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

European principles of haemophilia care

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Summary. As the management of haemophilia is complex, it is essential that those with the disorder should have ready access to a range of services provided by a multidisciplinary team of specialists. This document sets out the principles of comprehensive haemophilia care in Europe. Within each country there should be a national organization which oversees the provision of specialist Comprehensive Care Centres that provide the entire spectrum of clinical and laboratory services. Depending upon the size and geographical distribution of the population, a network of smaller haemophilia centres may also be necessary. There should be arrangements for the supply of safe clotting factor concentrates which can also be used in home treatment and prophylaxis programmes. A national register of patients is recommended along with collection of treatment statistics. As comprehensive haemophilia care is multidisciplinary by nature, the need for education and research programmes for all staff members is emphasized: Members of the Interdisciplinary Working Group not represented in the list of authors are mentioned in Section 4 of this document.

Keywords: haemophilia, haemophilia care, management, principles, treatment

Contents

Other members of the Inter Disciplinary Working Group are listed in the Appendix.

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Section 1: European principles of haemophilia care

We call upon European and national healthcare policy makers to join us in taking strong and decisive action to ensure that people with haemophilia have access to safe treatments and optimum care throughout Europe. We endorse the following principles, as elements of haemophilia care provision that should be available in each European country.

A Central Haemophilia Organisation with supporting local groups

In each country there should be a central organization for haemophilia care supported by centres operating at the local level. These organizations should be responsible for accurate record keeping and the effective administration of haemophilia

care. Such an approach also facilitates the exchange of best practice and the co-ordination of research.

National Haemophilia Patient Registries

Each country should have a national haemophilia patient registry administered by the Central Haemophilia Organisation. Patient registry data can be used to facilitate resource planning and allocation, as well as provide accurate data on patient numbers, prescribing patterns, geographical spread and adverse events.

All registers should be held with suitable attention to confidentiality, national regulations and local best ethical practice.

Comprehensive Care Centres and Haemophilia Treatment Centres

Comprehensive Care Centres (CCCs) and Haemophilia Treatment Centres (HTCs) should be established to ensure that people with haemophilia have access to the full range of clinical specialties and appropriate laboratory services.

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 organizations that deliver haemophilia care via a formal mechanism such as a National Haemophilia Co-ordinating Group.

Safe and Effective Concentrates at Optimum Treatment Levels

People with haemophilia need to have access to safe and effective treatment at optimum levels. This improves physical health, life expectancy and quality of life and reduces the psycho-social and economic impact of this bleeding disorder on the patient and his/her family. It also reduces the amount of long-term support needed from healthcare provider resources.

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 children and adults with haemophilia to have the freedom to lead lives that are as normal as possible.

Prophylaxis (Preventative) Treatment

Prophylaxis 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 and reduces the burden of the condition.

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 to skilled care through Accident & Emergency departments and to the range of specialists required to ensure their safety.

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 tolerance 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.

Education and Research

Recruitment and education of doctors 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, with priority areas for investigation being modified factor VIII and IX agents with longer half-life and reduced immunogenicity, new administration techniques, better understanding and prevention of the development of inhibitors and gene therapy. Other areas of research are required to further the development of care for patients and families, including examination of different service delivery models, outcomes and quality of life measures.

Section 2: European principles of haemophilia care – detail & references

A Central Haemophilia Organisation with supporting local groups

In each European country there should be a central organization for haemophilia care. Each local facility should maintain proper records and have an adequate administrative base.

These organizations will provide a focus for the provision of safe concentrates, effective allocation of resources, the collection of data on concentrate usage, the recording of adverse reactions, the sharing of developments in care and the coordination of research.

In geographically small countries with dense populations, a centrally located model of care delivery with links radiating out to smaller peripheral centres ('hub and spoke'), may be appropriate. Different solutions may be preferable where distances between towns are very large, or where the population is scattered or is concentrated in very few areas. It is not appropriate to define the number of centres required for a particular population, given the varying geography and population densities within Europe.

Several studies have reported results of economic capacity and centralized care on outcome of haemophilia patients. An overview of parameters used in studies on outcome of centralized haemophilia treatment is shown in Table 1.

All studies describe the large effects of improved haemophilia care on life expectancy. Starting with the availability of replacement clotting factor treatments and the increase in clotting factor consumption, life expectancy for patients with severe haemophilia increased from 19 years in the 1930s, to 71 years in 2001 [1,2]. This trend is also observed in developing countries: the ratio of the adults/children <13 years increases from 0.35 in countries with a gross national product (GNP) of less than $2000 per capita, to 3.7 in countries with a GNP over $10 000 per capita [3]. The institution of home treatment provides better access to treatment, but also reduces direct medical costs [4].

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.

Centralized care improves outcome, both in developing [3] and Western countries. Soucie *et al.* reported a reduced mortality rate in American patients treated in HTCs [5]. In addition, several studies have reported improved short-term outcome as a result of centralized care. Main parameters used were hospital visits, hospital admissions and unemployment rates. Several studies on short-term outcome have been summarized by Baker *et al.* [6].

Both the early and more recent UK [7,8] and American [9] guidelines state that haemophilia care should be centralized in designated HTCs. In addition, these guidelines provide detailed requirements for these HTCs.

The main points are:

- maintaining expertise and providing trained personnel for delivery of care;
- providing care for at least 40 patients with FVIII/IX <2% (UK recommendations only);
- providing multidisciplinary comprehensive care teams;
- offering specialized services, e.g. prenatal diagnosis, orthopaedic surgery and genetic counselling;
- supporting home treatment for patients;
- maintaining a national network of care;
- providing a National Registry (UK recommendations only) and
- doing research to improve care.

These main points were confirmed by a recent publication from the USA [6] and a review from the United Kingdom [10].

For developing countries, Isarangkura identified four areas of care: clinical care, laboratory facilities, availability and production of blood products and patient organization. For each area of care, levels of care were identified; ranging from 1 (not available) to level 6 (most specialized form of care, e.g. reference centre for haemostatic disorders) [11]. These findings were corroborated by Chuansumrit and a recommendation by the World Federation of Haemophilia (WFH) [12,13]. In addition to emphasizing centralized care, these publications suggested that it is very important to integrate haemophilia care into existing healthcare systems and provide constant education to all healthcare workers. In this case, local production of cryoprecipitate or other blood products was

considered very important to promote constant availability of treatment.

Principle 1: References

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National haemophilia patient registries

Each country should have a national haemophilia patient registry.

A national patient registry is an effective vehicle for collecting key information on rare conditions such as haemophilia and related disorders. Such information may permit accurate assessment of disease prevalence and distribution of patients and provide valuable insight into natural history and treatment patterns [1–3].

Registry data allows analysis of standards of care, and may be used as a tool for auditing clinical and laboratory services. This in turn could support the development of better quality of care and resource planning.

It is essential that registries collect all relevant clinical and laboratory data. This ensures the quality of the information generated but also facilitates the creation of a haemophilia communication network for the distribution of information, educational material and other notices important to the health and well-being of individuals with haemophilia. The work of clinical networks such as haemophilia genetic groups may also be greatly enhanced by high-quality registry data [4].

National registries and international registry networks may form the basis of comprehensive and effective surveillance systems for monitoring the safety of haemophilia treatments. Registries are ideally placed to collect data on incidence of inhibitors, transfusion transmitted infection and other treatment-related adverse events. Power calculations show that to detect an increase in inhibitors in previously treated patients of 1–3% with an α of 0.05 and a power $(1 - \beta)$ of 90%, a sample size of at least 430 patients is needed. This is illustrated by the Dutch study detecting increased inhibitor incidence after introduction of a new FVIII concentrate [5] and the Canadian surveillance of the effects of switching to recombinant concentrate [6]. Inhibitor incidence in previously untreated patients is a particularly important issue at the time of introduction of new concentrates. Postmarketing studies on new products often report data on <100 patients, but power calculations show that to detect an increase in inhibitor incidence by 30% (from 28% to 38%), 225 patients need to be studied to reach power of 90% with an α of 0.05.

To improve the efficacy of surveillance, national patient registries should strive to ensure compatibility with other international registries.

Close attention must be paid to the issue of confidentiality, compliance with national regulations and best ethical practice [7].

Principle 2: References

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Comprehensive Care Centres and Haemophilia Treatment Centres

Haemophilia is a complex disorder to diagnose and manage. The keys to the improvement of health and quality of life include:

- Prevention of bleeding.
- Long-term management of joint and muscle damage.
- Management of complications from treatment including:
  1 Management of inhibitors that prevent the treatment from working, leading to dangerous uncontrolled bleeding.
  2 Viral infection transmitted through blood products in the past, requiring long-term management.

These goals are best met by a team of health care professionals providing comprehensive care as recommended by the World Health Organisation and the WFH. CCCs and HTCs are centres of expertise in haemophilia care, offering facilities appropriate to the local population within the context of (i) a country's physical and political geography and (ii) the population density and distribution.

All people with haemophilia have the right of access to a CCC and the number of CCCs should be co-ordinated to provide optimal care for the haemophilia population. Attention must also be paid to the regulation of HTCs to ensure that adequate care is offered and HTCs caring for smaller numbers must be competent and have the necessary expertise to treat people with haemophilia, with appropriate support.

It is essential that there is a close relationship between the CCCs and the HTCs to preserve and promote the overall quality of haemophilia care.

The concept of a CCC derives from the WFH, which specifies that a CCC should care for at least 40 people with severe haemophilia.

A CCC should:

- provide 24-h service with experienced staff;
- provide inhibitor care;
- have access to an immune tolerance service, with priority being given to newly developed inhibitors;
- provide people with haemophilia with safe and effective factor concentrate. People and especially children, should receive the product with the lowest possible risk of transmission of pathogens;
- provide 24-h, hospital based, experienced medical cover with one or more whole-time equivalent doctors;
- have designated nursing staff to co-ordinate treatment, treatment supplies, the home treatment programme and patient and family education;
- provide community liaison, including appropriate home and school visits;
- have a laboratory that provides 24-h assay cover and is able to measure the potency of inhibitors in a timely manner;
- have a laboratory that is subject to external quality assurance;
- have hospital-based nursing staff. Some centres may also find that hospital-based nurses offering community outreach are valuable;

- have available a dedicated physiotherapy service;
- have access to a social worker;
- have effective and dedicated data management;
- have access to rheumatology and/or orthopaedic services;
- have access to dental services;
- have access to obstetric and gynaecology services;
- have access to psychological support;
- if children are treated, have a paediatric Accident & Emergency department, paediatric day care, a paediatric ward and paediatric nurses;
- have access to a genetics laboratory;
- be able to manage the process of genetic counselling;
- have access to an antenatal diagnostic service;
- be able to care for patients with HIV and hepatitis C infection;
- be accessible for people with disabilities;
- follow-up patients regularly;
- provide home treatment for patients;
- be able to provide prophylaxis, especially for children and where otherwise indicated;
- keep reliable records;
- carry out clinical audit. Internal audit is essential; external audit is desirable;
- undertake medical education;
- participate in research;
- have broad experience in haemostasis and
- adhere to consensus guidelines in haemophilia, which should be available in each European country.

An HTC should:

- provide 24-h, appropriate haematological cover;
- operate inhibitor care and immune tolerance services in co-operation with a CCC;
- provide people with haemophilia with safe and effective factor concentrate. People and especially children, should receive the product with the lowest possible risk of transmission of pathogens;
- provide 24-h, appropriate haematological cover by one whole-time equivalent doctor with experience in haemostasis;
- ideally be able to provide 24-h assay cover, but it is appreciated that there may be delay at night;
- have a laboratory that is subject to external quality assurance;
- have access to nursing staff;
- have available a social worker;
- have effective data management;
- have a strong relationship with rheumatology/orthopaedic services at a CCC. Ideally, the HTC should have access to the services of a local physiotherapist with an awareness of the problems of haemophilia patients. At smaller centres, there should be physiotherapy support and a close relationship with a CCC to deliver the full service;
- have access to obstetric and gynaecology services;
- if children are treated, have a paediatric Accident & Emergency department, paediatric day care, a paediatric ward and paediatric nurses;
- be able to provide preliminary genetic counselling, followed by referral to a CCC for full review;
- have access to HIV and hepatitis C care, if necessary through a CCC;
- be accessible for people with disabilities;
- be able to offer regular follow-up and home treatment in co-operation with a CCC;
- be able to provide prophylaxis in co-operation with a CCC, especially for children and where otherwise indicated;
- keep reliable records;
- carry out clinical audit. Internal audit is essential; some form of external audit is very important in collaboration with a CCC;
- undertake medical education;
- participate in research, though this is desirable rather than essential;
- have experience in haemostasis and
- adhere to consensus guidelines in haemophilia, which should be available in each European country.

See references to Principles 1 and 2

Partnership in the delivery of haemophilia care

Haemophilia is a complex disorder and effective management requires the provision of a comprehensive care programme delivered by a multidisciplinary team. It is essential that this range of disciplines is represented in discussions leading to agreement on treatment protocols and on all aspects and standards of care.

Optimum care results where representatives from the specialized clinicians, the national haemophilia patient organization, the Ministry of Health and/or the funding authority work together in a National Haemophilia Co-ordination Group [1]. This group might be organized on a statutory or non-statutory basis and should operate with clear terms of reference. These could include provision of advice and recommendations on [2]:

1 all aspects of care and treatment;
2 funding; to ensure the adequate provision of the range of services required;
3 the organization, delivery and confidentiality of services, including specialist services;
4 quality management systems and audit;
5 education and training of healthcare professionals;
6 education, awareness and health promotion for people with haemophilia and their families;
7 developments arising from research into haemophilia and
8 the publication of information on haemophilia.

A national Haemophilia Co-ordination Group would be able to enhance co-operation between key stakeholders, agree organization of care and assess national priorities for concentrate procurement. Such a group would increase understanding of the particular needs related to haemophilia care provision by health authorities as key health officials would be integrated into the planning of required resources for treatment and care systems. Such a group could be an effective partnership model leading to agreed national priorities and resource allocation, in addition to providing a formal mechanism to resolve differences of opinion which may arise [3–5].

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Safe and effective treatment at optimum levels

Haemophilia is treated by the replacement of missing blood clotting factors. This is usually achieved by the intravenous injection of appropriate treatment which is administered:

- when a bleed occurs. This is called 'on-demand' treatment. It causes the bleeding to stop when sufficient clotting factor reaches the affected area and
- at regular intervals to prevent bleeding, which is called 'prophylactic' treatment.

The need for safe treatments The first factor replacement therapies were derived from human plasma. However, it is now recognized that this introduced the potential for the transmission of viruses. The impact of HIV was particularly devastating, with large numbers of people with haemophilia being infected in the 1980s. For many years it had also been known that there was a risk of hepatitis, which later proved to be due to hepatitis C.

Twenty years on, the proportion of the patient populations that live with HIV and/or HCV because of viral transmission is still important [1].

In response to the continued concern over transfusion-related infections [which, as well as HIV and HCV, include hepatitis B virus, hepatitis A, Parvovirus B19 and unknown pathogens and prions], treatments continue to be developed aiming to minimize the risk of viral or pathogen transmission. Treatment evolution has led to:

- safety improvements to factor replacement treatments derived from human plasma through enhanced donor selection and donor screening tests as well as the introduction of viral inactivation and removal steps in the manufacturing process;
- the development of recombinant (genetically engineered) factor replacement treatments, which are not derived from human plasma, but contain human- or animal-derived materials at different manufacturing process levels and
- the development of recombinant factor replacement treatments with no human- or animal-derived materials content.

The need for optimum treatment levels Disparities currently exist across the EU in terms of access to sufficient levels of safe replacement factor treatments to ensure the survival and well-being of people with haemophilia [1]. The table shows the differences in causes of mortality among people with haemophilia when access to sufficient amounts of replacement factor treatment are not available – as has been the case in Romania (Brian O Mahony, personal communication).

Causes of mortality for people with haemophilia 2005:

Switzerland	Romania	Germany
AIDS: 29.16%	Haemorrhage: 90%	AIDS: 14%
Cancer: 20.83%	AIDS: 5%	Hepatic cirrhosis: 14%
Cardiovascular: 12.5%	Other: 5%	Cancer: 23%
Haemorrhage: 16.66%		Haemorrhage: 10%

Plasma-derived factor replacement treatments

In the case of plasma-derived treatments, an indirect indicator of viral safety is the absence of reports in the literature in recent years of clinical illness and/or seroconversion detected in single cases or clusters of patients. However, to gain accurate information, follow-up on large cohorts of people with haemophilia is far more significant.

The Universal Database of the Centre for Disease Control in the USA studied viral seroconversions in people with haemophilia between 1988 and 2002. While no patients had seroconverted to HIV and only one patient had seroconverted to HCV, all other seroconversions registered were due to vaccination against hepatitis A and B. Similarly, lack of product-related infectious disease was found in 81 Austrian patients followed in a mixture of a retrospective and a 2 years prospective trial covering 772 patient-years [2,3].

Parvovirus B19 is a viral contaminant marker that displays high resistance to viral inactivation procedures. Although somewhat reduced in load during purification procedures in factor concentrate manufacture, various forms of Parvovirus B19 may still be found in plasma-derived concentrates [4].

An issue still pending concerns the possibility that the prion caused variant Creutzfeld-Jakob disease may be transmitted by blood from an apparently healthy blood donor during the incubation period. No such transmission in people with haemophilia has until now been reported in the literature, and the risk is assumed to be extremely small.

Recombinant replacement factor treatments

Factor concentrates produced by recombinant technologies have been available in several countries since the mid-1990s. During their prelicensure testing as well as in postmarketing surveillance studies, safety against human viral pathogens such as HIV-1 and hepatitis C has been investigated and the currently licensed products have been found to be safe in this regard.

Recent progress in recombinant manufacturing technologies has led to a stepwise elimination of human and animal protein constituents during manufacture.

Principle 5: References

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Home treatment and delivery

For more than 30 years it has been recognized that people with haemophilia can treat themselves at home [1–3]. Treating haemophilia at home, as opposed to in a hospital setting, reduces the economic impact on healthcare systems and improves the quality of life for both the person with haemophilia and his family [4].

With home therapy, factor replacement concentrates can be administered as soon as bleeding starts, minimizing the amount of treatment product needed, reducing short-term disability and avoiding long-term joint damage, resulting in preservation of functional independence. Early treatment results in the use of slightly less factor coupled with a significant decrease in morbidity because of more rapid recovery from bleeding episodes. The proportion of patients with progressive arthropathy is reduced but not abolished, with the failure rate being the highest in older people with haemophilia. Home treatment also allows patients to benefit from prophylactic treatment, reduces the frequency of visits to a local centre or general practitioner for urgent infusions and enables such patients and their families to lead lives that are as normal and active as possible.

Home treatment and self-infusion have enabled people with haemophilia to travel widely on their own. The regulations, concerning transportation of pharmaceuticals, especially liquids and sharps, such as needles and other necessary medical devices, have recently been tightened because of threats to international security but ways must be found, in discussion with the relevant authorities, to maintain the vital autonomy of the haemophilia community.

Home treatment programmes should be directed from a haemophilia centre that is integrated into the existing healthcare system. However, it is important that there is a practical educational programme with community outreach so that clotting factor is used appropriately. Advice must be sought when significant bleeds occur, or do not respond rapidly to treatment. Intensive education and training of patients and family members incorporates them into valuable members of the healthcare team and can produce significant benefits.

In countries where home therapy is available, there is a reduction in clinic visits and hospital admissions, easing the burden on public health facilities. It is important, however, to ensure that there are regular, albeit less frequent, clinic visits so that an overall assessment of health and factor use can be made and accuracy of record keeping determined [5,6].

Record keeping is an essential part of a home treatment programme. It is important to the haemophilia clinic as an aid to managing treatment and an alert to particular problems. It can improve a patient's ability to highlight his particular needs and improve communication among all parties. Record keeping allows greater control over product inventory, minimizing wastage and thus ensuring best use of an expensive resource. Computer-based systems for monitoring home therapy are being developed and should make such monitoring easier [7].

Home therapy, while allowing more independence from the haemophilia centre, still requires the factor and supplies to be collected from such a centre.

Home delivery packages have been developed whereby a home delivery service or supplier is responsible for the purchase of product, its storage and delivery to the home through a contract with the healthcare provider. This can be of financial benefit as well as increasing the convenience of supply to the patient.

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Prophylactic treatment

The provision of early prophylaxis for children with severe haemophilia can wholly or largely prevent life-threatening bleeds, chronic joint disease and disability thereby reducing the need for surgical interventions and contributing to both improved health and social well-being for people with haemophilia [1–3].

Current data strongly support that prophylaxis has significant advantages over on-demand treatment for people with haemophilia [4,5]. All comparative clinical trials demonstrate a reduction in bleeding frequency for patients who received prophylaxis.

As outcomes of treatment (including cost–benefit analyses), are scrutinized more closely and comparisons made across Europe and internationally, it is important that standard definitions for prophylaxis are agreed [6]. In general, however, primary prophylaxis is started with the aim of preventing bleeding and its consequences, and is therefore commenced at an early age, often before any bleeding or at the time of the first joint bleed. It has the disadvantage of being costly, due to increased use of clotting factor, at least in the initial stages. Secondary prophylaxis is started in those with haemophilia to prevent recurrent bleeding and avoids the use of factor in the early years, but inevitably is associated with more joint damage.

Prophylaxis was first considered as far back as the 1950s. Due to scarcity of factor, low doses were used

and prophylaxis was often started after arthropathy had already developed. Nevertheless, substantial improvements were noted both in the condition itself and in the patient's quality of life. Over the years, where possible, prophylaxis regimens have intensified and have been started earlier [2]. Another benefit of prophylaxis compared with on-demand therapy is that it seems to be associated with a lower risk of inhibitor development [7,8].

Several studies comparing clinical benefit of prophylaxis vs. on-demand treatment, historically or prospectively, indicate a significant reduction of bleeding frequency and subsequently less pain and joint disability for the groups so treated. Although the best results are seen in those patients who begin treatment early with minimal or no joint bleeding, those who receive any level of prophylaxis have better joint outcomes when compared with those using on-demand therapy [1–3,5]. In young adults, it has been shown that the cost of on-demand treatment and intermediate-dose prophylaxis is similar but with a significant improvement in number of bleeds and development of arthropathy in the latter group. High-dose prophylaxis doubles the cost of therapy with only slight further benefit [9]. Others have shown that although the cost of secondary prophylaxis is higher than on-demand therapy, this is accompanied by clinical improvement and greater patient well-being [5].

Further work is required to evaluate the use of prophylaxis in adult life but its value in protecting target joints and preventing bleeds at times of increased risk is well established. It is possible that those with a milder phenotype may be able to switch to on-demand treatment without significant deterioration in their clinical condition. Continuing efforts are necessary to maintain service provision already achieved in some European countries and to promote prophylaxis where it has not been possible to provide it.

Principle 7: References

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Specialist services

Effective co-ordination of services is needed for people with haemophilia who often need consultations with a variety of specialists.

The main areas in which combined clinics or joint consultations are required are:

- emergency medicine and acute surgery;
- paediatrics;
- infection and immunity (especially HIV and hepatitis C);
- rheumatology, orthopaedics and physiotherapy;
- dentistry;
- obstetrics and gynaecology;
- genetics;
- social and psychological support and
- pain management.

General surgery, urology, otolaryngology and neurosciences (neurosurgery, neurology and psychiatry) are also important disciplines that should be available to CCCs.

Despite the current safety of treatment for haemophilia, the previous treatment-related health hazards will continue to place a strain on the demand for resources to support patients with HIV/AIDS and hepatitis C and their families [1].

The French registry of a 10-year (1991–2001) experience of intracranial haemorrhage (ICH), its clinical presentation and management as well as prognosis in 103 patients with haemophilia, was

recently published [2]. Of 123 ICH bleeding episodes registered, 2/3 occurred in patients with severe haemophilia, but mildly and moderately affected patients were also at significant risk of major complications (as their treatment is usually on-demand and their understanding of the condition may be limited). Half the cases occurred in children under the age of 15 years and 67% were associated with trauma. Ten patients were neonates and three of them died. Overall mortality was 22% and long-term morbidity occurred in 60%. The prognostic factors included thrombocytopenia, HCV infection and intraventricular or parenchymal bleeding. In 43% of cases there was a delayed diagnosis and replacement therapy was delayed in 37%. Half the cases were treated in emergency wards. The importance of early recognition of the symptoms and information regarding the typical presentation and poor prognostic factors in ICH should be emphasized to treaters, patients and their relatives.

Before a diagnosis of haemophilia is established, a variable delay can be demonstrated in children who attend emergency units [3,4]. In the quoted study the number of visits to the emergency wards before the diagnosis was made varied from 1 to 19, with a mean value of four visits. The delay was partly associated with the high prevalence of new mutations (30%) without a family history of the disease. The family were aware of a delay in over 60% of the cases, whereas objectively 80% of the diagnoses were delayed. The most common presenting symptom was easy bruising, but haemarthroses occurred in 39% and other bleeding episodes in 22% of cases. In 24% of cases the question of child abuse by the parents was raised. Increased awareness of the clinical and laboratory features that help to identify the condition is important.

A special group of children with haemophilia include economically disadvantaged families [5]. Children with chronic complex illnesses are the most common consumers of the services of emergency units and include haemophilia, juvenile diabetes, anaemia, asthma and epilepsy.

Emergency care

It is dangerous for people with haemophilia to wait in Accident & Emergency departments where many sick patients compete for resources. The CCC or HTC should arrange for people with haemophilia attending for emergency treatment to by-pass A&E to attend a dedicated day ward during working hours. At night and at weekends arrangements must be made for skilled staff to be available at all times to assess and treat appropriately.

In the case of critical injury or illness, management in an A&E department is, however, appropriate and haemophilia centre staff must be prepared to attend to give advice and specialist support without delay. Suitable arrangements must be available for the treatment of children.

A special medical card or other portable record should be issued to patients or parents to facilitate the management of this policy.

In the future electronic alerts will serve best to:

- recognize the medical urgency of replacement therapy in haemophilia before other measures are taken;
- identify the appropriate individual replacement therapy and dose;
- list other medical conditions affecting treatment, i.e. HIV/AIDS and hepatitis C and
- provide advice on the importance of immediate consultation with a CCC.

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Management of inhibitors

Some people with haemophilia develop 'inhibitors', when their bodies inactivate the replacement clotting factor treatment. The development of inhibitors to clotting factors represents the current most devastating complication in the management of haemophilia.

The incidence is approximately 30% in patients with severe haemophilia A but prevalence is less, indicating that some inhibitors disappear spontaneously. Inhibitors occur much less frequently in those with severe haemophilia B [1]. The management of these patients is challenging, as inhibitors compromise the mainstay of treatment, namely clotting factor replacement, rendering the treatment of bleeding episodes more difficult and surgery more hazardous and requiring an enormous amount of human and economic resources [2].

The management of patients with haemophilia and inhibitors is based on:

- timely diagnosis of inhibitor development and thorough follow-up;
- eradication of inhibitory activity;
- treatment of bleeding events;
- prevention of bleeding during surgery and
- prophylaxis of haemophilic arthropathy.

Every patient with haemophilia should be considered at risk of inhibitor development and timely diagnosis is vital. Diagnosis of inhibitor incidence and regular monitoring of inhibitor levels should be measured by the Bethesda assay, with Nijmegen modification (as endorsed by the Factor VIII and Factor IX Scientific Subcommittee of the International Society of Thrombosis and Haemostasis), to increase specificity and reliability [3]. Nevertheless, there is still a very high coefficient of variation (CV) of about 25% and further improvement in specificity, sensitivity, inter-laboratory and intra-laboratory CV is necessary.

Eradication of the inhibitor in patients with haemophilia represents the main goal of treatment because it allows replacement therapy with standard clotting factor concentrates, which is the therapy with the most favourable cost-efficacy ratio [4]. Inhibitor eradication has been demonstrated to be achievable in three quarters of patients through ITT, based on regular infusions of high doses of clotting factor concentrates. Both children and adults with high-responding inhibitors (>5 BU mL^{-1}) should therefore undergo ITT as soon as possible after inhibitor development.

Bleeding events and even minor surgery can put at risk the life of these patients, so treatment should be well timed and appropriate. Successful haemostasis may be achieved in patients with low-level inhibitors (≤5 BU mL^{-1}) using high doses of the deficient factor, but in patients with high level inhibitors (>5 BU mL^{-1}), the need for FVIII or FIX can be by-passed with preparations containing activated coagulation factors. Unfortunately, there is no simple laboratory test that can predict the efficacy of treatment with these agents, which in addition have a small but definite risk of causing thromboembolism and are extremely expensive [5].

Major surgery and long-term prophylaxis in people with inhibitors continue to present a difficult, costly and partly unanswered challenge.

It is essential that CCCs are able to:

- diagnose patients with inhibitors in a timely way;
- monitor patients to manage bleeding events optimally;
- treat patients appropriately during surgical procedures;
- start inhibitor eradication as soon as possible;
- continue it in the most proper manner and
- plan measures to prevent or slow down the development of arthropathy.

Many issues of vital importance for the European haemophilia community are still unresolved. It is not clear which dosage and product should be used for ITT, which by-passing agent and dosage should be chosen in the different clinical situations, whether or not prophylaxis with by-passing agents is feasible and effective in inhibitor patients and how to manage the high costs involved. The answers to these issues can only be provided by clinical trials, preferably controlled and randomized, which should also take into account health-related quality of life and cost.

Europe is potentially well placed to promote and expand clinical research in this field and to support national and international registries for the management of inhibitors to provide a better estimate of the frequency of adverse events of the various therapeutic options.

Principle 9: References

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Education and research

A multiprofessional approach should be taken when addressing haemophilia care and research. The sharing of education and management information across countries and languages within Europe, should be encouraged.

Education A key issue facing people with haemophilia in Europe is the decreasing number of healthcare professionals who specialize in the condition.

A new curriculum for specialist doctors has been developed to facilitate the recruitment and education of doctors in the area of thrombosis and haemostasis (document ready for submission to an International Journal). However, more still needs to be done to encourage doctors to enter the speciality. Nurses, physiotherapists and other professionals also require ongoing specialist education and development for practice in this field.

Research Further research into haemophilia is required, with priority areas for investigation being:

- modified FVIII and FIX agents (with longer half-life and less immunogenicity) [1];
- ways to prevent the development of inhibitors;
- gene therapy [2];
- the pathogenesis of joint destruction following haemarthrosis [3];
- quality of life for people with haemophilia and their families and
- alternative factor concentrate administration methods, especially for young children on prophylactic treatment.

Principle 10: References

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Section 3: Compendium of haemophilia care guidelines

Country	Document
European Medicines Evaluation Agency (EMEA)	EMEA/CPMP/BWP/2879/02/rev 1, 23 June 2004, CHMP Position Statement 2004 on Creutzfeldt-Jakob Disease and Plasma-derived
Germany	Konsensus Empfehlungen zur Hämophilie-Behandlung in Deutschland, Hämophilie-Blätter 2/2000, 'Gesamtstrategie Blutversorgung angesichts vCJK', Bericht der Arbeitsgruppe Paul-Ehrlich-Institut/Robert Koch-Institut, 2001
Hungary	Nemes László N. A haemophilia elõfordulása, öröklõdése, diagnosztikája, szövõdményei, kezelési alapelvek. *Hematológia* 2006
Italy	Gringeri A. *et al.* Italian guidelines for the diagnosis and treatment of patients with haemophilia and inhibitors. *Haemophilia* 2005; 11(6): 611–9.
Netherlands	Mauser-Bunschoten E.P. *et al.* Treatment protocols in the Netherlands. *Haemophilia* 1998; 4(4): 428–9. Mauser-Bunschoten *et al.* Product choice and haemophilia treatment in the Netherlands. *Haemophilia* 2001; 7(1): 96–8.
Sweden	Berntorp E. Guidelines on treatment of haemophilia in Sweden. *Haemophilia* 1998; 4(4): 425–6.
Switzerland	http://www.shg.ch
UK	Several comprehensive guidelines on management of haemophilia and allied disorders, including guidelines on the selection and use of therapeutic products to treat haemophilia and other hereditary bleeding disorders. *Haemophilia* 2003; 9(1): 1–23. UKHCDO (http://www.ukhcdo.org)
World Federation of Hemophilia	Guidelines for the Management of Hemophilia (http://www.wfh.org)

Section 4: Authorship

The European Principles of Haemophilia Care were developed by an interdisciplinary working group of 45 leading haemophilia doctors from 19 European countries. Over a 2-year period, this group reviewed current best practice care and guidelines, as well as assessed the needs of those both providing and receiving haemophilia care and treatment in Europe. Representatives from haemophilia patient organizations and specialist haemophilia nurses were also consulted in this process.

This document represents the expert view of specialist clinicians in haemophilia concerning the future of haemophilia care and treatment in today's Europe.

This document was also unanimously endorsed by all working group members not represented in the list of authors:

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Disclosures

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