OF PATIENTS ASSOCIATIONS

- BELGIUM

- EUROPE

- GLOBAL

European Haemophilia Consortium
Predictable and sustainable access to treatment for all

Lack of access to treatment presents an urgent need and important public health challenge

Collective effort is needed among companies, countries, and the hemophilia community
CONCLUSIONS

• Major advances in the treatment of haemophilia over the last decades

• Replacement therapy with concentrates represents most of the cost of the disease management with much variability between countries

• Major recent innovations achieved that could further improve the disease management and quality of life of haemophilia patients

• New strategies for “sustainable” haemophilia funding should be identified to allow implementation of new treatment strategies including gene therapy