



Programme of the European Haemophilia Consortium
Conference 2011 Budapest
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Economics and optimal care

New and modified recommendations on optimal use of factor concentrates

Prof. Dr. Wolfgang Schramm
University of Munich
Dept. for Hemostasis and Transfusion Medicine
Munich, Germany





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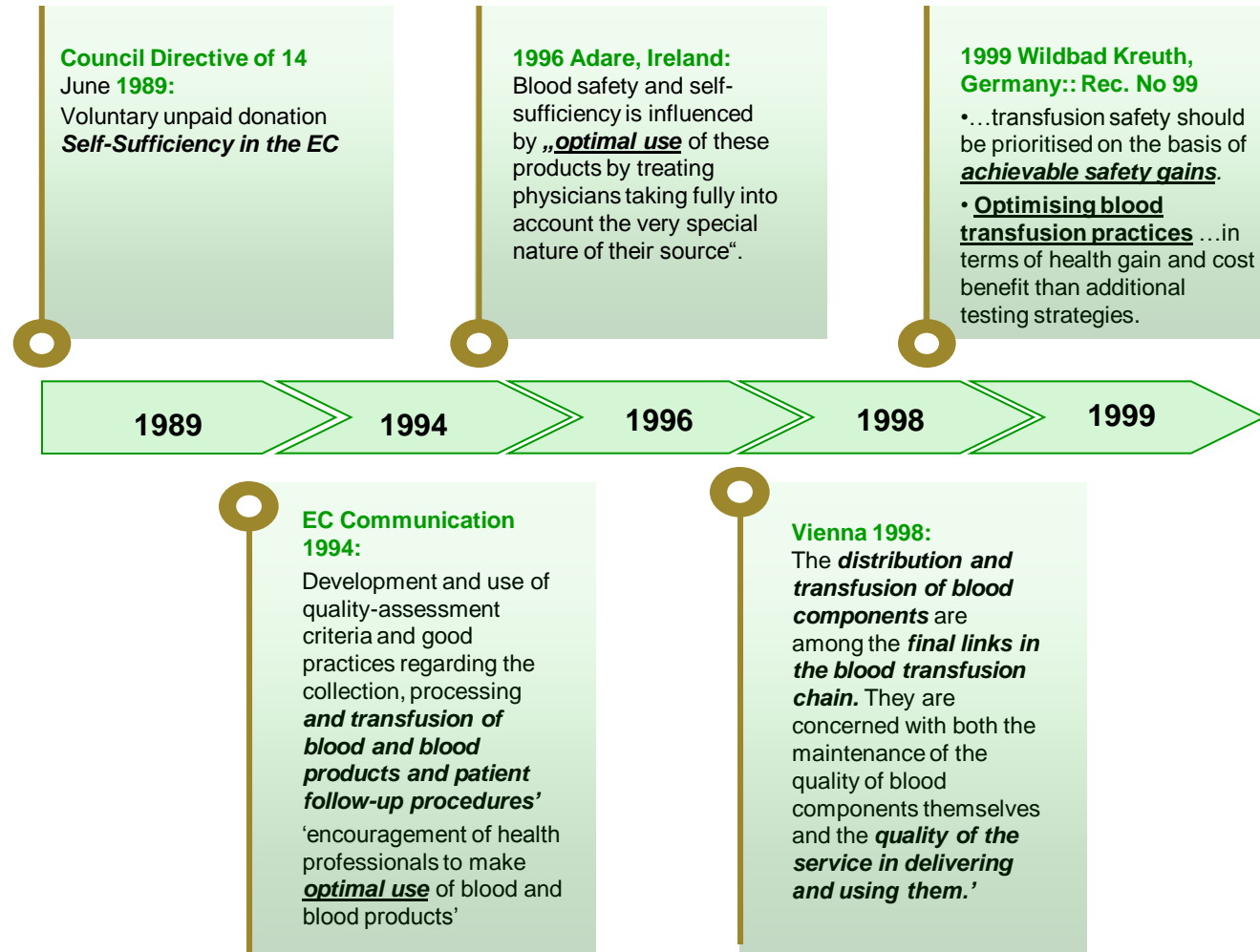
Economics and optimal care

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From Self- Sufficiency to Optimal Use of Blood and Blood Products in Europe: < 2000





Blood Safety in the European Community: Ithe Wildbad Kreuth initiative (I) for optimal use 1999

- Conclusions and Recommendations:
Haemophilia Care

How to define optimal use?

Optimal Use is to avoid¹ ...

- **Overuse**
- **Underuse**
- **Inappropriate use**

Optimal Use requires² ...

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

Future Perspectives in Haemophilia Care: the Wildbad Kreuth Initiative *Organisation of Haemophilia Care*



- Many patients are treated by general practitioners / paediatricians and **lack access to specialists** with specific haematological training.
- Need for the establishment of **centres specifically designed** to provide medical care for such patients. These centres, which have been identified as **Comprehensive Care Centres (CCCs)**, would bring together the collective experience of individuals involved in the treatment of haemophilia patients including, as the:

primary team:

- adult / paediatric haematologist
- nurse
- orthopaedic surgeon
- physiotherapist
- generic counsellor
- social worker

with additional support from :

- a dentist,
- specialists in infections disease
- and in hepatology

Future Perspectives in Haemophilia Care:
the Wildbad Kreuth Initiative –
Choice of Blood Products

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



Future Perspectives in Haemophilia Care: the Wildbad Kreuth Initiative - *Therapy*

Harmonisation of the numerous guidelines
from medical bodies throughout the European Community,
including advice on dosages for treating common problems

Future Perspectives in Haemophilia Care: the Wildbad Kreuth Initiative

Therapy for Haemophilia: Immune Tolerance

- „It is accepted:
that immune tolerance is effective in the majority of cases
and should be offered to all patients with *severe congenital
haemophilia* who develop *new inhibitory antibodies*“
- „Controversy remains:
over the precise dosage regimen for establishing immune
tolerance“

Future Perspectives in Haemophilia Care: the Wildbad Kreuth Initiative



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

Future Perspectives in Haemophilia Care: the Wildbad Kreuth Initiative - Recommendations



125. In order that future requirements for expensive blood products within the European Community can be assessed, registers of patients with haemophilia and related disorders should be established and maintained in each Member State of the Community.
126. A haemovigilance or pharmacovigilance programme should be established in the Community... to gather information on patient complications ...
127. A network of Comprehensive Care Centres should be established ... provide 24-hour clinical and laboratory service and be accessible to all patients.

Future Perspectives in Haemophilia Care: the Wildbad Kreuth Initiative - Recommendations

128. Adequate amounts of coagulation factor concentrates for the treatment of patients with haemophilia and related disorders should be available in each Member State. Quantities of both plasma-derived and recombinant products should be maintained ... Individual patient preferences should be taken into consideration when choosing products.
129. Particular attention needs to be taken by the European Community on the possible adverse consequences should a monopoly for the production of coagulation factor concentrates emerge. Research on the development of emerging recombinant technologies in the Community needs to be encouraged and funded.

Future Perspectives in Haemophilia Care: the Wildbad Kreuth Initiative - Recommendations



130. The numerous guidelines from medical bodies in the various Member States should be harmonised and expanded to include advice on dosages for the treatment of common spontaneous bleeding problems.
131. As a general rule, prophylactic treatment for children with severe haemophilia is recommended.
132. Immune tolerance should be offered to all patients with haemophilia who develop new inhibitory antibodies.
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.

Wildbad Kreuth Initiative: Translation into clinical practice

Example: Germany, Clotting Factor-Concentrates

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

- DHR (Deutsches Hämophileregister) at the Paul-Ehrlich-Institute, Langen
- Establishment of hemovigilance registers
- Germany: The Advisory Council on the Assessment of Developments in the Health Care System promotes comprehensive hemophilia care: Report Appropriateness and Efficiency 2000/2001, Addendum
- Growing awareness on proph. treatment
- Studies on proph. treatment were initiated
- Increasing expert discussion on prophyl. Treatment
- In consequence of the retrospect. European Socioeconomic study a prospective study has been initiated: ESCHQoL

German medical association: implications for replacement therapy using factor concentrates modified according to the “Cross-sectional guidelines for therapy with blood components and plasma derivatives”
 German medical association in the 4th revised edition, 2009

Treatment Principles	Overall assessment; classification	Assessment of the methodological validity of the underlying data; Implications
Factor replacement on demand shall be performed during spontaneous or traumatic bleeding episodes at any bleeding site if the bleeding exceeds a minimum degree (e.g. minor skin bleeding) [23, 24].	1 C+	No randomized, controlled studies, but unambiguous data available. Strong recommendation
Full-time prophylactic replacement therapy shall be carried out mostly in children and adolescents with severe hemophilia in the form of physician-controlled self-administered treatment with the main intention of preventing hemophilic arthropathy [25-30].	1 A	Randomized, controlled studies without essential methodological flaws with unambiguous results. Strong recommendation
Full-time prophylactic replacement therapy can be carried out individually in adults with the intention of preventing the development of arthropathies as a late consequence [25, 31-33].	2 C+	No randomized, controlled studies, but data can be extrapolated from other studies. Weak recommendation
Prophylactic therapy to prevent bleeding shall be provided before and after surgical interventions.	1 C+	No randomized, controlled studies, but unambiguous data available. Strong recommendation
Temporary prophylactic therapy to prevent bleeding should be provided during periods of major physical or psychic stress (e.g. rehabilitation, exams) [34, 35].	1 C	Observational studies without control group, but with convincing results. Medium strong recommendation

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.

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.



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 improve health care both at the individual and population level“

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

From Self- Sufficiency to Optimal Use of Blood and Blood Products in Europe: > 2000

Council Directive of 14 June 1989:
Voluntary unpaid donation
Self-Sufficiency in the EC

1996 Adare, Ireland:
Blood safety and self-sufficiency is influenced by „**optimal use**“ of these products by treating physicians taking fully into account the very special nature of their source“.

1999 Wildbad Kreuth, Germany:: Rec. No 99
• ...transfusion safety should be prioritised on the basis of **achievable safety gains**.
• **Optimising blood transfusion practices** ...in terms of health gain and cost benefit than additional testing strategies.

European Symposium on „Optimal Clinical Use of Blood Components“
April 24th – 25th 2009
Wildbad Kreuth, Germany

Discussion of future challenges

1989

1994

1996

1998

1999

2007

2008/2009

EC Communication 1994:

Development and use of quality-assessment criteria and good practices regarding the collection, processing **and transfusion of blood and blood products and patient follow-up procedures**

‘encouragement of health professionals to make **optimal use** of blood and blood products’

Vienna 1998:

The **distribution and transfusion of blood components** are among the **final links in the blood transfusion chain**. They are concerned with both the maintenance of the quality of blood components themselves and the **quality of the service in delivering and using them.**

The EU optimal use project 2007:

The aim of this project is to encourage the optimal use of blood components across Europe through sharing of information and best practice for the benefit of patients voluntary unpaid donation

European Association For Haemophilia and associated disorders (EHAD)

European Principles of haemophilia care.

Colvin B.T. et al Haemophilia (2008), 14,361-374

24-25 April 2009

Optimal Clinical Use of Blood Components

*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

European Symposium on “Optimal Clinical Use of Blood Components”

April 24th-25th 2009, Wildbad Kreuth, Germany

Pre conference period

Invitees

- Experts in transfusion medicine
- Regulators
- Authorities
- Daily professional users
- Repres. Of the European Committee on Blood Transfusion of the Council of Europe
- Repres. WHO

Survey on „optimal use of blood components:

- Guidelines
- Quality management in clinical use of blood products
- Provision of blood products in the individual countries

Conference (110 participants)

Plenary presentations

Working Group discussions

- Blood products: red cells, platelets, FFP, album
- Clotting factor concentrates and haemophilia treatment
- Quality management in clinical use
- Efficacy in terms of outcomes



Rainer Seitz
Paul-Ehrlich Institute
Langen, Germany



Jean-Marc Spieser
European Directorate for the Quality of
Medicines & Health Care (EDQM)
Strasbourg, Frankreich



Wolfgang Schramm
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Dept. for Hemostasis and Transfusion
Medicine
Munich, Germany

Survey European Symposium „Optimal use of blood components“

Results

76 participants completed the questionnaire, most of them working at transfusion services.

Transfusion service	47 (62,67%)
Clinician in daily clinical routine care	22 (29.73%)
Governmental / Regulatory Authority	12 (16.00%)
Other	2 (2.67%)
unknown	2 (2.67%)

The majority of participants use guidelines (international and/or national) in daily practice and consider them useful.

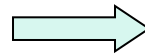
	No (N / %)	Yes (N / %)
Do you use international recommendations or guidelines for the clinical use of blood products	19 (25,68%)	55 (74,32%)
Do you use any specific national guidelines for clinical use of blood products?	24 (32.00%)	51 (68,00%)
Are these national guidelines regularly updated	23 (35,94%)	41 (64,06%)
Do you consider guidelines useful for the daily routine practice	4 (6.15%)	61 (95.31%)

(multiple choices possible)

Survey European Symposium „Optimal use of blood components“

Efficacy in terms of outcomes and economics

	No (N (%))	Yes (N / %)
Do you consider it as important to assess efficacy / outcomes of transfusion?	2 (2.63%)	70 (92.11%)



What is the parameter of success?	
Laboratory parameters	48 (51.06%)
Outcomes in terms of morbidity	50 (65.79%)
Outcomes in term of mortality	46 (48.94%)
Others	16 (21.05%)

(multiple choices possible)

There is a clear commitment to measure outcomes in transfusion medicine. However, only limited publications on outcomes show that possible study designs, study endpoints and statistical methods have to be discussed.

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

Table 1. Parameters studied to describe outcome of centralized haemophilia care.

Parameters studied	Evidence	
Determinants of care	Clotting factor use (GNP)	
	Centralized care (HTC/CCC)	
	Home treatment	
Outcome parameters	Survival	+++
	Short term: costs	+
	Visits, hospital admission	++
	Unemployment	++
	Long term: joint status	No data
	Disability	No data

HTC, Haemophilia Treatment Centre; CCC, Comprehensive Care Centre.

Survey European Symposium „Optimal use of blood components“

Supply – Demand - Economics

Past

	No (N / %)	Yes (N / %)
Do you encounter periods of shortage of any blood product?	17 (22.67%)	58 (77.33%)

Future

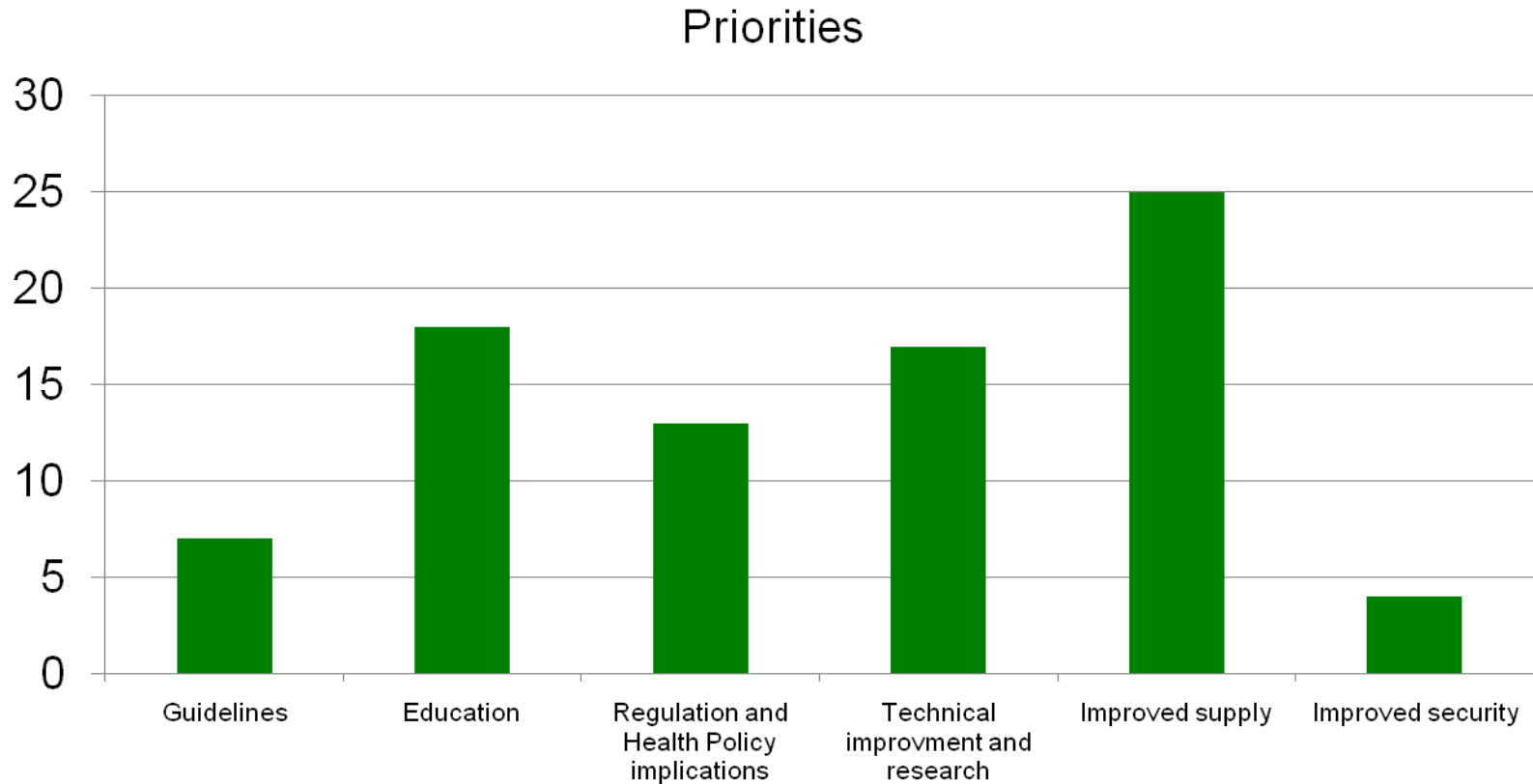
Analysing the actual trends, how will these trends influence the supply and provision of blood products in the next years?	
Shortage	35 (46.67%)
Price increase	31 (41.33%)
Structural changes	33 (44,00%)
Others	1 (1.33%)

(multiple choices possible)

Supply and provision of blood components will be under pressure in the near future. Therefore strategies are expected to come from stakeholders (clinicians, providers, authorities).

Survey European Symposium „Optimal use of blood components“

Priorities for the next years to achieve optimal provision of blood products



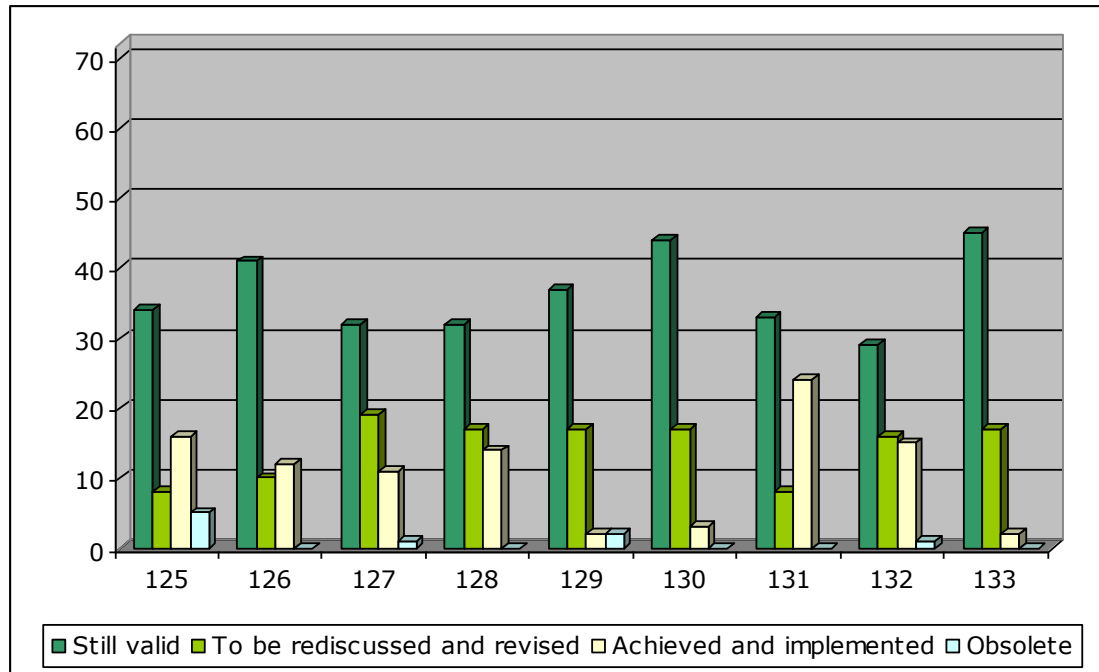
(multiple choices possible)

Specific subgroups were identified and answers were distributed according to the subgroups.

Survey European Symposium „Optimal use of blood components“

Actual perspective on the published recommendations of the Wildbad Kreuth Initiative 1999

Clotting Factor Concentrates



Total no. of questionnaires: 72. Multiple choice answers were possible

All recommendations have been assessed „still valid“ and / or that they should „be re-discussed and revised“.

Recommendations from the working groups

Clotting factor concentrates and haemophilia care

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 miscellaneous adverse 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

Recommendations from the working groups

Clotting factor concentrates and haemophilia care

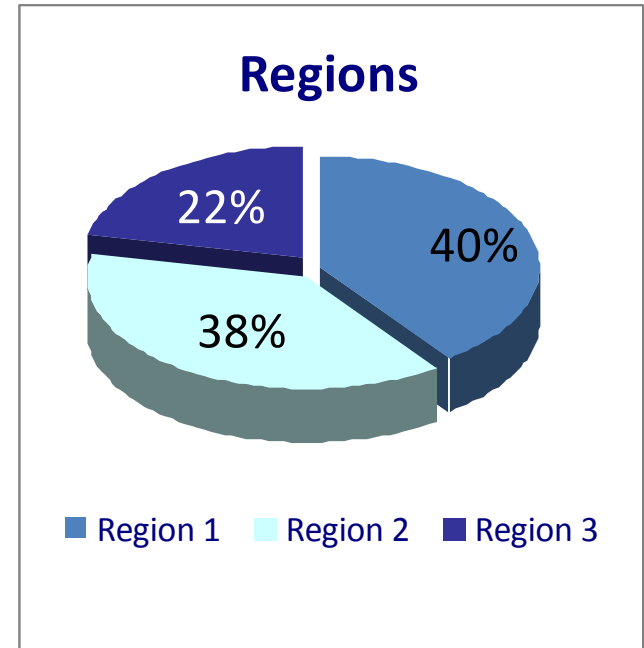
Modified Recommendations on clotting factor concentrates:

(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.**

Results – Clinical Outcomes

- **Region 1 (> 5 IU):** (N=562)
- Austria, Denmark, France, Germany, Sweden, United Kingdom
- **Region 2 (2-5 IU):** (N=540)
- Belgium, Finland, Greece, Hungary, Italy, Portugal, Slovenia, Slovakia, Spain, Switzerland
- **Region 3 (≤ 2 IU):** (N=305)
- Czech Republic, Lithuania, Poland, Romania, Turkey



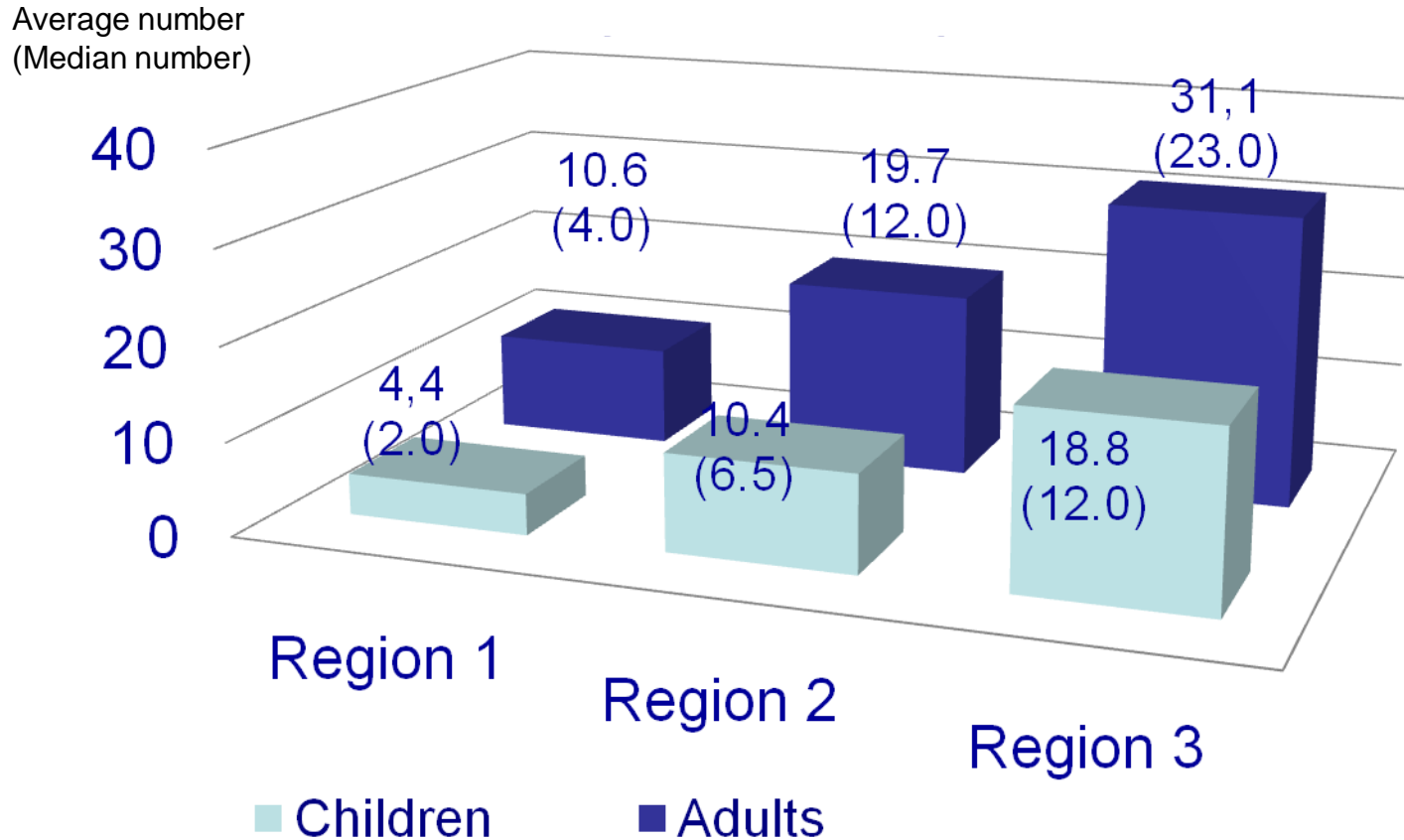
Definition of regions is based on historical data (2004) from different resources e.g. WFH, market research data



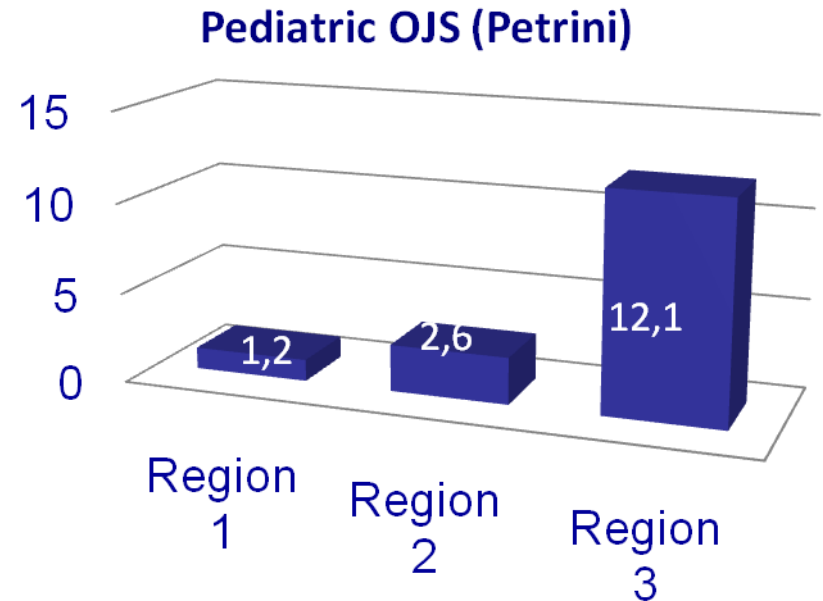
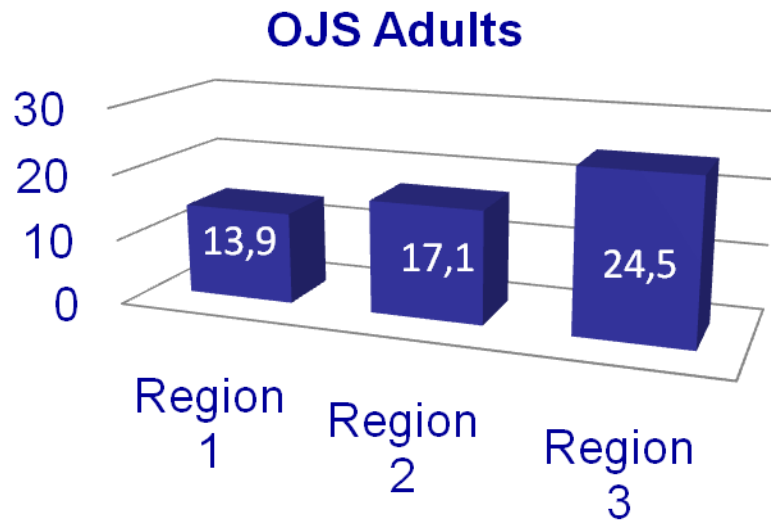
European Study of Clinical, Health economic and Quality of Life outcomes in Haemophilia treatment

Funded by: European Commission - DG Research Projekt - QL7-CT-2002-02475

Average annual bleeds



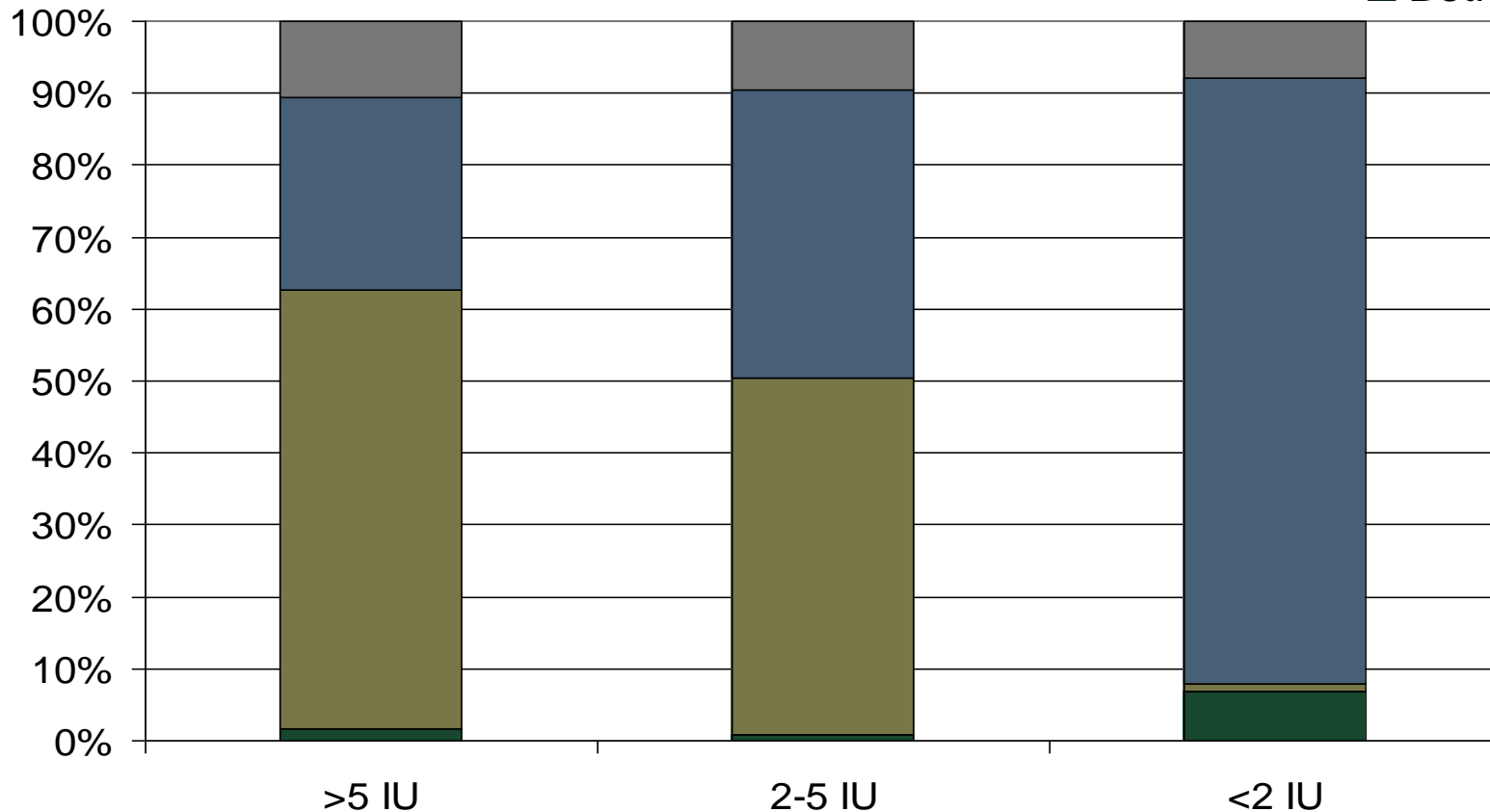
The joint scores showed substantial differences between the different regions, especially for children



Treatment of Children by Region

Average dose per capita
severe, moderate and mild patients

- None or not given
- Plasmaderived
- Recombinant
- Both



Recommendations from the working groups

Clotting factor concentrates and haemophilia care

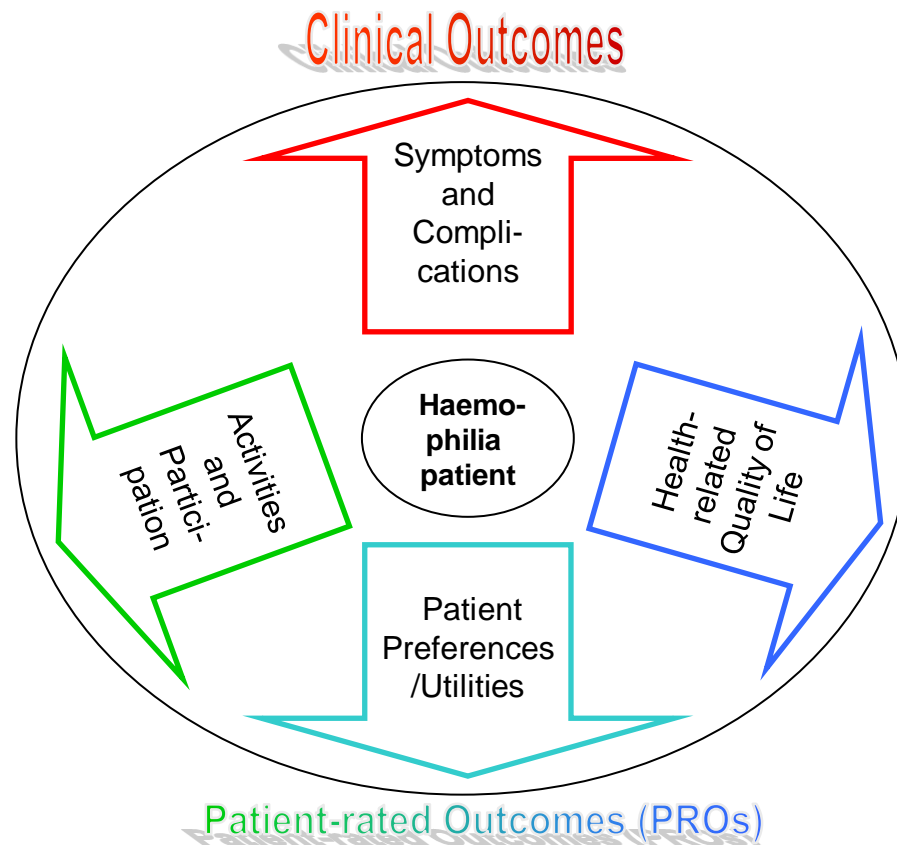
Modified Recommendations on clotting factor concentrates:

(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.**

Due to the **chronic course of haemophilia** the presentation of **outcomes** over a mid term to a **long term perspective** are of importance when **justifying optimal care**.



Recommendations from the working groups

Clotting factor concentrates and haemophilia care

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.

Recommendations from the working groups

Clotting factor concentrates and haemophilia care

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**.

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.



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“



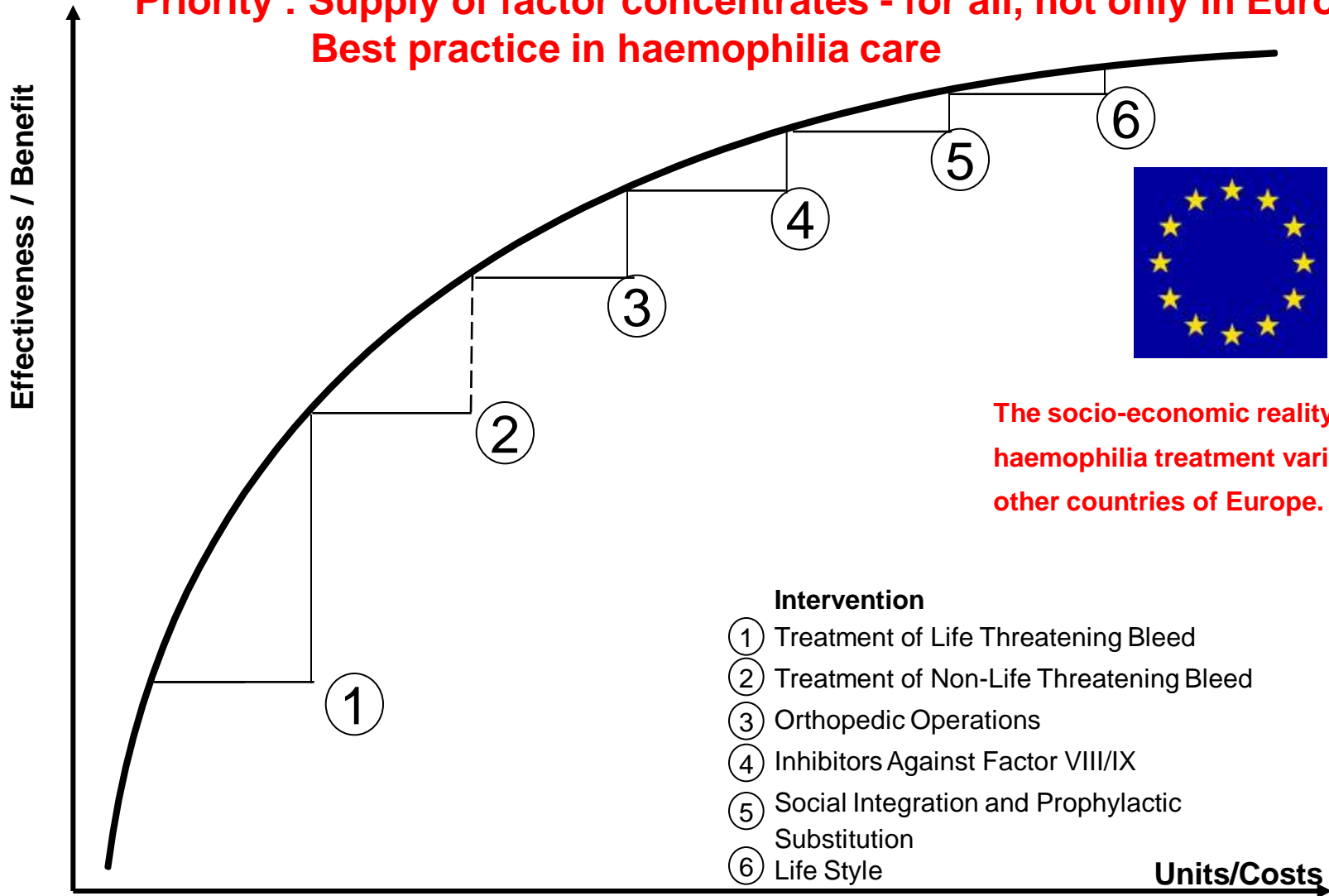
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Clear evidence on outcomes / effectiveness is a key element for access to and reimbursement of factor concentrates

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

For more details please see...

<http://www.pei.de/DE/infos/fachkreise/blut-fach/kreuth-symposium-blood-proceedings.html>

Biologicals. 2011 Apr 23. [Epub ahead of print]

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

Berger K, Klein HG, Seitz R, Schramm W, Spieser JM.

University Hospital of Munich, Department of Transfusion Medicine and Hemostasis, Marchioninistrasse 15, D-81377 Muenchen, Germany.

Recommendations from the working groups

Efficacy in terms of outcomes (including economical aspects)

New recommendations should be added:

- Transfusion therapy should be regularly reviewed, and revised according to evidence
- There is an **urgent need to define relevant clinical outcomes** from transfusion, such as QOL and functional status
- 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
- **Transfusion specific tools to measure clinical outcomes need to be developed and validated**
- Consequences of withholding or giving transfusion need to be measured in relevant patient groups
- A better understanding of the optimal correction of anaemia and the optimum duration of correction is needed, for major patient groups, eg major surgery; chronic anaemia.
- **Observational studies are needed to focus prospective studies on the outcome of transfusion therapy**
- Large adequately powered randomised clinical trials in transfusion medicine are needed to optimise blood use
- Evaluate zero-risk versus risk-based analysis for overall decision making process for assessing safety and effectiveness of blood transfusion and cellular therapies
- Data from haemovigilance programmes should be used for learning and improvement
- **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.

Treatment of Adults by Region

**Average dose per capita
severe, moderate and mild patients**

- None or not given
- Plasmaderived
- Recombinant
- Both

