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CONTROL OF HAEMOPHILIA:

HAEMOPHILIA CARE IN DEVELOPING COUNTRIES

Report of a Joint WHO/World Federation of Haemophilia Meeting

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1. INTRODUCTION

The successful treatment of haemophilia and related inherited disorders of coagulation is now well established in developed countries. Given adequate, virally-safe replacement therapy with the clotting factor relevant to the diagnosis, the prognosis for most children with haemophilia in these countries is excellent. They can expect to grow to adulthood without the severe arthritis associated with untreated haemophilia and they can expect to become productive members of the community. Whilst they continue to need the provision of skilled medical care should problems arise, together with regular follow-up and clinical audit, the majority of patients learn to treat themselves at home, they and their families becoming almost as self-sufficient as their unaffected peers. This shift from hospital-based to community care saves both medical resource and money.

Within many developing countries people with haemophilia fare less well. The facilities for accurate diagnosis and sustained therapy are lacking, and more common health problems take precedent. Few children with severe haemophilia can expect to survive beyond adolescence, and those that do will have incapacitating and painful arthritis. Throughout their lives they are likely to have been dependent on their communities, thus diverting much of the time and energy needed by others to sustain productive work and family support, let alone survive. Treated well, haemophilia becomes part of normal life; treated badly, haemophilia drains the physical, psychological and financial resources of both the patient and those who care for him.

The treatment of haemophilia in both the developed and developing world countries need not be complicated. The person with haemophilia can be treated and managed by common sense and the application of basic knowledge and understanding of its physiology and pathology. Within the treatment of haemophilia, emphasis needs to be placed on training people rather than on technology in the areas of clinical, laboratory and blood transfusion medicine, and rehabilitation medicine. Within these specialities, there are a number of practical aspects where a critical degree of expertise is required. Such expertise may not be available in the developing country and hence the need for the exchange of knowledge, technology, resource and goodwill. This exchange lies at the heart of the World Federation of Hemophilia (WFH) Strategy. In implementing this strategy it is hoped that the health of people with conditions other than haemophilia will also benefit.

It has been estimated that, by the year 2020, there will be around 550 000 people with haemophilia who require replacement therapy in the world[1]. At the present level of care most will be undiagnosed and most will have no recourse to the appropriate therapy. It is the mission of the WFH to reach these people and ensure that they receive the help they need. In support of this overall aim, since 1990 WHO and WFH have held a series of joint meetings on the control of haemophilia[2,3,4]. This report of the fourth meeting, held under the auspices of the WHO Human Genetics Programme, in Geneva in 1997, is based on papers presented and discussed by all participants. The full versions of all the individual papers presented at the meeting will be found in a future Supplement to *Haemophilia*, the official journal of the World Federation of Hemophilia.

2. PROBLEMS WITH HAEMOPHILIA CARE IN THE DEVELOPING WORLD

Major advances have occurred over the last two decades in every aspect of care of patients with haemophilia.[5,6] These include early recognition and accurate diagnosis, safe therapeutic products sufficient to provide even prophylactic therapy for a near normal life style and carrier detection and antenatal diagnosis to bring down the incidence of severe disease. Unfortunately, these benefits are available to only 20% of patients who reside in developed countries.[1,7] For most of the other patients who live in the developing world, severe hemophilia continues to be the personal and social disaster that it was known to be[8].

Haemophilia has an uniform universal incidence of about 1 in 5-10,000 male births although its prevalence can vary.[9] It is estimated that there will be about 450,000 patients with severe or moderately severe haemophilia A or B by the end of this century. About 80% of them would be in the developing world.

Financial constraints are the foremost reason for inadequate haemophilia care in these countries. Most developed countries have a per capita clotting factor consumption of between 2-5 units.[10] To achieve a factor supply of even 1 unit per capita in the developing countries would require 4.9 billion units by the year 2000. This would cost about US$1.25 billion at present prices if plasma derived intermediate purity products are used. This is no mean amount especially if there is almost no support from the state or the insurance sector. It should, however, be mentioned that the developing countries together spent US$172 billion on defence expenditure in 1987, accounting for about 20% of their governmental budget[11]. It is therefore not only a question of lack of resources but also a matter of social and political priorities in these nations.

There are also many non-financial barriers that preclude adequate haemophilia care.[12] Insufficient knowledge about haemophilia among the medical community is the most significant. Combined with the absence of proper health care infrastructure, a low literacy rate and lack of social and financial support for patients and their families[11], delivery of care for any chronic illness that requires recurrent intervention becomes extremely difficult particularly if this is frequent and expensive as is the case with severe haemophilia.

3. POSSIBILITIES AND PRIORITIES FOR HAEMOPHILIA CARE IN THE DEVELOPING WORLD

While the difficulties mentioned above make it impossible to provide state-of-the-art haemophilia care in developing countries, much can still be achieved. Over the last decade, considerable progress has been made in this regard in several developing countries including Thailand[13], Malaysia[14], Brazil[15], Argentina[16], Costa Rica[5] and Zimbabwe.[17] Some success has also been achieved in India[18] where the size of the country and extremely large numbers of patients slow down progress. The experience with trying to provide services for haemophilia in these diverse situations has shown that there are a few core components that require attention:

- Training of care providers and establishing care centres.
- Identification and registration of people with haemophilia.
- Educating patients and families about haemophilia care.
- Providing safe therapeutic products.
- Improving social awareness of haemophilia.
- Prevention of haemophilia.
- Developing a programme for comprehensive care.

3.1 Training of care providers and establishing care centres

Haematology is a relatively new medical specialty in developing countries, and there is usually no structured training programme available. Knowledge of the subject is limited. It is not therefore surprising that physicians are not familiar with the management of patients with bleeding disorders.[12] This results in incorrect diagnosis and mismanagement causing iatrogenic complications for problems that could have been treated easily. A well trained haematologist is most important for establishing services for haemophilia. The infrastructure developed to run a general haematology service provides a system for supporting haemophilia care sometimes even at

subsidized costs. Short training courses may provide a start for physicians with some exposure to the care of patients with bleeding disorders but cannot be a substitute for comprehensive training. Training of other members of the team, particularly the orthopaedic surgeon and the physiotherapist may be achieved in a short term. The ultimate aim should be to provide a team for good comprehensive care for patients with haemophilia including those with social and psychological problems. A significant proportion of people with severe haemophilia in developing countries are infected with the human immunodeficiency virus (HIV)[19] and need services directed towards their specific problems. Centres with graded facilities ranging from basic support to advanced comprehensive care need to be established, depending on local circumstances.

3.2 Identification and registration of people with haemophilia

Identification of patients with haemophilia remains a major problem. Even in countries which have made concerted efforts to establish haemophilia care facilities, only 10-60% of the expected number of patients in the population have been registered. With the exception of Argentina where 1570 of the estimated 1650 patients have been identified[16], only 712 of 1400 in Malaysia[14], 193 of 500 in Zimbabwe[17], 693 of 2000 in Colombia[20], 6064 of 9500 in Brazil[15] and about 4500 of 50,000 patients in India[19] are registered with the national haemophilia organizations. This not only prevents utilization of established facilities by these patients but also deprives the cause of haemophilia of the efforts of these people and the momentum of a larger body. Unfortunately, sometimes even those noted to have a bleeding disorder do not receive an accurate diagnosis because of inadequate facilities. Most developing countries do not have a registry for patients with bleeding disorders. This needs to be established.

3.3 Educating patients and families about haemophilia care

Once the diagnosis is established, the patient and his family should be given adequate information about the disorder. The pressure of large numbers of patients often makes it very difficult for physicians to spare enough time for this. Formal facilities for counselling are scarce. Low literacy rates make communication difficult. Therefore, many patients continue to be unaware of the basis of the disorder and its implications. An informed patient and family can cope better with the hazards of living with severe haemophilia especially when factor replacement therapy is scarce.[22] Familiarity with measures other than factor replacement that can be taken to manage minor bleeding can greatly help in reducing morbidity.[23] Knowledge of the risks of bleeding and how to minimize them will allow the family to let the child with haemophilia grow as normally as possible without being overprotected. Understanding the genetics of the disease will encourage partners to seek counselling and antenatal diagnosis when facilities become available.

3.4 Providing safe therapeutic products

The anguish of a person who is suffering acutely from a bleeding related complication without access to replacement therapy is unbearable. While alternative measures can be attempted to control bleeding,[23] there is no denying that certain complications require factor replacement. If some form of replacement therapy is not available for these situations, it is extremely frustrating for the patient and the physician. Availability of replacement therapy also provides the much needed motivation for the affected person and other interested people to remain actively involved in this cause. It is estimated that 20,000 units of factor VIII concentrate would be required every year for 'minimal' level of treatment for a 70kg person with severe haemophilia.[24] It is necessary to establish a system by which products for at least this level of factor replacement will be available if the morbidity associated with severe haemophilia is to be reduced. Hardly any factor concentrate is produced in the developing countries because apart from lacking technology, transfusion services continue to be inadequate and unsafe.[25] Measures taken for improving blood

transfusion services as part of the strategy for prevention of spread of HIV infection have not had the expected impact even after a decade.[26] New strategies and renewed effort are required to address the transfusion needs of all patients, including those with both inherited and acquired bleeding disorders. This is an example of one area in which "linkage" between haemophilia care and the treatment of other conditions can lead to substantial improvement in general medical care in a developing country.

3.5 Improving social awareness of haemophilia

Limited social awareness of haemophilia[18,27] affects haemophilia care in many ways. It tends to keep haemophilia out of the focus of the government and health planners so that almost no budget is allocated for these patients. Patients with severe disease do not receive the support and sympathy that they deserve from society and are often discriminated against at school and in employment. Health insurance is difficult. The cost of care for a person with haemophilia is so great that most individuals in the world cannot personally afford this treatment.[28] In developing countries with a low per capita income and minimal health care support, it is necessary that society accept some responsibility for these individuals who, with support, can markedly improve their quality of life.

3.6 Prevention of haemophilia

Little progress has been made towards prevention of haemophilia. Advances in techniques of molecular biology have made it possible to document the mutations that cause haemophilia.[29] This has made rapid and accurate carrier detection and prenatal diagnosis possible in a majority of patients.[30] Basic molecular biology facilities are available in most developing countries. If not, the investment required to establish them, in terms of personnel and equipment, is small compared to the cost of treating these patients. About two-thirds of patients with haemophilia have other members in the family who have been previously affected. Prevention of further cases in these families by genetic counselling, carrier detection and antenatal diagnosis is possible and has been shown to be an effective strategy.[31]

3.7 Developing a programme for comprehensive care

A multifaceted approach is required to ensure that the medical, social, educational, vocational and psychological needs of people with haemophilia are met.[32] This requires involvement of a variety of health care professionals and other interested people. Most developing nations lack a co-ordinated national programme for haemophilia. Establishing such a programme is essential and requires a team of skilled and committed people with very determined leadership.[33]

4. DELIVERY OF HAEMOPHILIA CARE IN THE DEVELOPING WORLD: IMPLEMENTATION

The crucial difference between the developed and the developing countries with respect to haemophilia care is that there is minimal or no support from the government and insurance companies in the majority of the latter. While efforts should certainly be made to encourage support for haemophilia from the health budget as well as the insurance sector, it is possible that this may not be forthcoming in a significant way given the economic realities of most of these countries and the justified priority for nutritional and infectious diseases.[34] Haemophilia care in most developing countries is being supported and co-ordinated predominantly by non governmental organizations, usually the national haemophilia societies. However, it should be noted that nearly all the countries where haemophilia care has significantly improved over the last decade are those

with governmental support of their programme. Lobbying for support from the health budget of the country therefore becomes crucial for successful implementation of such programmes.

4.1 Establishing appropriate medical facilities

There must be at least one centre in each country that can measure up to international standards in providing comprehensive care. It is essential, therefore, to identify and train in haematology at least two physicians, committed to the cause of haemophilia, who can then help train others in the country. More emphasis should be placed on the management of bleeding disorders, indeed haematology in general, in the medical curriculum in developing countries. Annual workshops held in different regions, often with international participation, to emphasize various aspects of haemophilia care can significantly improve the understanding and skills of the care providers. WFH International Haemophilia Training Centre fellowships, workshops and the twinning programme (see below) have been useful in rapid transfer of information and expertise but their numbers should be increased to cover more countries sooner.

The number of care centres required in each country will depend on the geographical distribution of the patient population. The facilities at each centre will vary according to the level of expertise and infrastructure available (Table 1). The requirements for establishing such centres should be defined and made available as a detailed report with particular reference to clinical evaluation, basic diagnostic tests, storage and infusion of therapeutic products, and physiotherapy. While it would be best to integrate these services with the existing health care system in each country, it may become necessary to establish a separate system for the sake of expediency and quality. The diagnostic and clinical facilities at these centres will be useful for patients with other bleeding disorders as well. By offering services to other patients it may also provide the centre with a way to generate resources for haemophilia care

It is also important that, together with help for establishing diagnostic and treatment facilities, concepts of quality management in all aspects of the work involved be emphasized. A system of clinical audit should be established. All laboratories should be encouraged to participate in at least one external quality assurance programme. To this end, a WFH External Quality Assessment Scheme has been established for haemophilia centres in developing countries. Its purpose is to promote improved standards of laboratory performance and practice. The scheme involves distributions of lyophilized plasma to participating centres, and statistical analysis of results returned, enabling an assessment of individual laboratory performance in haemostasis screening tests and factor assays. Coupled with this are advisory and educational support roles for participants in the scheme.

4.2 Identification of patients and establishing a National Registry

Increasing awareness of the medical community and society to the problems of bleeding disorders will help identify more patients with haemophilia. Health surveys in educational institutions and work places will also aid in their detection. It is important that those suspected to have a bleeding disorder be systematically evaluated.[35] Once a correct diagnosis is established patients should be registered in a national registry. In addition to demographic data, clinical and laboratory details, prevalence of inhibitors, and viral infections and follow-up data should also be recorded. Such a data base will help plan intervention programmes. Periodic centralized audit of the data will serve as a quality assurance exercise. Discrepancies between the clinical and laboratory profiles of a patient can be used to alert the centre to review its work.

Accurate diagnosis, including knowledge of the factor VIII level in people with haemophilia A and of the typing of von Willebrand disease, are very important with regard to the possibility of using desmopressin (DDAVP) rather than blood products for treatment[36].

4.3 Educating patients and families about haemophilia care

Patients and their families should be counselled and informed about all aspects of the disorder, including details of its inheritance and the possibility of antenatal diagnosis, treatment, common clinical problems, 'do's and don'ts' in daily living, importance of regular exercise and basic management of acute and chronic complications. They should also be told about the facilities available at various centres within the country and overseas. This will prevent situations where patients do not receive appropriate care for lack of awareness. HIV positive patients need particular attention and counselling.[36]

It would therefore be very useful if, at the time of diagnosis and registration, a standardized information booklet in the local language were given to each patient and his family. This would not only provide essential information immediately, but would also compensate to some extent for lack of proper counselling facilities at the centre where the diagnosis was made. It could later be supplemented by discussions regarding specific problems.

4.4 Providing safe therapeutic products

This is the most difficult and often frustrating part of providing haemophilia care in developing countries. Factor concentrates are not usually manufactured locally and imported products are mostly unaffordable. Operation Access and other WFH programmes have been very useful because they provide factor concentrates to at least a few countries at any time. The impact of such intervention needs to be evaluated in Chile which is the current beneficiary of the programme. Whilst it would help if the scope of these projects could be widened to cover more people, it is equally important that developing countries try to establish a system of self-reliance in the production of therapeutic material.

The first step in this direction is to have an efficient blood transfusion service that would harness enough plasma to meet the needs of society.[37] Components will help meet the needs of patients with bleeding disorders other than haemophilia, and transfusion dependent diseases like thalassaemia. This should be made a priority for health care in these countries. Unfortunately, the high prevalence of HIV and hepatitis viruses[38,39] in the population in some countries will affect the safety of 'wet' products. Sixty percent of people with haemophilia treated with cryoprecipitate in Malaysia are hepatitis C virus (HCV) antibody positive.[14] Introducing methods for viral inactivation of 'wet' plasma products should be considered.[40] Facilities for lyophilizing fresh plasma or cryoprecipitate prepared from plasma pooled from a limited number of donors may make home therapy possible.[13] The experience in Thailand, where commercial factor concentrates have become widely available only from 1995, has shown that a reasonable level of care is possible with fresh frozen plasma and cryoprecipitate[41]. The goal of replacement therapy in developing countries over the next decade should be to provide home therapy for all those with haemophilia, at least with lyophilized virally inactivated cryoprecipitate.

However, since the safety and effectiveness of these products can never match that of factor concentrates, provision of virus inactivated factor concentrates and recombinant products should remain the ultimate objective. With the increasing demand for high purity and recombinant factor concentrates in the developed countries[42,43] and the need for continuing plasma fractionation to supply intravenous immunoglobulin and albumin, plasma derived intermediate purity products are becoming available at lower costs in the developing countries. It is possible that locally produced

products could be even cheaper.[41,44] Establishing non-profit organizations for this purpose is a necessity.

Until self-sufficiency in therapeutic products can be achieved in each country, it will be necessary to collect funds from as many sources as possible - government, insurance agencies, employers, philanthropic organizations and society in general - for importing factor concentrates. Since most multinational companies do not market their products directly in many developing countries, it is necessary to find an agency that will import these products in bulk, store them appropriately and co-ordinate their utilization. This is more practical than every individual or care centre trying to import these products separately. In India, the national haemophilia organization has done this over the last decade. Although this may not be desirable because it can lead to inappropriate use and inequitable distribution of therapeutic products, in many developing countries there may be no other options. Factor concentrates should be exempt from taxes and their import liberalized in these countries.

It appears then that in developing countries both options of replacement therapy - locally produced plasma products as in Thailand[41] and commercially available factor concentrates as in Malaysia[14], Brazil[15] and Argentina[16] - should be pursued to suit the needs of different sections of society since social security is not uniform.

It should be remembered that people with mild haemophilia A, and most of those with von Willebrand disease, should respond to desmopressin (DDAVP) and not require a blood product for treatment[45]. Desmopressin may be given by intravenous, subcutaneous or, at high concentration, the intranasal route and may be used in home therapy, and to cover surgery or dental extractions.

4.5 Improving social awareness of haemophilia

Society has to be made more aware of the problems of haemophilia and more sensitive to the needs of individuals and families affected by this disease. Key persons in the health administration need to be approached and informed. Specific measures aimed at improving diagnostic facilities and providing therapeutic products need to be discussed. The public can be made aware by presentations in educational institutions, work places and social organizations. The tremendous reach of the media and the information technology network should be utilized to disseminate information about haemophilia. This will help the identification of more cases and attract people supportive of the cause of haemophilia. Steps should also be taken to prevent discrimination against people with haemophilia in education and employment. Patrons should be identified for supporting individuals and care centres. Efforts to change social attitudes towards blood donation are also essential because there is a general reluctance among people in many developing countries to donate blood voluntarily.[46]

4.6 Prevention of haemophilia

While there may not be enough state budget available for the treatment of haemophilia, it should be possible to provide funds to initiate a prevention programme. Each country should have at least one centre that is capable of genotypic evaluation and mutation detection. All comprehensive care programmes should therefore incorporate a system for DNA analysis from as many affected individuals and their families as possible. This data will help formulate the strategy for carrier detection and antenatal diagnosis in each country.[47] Having lost the initiative in the treatment of haemophilia, developing countries would do well not to lag too far behind the rest of the world in initiating preventive programmes.

4.7 Developing a programme for comprehensive care

To achieve all that has been mentioned earlier, it is necessary to have a group of people including professional managers, patients and other interested people apart from medical personnel who can co-ordinate and organize a comprehensive care programme. They should also promote the cause of haemophilia in society - meeting government representatives to encourage them to support services for haemophilia, raising funds and finding patrons for various activities and identifying philanthropically minded people to help in any way possible. The recently published manual with detailed information for developing national programmes for haemophilia care[33] is very useful but some of the recommendations may need to be modified for some countries.

Four particular aspects of comprehensive care are especially important because they involve preventive medicine and are very cost effective. Firstly, the majority of people with haemophilia in developing countries are children. Effective paediatric haemophilia care reduces or even eliminates the natural progression to chronic haemophilic arthropathy. As a result patients remain independent and as capable of economically productive lives in their families and communities as those without haemophilia. Secondly, most haemophilia care can be carried out by suitably trained family members with nursing support. It rarely requires the more expensive and limited resource of medical supervision on a day-to-day basis. Nor does it require hospitalization; the majority of patients may be treated very satisfactorily at home. Third, the role of the physiotherapist is crucial to good haemophilia care. Constant attention to musculoskeletal health helps prevent bleeds and consequent synovitis, and the maintenance of optimal activity. Fourth is the value of continuing education of both health care professionals and families[48,49].

The comprehensive care of any chronic disorder like haemophilia is complex. It requires the integration of many disciplines, the management of acute episodes of ill health, and a long-term commitment to the well-being of patients and their families. These needs are best met by planning and funding programmes that place patients, clinicians and the community at the centre of priority setting. This, in turn, should encourage high quality evidence-based and integrated care, and establish a long-term view of health needs and of how they might be financed and delivered.

4.8 Research

Certain aspects of care of people with haemophilia have not been evaluated in carefully controlled studies. These include level and duration of factor replacement in various bleeding complications including post-surgical haemostasis and intra-cranial bleeds, management of chronic synovitis with frequent bleeds and doses of products to be used in patients with inhibitors.[50] Many of the recent recommendations[51] that constitute ideal management in the economically privileged countries are not feasible in the less economically sufficient situations. It is possible that lower levels of replacement and less expensive options can be used with almost similar effectiveness in some of these conditions.[52,53,54] It is therefore necessary to collect data from carefully co-ordinated work in developing countries to define what is optimal and most cost-effective. The potentially large numbers of patients available provides an opportunity to evaluate different management approaches. Standards other than those applicable to the developed countries will need to be defined to serve as guidelines for haemophilia care in the developing world keeping in view the local realities. It is possible, of course, that some of this work may provide useful data for optimizing recommendations even for the developed countries.

Table I

CLINICAL AND LABORATORY FACILITIES FOR HAEMOPHILIA CARE IN DEVELOPING COUNTRIES

1. LEVEL OF CLINICAL CARE	FACILITIES AVAILABLE
a. Haemophilia Primary Care Centre	*Clinical evaluation of patients with diagnosed bleeding disorders during working hours and maintaining records of all interventions and complications *Storage and administration of therapeutic products, as available *Participation in appropriate clinical audit
b. Haemophilia Treatment Centre	All facilities mentioned above and *24-hour basic clinical service *24-hour laboratory service for screening tests for bleeding disorders. Facilities for factor assays and screening for inhibitors, if possible *Physiotherapy *Counselling and advisory services *Advice on home therapy, where appropriate
c. Comprehensive Care Centre	All facilities mentioned above and *24-hour clinical service capable of handling emergencies and advising other centres *Laboratory facilities for assays of factor levels and inhibitors *Specialist service for surgeries, infectious diseases and social issues
d. Reference Centre for Haemostatic Disorders	All facilities mentioned above and *Reference laboratory for evaluation of atypical cases and other bleeding disorders *Genotypic evaluation, carrier detection and antenatal diagnosis *Training of members of the comprehensive care team *Co-ordination of quality control programmes and clinical audit *Research projects and formulation of national policies
II. LEVEL OF LABORATORY	**TESTS AVAILABLE**
a. Coagulation Laboratory	Blood film, platelet count, clot retraction, bleeding time (BT), prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), correction studies with 'control', 'adsorbed', 'aged' and factor VIII and factor IX deficient plasma from patients and inhibitor screening, qualitative factor XIII
b. Comprehensive Coagulation Laboratory	All tests mentioned above and factor assays (VIII, IX, I, II, V, VII, X, XI), inhibitor assays, platelet function tests, von Willebrand factor (vWF) activity
c. Reference Coagulation Laboratory	All tests mentioned above and vWF multimers, vWF antigen, factor IX antigen, genotypic analysis, carrier detection, prenatal diagnostic tests and evaluation of rarer coagulation disorders

5. THE INTERNATIONAL HAEMOPHILIA TRAINING CENTRE (IHTC) PROGRAMME

Background

The IHTC Programme was first defined and approved at the WFH Congress in Moscow in 1969. By 1973 the programme had became operational with the first group of training fellowships awarded and the organisation of a first regional workshop in Mexico. The programme has since then continued implementing educational activities to improve the standards of haemophilia care worldwide. Between 1973 and 1996, a total of over 150 fellowships had been awarded and more than 35 workshops had been organized.

Current situation

5.1 Programme objectives

The aim of the Programme is to disseminate medical knowledge and experience in the diagnosis and management of haemophilia and other coagulation disorders in order to improve the quality of haemophilia care and services in developing countries.

This overall objective is achieved through two main fields of activity:

(a) Training fellowships awarded to physicians and health care workers from developing countries
(b) Regional workshops providing theoretical lectures and practical demonstrations on the care of haemophilia.

5.2 Programme description

The IHTC fellowship programme is intended for basic clinical and laboratory training for physicians and paramedical staff at one of the designated IHTC centres of the WFH. Fellowships range between US$1,000 and US$5,000 according to the period of training which usually varies between six weeks and three months.

Candidates are chosen on their potential to help local health authorities in the implementation of haemophilia care programmes, after the completion of their training period. The training centre and the awarded sum are designated on the basis of distance of applicant to the IHTC, the candidate's preference, language, rotation, period of training and facilities made available for meals and accommodation by the various IHTC.

The workshops on haemophilia are given in countries where a considerable influx from adjacent countries is expected. Lecturers and teachers of workshops are selected from the staff members of designated IHTCs.

5.3 IHTC Committee responsibilities

The IHTC Committee is responsible for:

- the final selection of applicants for training fellowships
- choice of IHTCs where trainees are to be assigned
- recommendations on selection of new IHTC centres
- organization of regional workshops

IHTC Directors are designated from each IHTC and are responsible for its activities. They are expected to participate personally or to send a representative to the meetings of the IHTC Committee. They are required to take part as lecturers in the workshops; to accept trainees selected from the applicants for WFH fellowships and to provide them with training and accommodation; to acknowledge in their scientific articles and other published materials that they are an IHTC and finally to produce a yearly report of their activities.

The 30 presently designated IHTCs are shown in Table 2.

Table 2

Buenos Aires, Argentina
Sydney, Australia
Vienna, Austria
Leuven, Belgium
Rio de Janeiro, Brazil
Helsinki, Finland
Kremlin-Bicêtre Cedex, France
Hôpital Cochin, Paris, France
Hôpital Necker, Paris, France
Tel Hashomer, Israel
Milan, Italy
Tokyo, Japan
Groningen, Netherlands
Utrecht, Netherlands
Malmö, Sweden
Basel, Switzerland (Cantonal Hospital - Marbert)
Basel, Switzerland (Children's University Hospital - Imbach)
Bangkok, Thailand (Isarangkura)
Headington, Oxford, UK
London, UK
Sheffield, UK (Peake)
Sheffield, UK (Preston)
Chapel Hill, North Carolina, USA
Los Angeles, California, USA
New York, New York, USA (DiMichele)
New York, New York, USA (Gilbert)
New York, New York, USA (Seremetis)
Philadelphia, Philadelphia, USA
Rochester, New York, USA
Worcester, Massachusetts, USA

Although the IHTC fellowship and workshop programme has accomplished much with very limited resources over the years, there are a number of prevailing weaknesses which need to be addressed in order to increase the level of efficiency and impact of this important educational programme. They include difficulties in assessing applicants who are likely to continue to work with haemophilia in the long-term, and problems with audit over time. It is important to match the training of candidates with the resources likely to be available to them on their return home, and to plan realistic workshops with probable long-term benefits to individual countries.

In order to address these weaknesses, there is an ongoing review process. The application form for fellowships has been simplified and the local National Member Organization (NMO) has been asked to prioritize and review these applications before forwarding them to the WFH. A small working group reviews the short list of candidates prior to the annual meeting of the IHTC Committee.

In terms of regular follow-up, upon completion of training each fellow is required to complete a report. Similarly, a report on the fellow from the relevant IHTC centre is also required. Standard evaluation forms are provided for this. There is an ongoing review of the 30 IHTCs in order to establish which are active and which are inactive.

5.4 Haemophilia Training Centres within countries[55]

In many countries outside the western world, small programmes are coming into existence. For instance in India, programmes for haemophilia care exist in Vellore, Bombay, Delhi, Bangalore and Pune. However, only 5-10% of patients with haemophilia in the country are identified and of these, factor VIII and factor IX are frequently not even separated. Diagnostic laboratories are rare, inaccessible and expensive. Russia has had the diagnostic capabilities for haemophilia for decades and yet knowledge and implementation of haemophilia care is minimal. Little cryoprecipitate is available. Concentrates, although available are not accessible to large numbers of patients. China, with its enormous population, has only identified a small minority of haemophilia patients and although some fractionation takes place in Shanghai, quality control and safeguards for viral safety are not rigidly monitored. Little concentrate is available and funding for it is not readily available. Turkey has no comprehensive care programme; however, there are a number of well-informed treaters. In 1997 for the first time in Turkey, there was a major effort to develop a comprehensive care programme with identification of a database. Inadequate financing means that insufficient product is available and the majority of patients are poor and must get their health care from government hospitals who buy product on bid and the supply is inadequate. As it is a Muslim country, circumcision is carried out either on an older child or on a young adult and these procedures use a large proportion of available product[personal experience]. South Africa, although it has informed treaters and sophisticated laboratory technology, has only identified around 50% of the affected population. In Johannesburg, a commitment has now been made to enter Botswana to initiate case finding in the black population but all product used is made from local plasma with no ability to import product.

Thus, under the present scheme of training fellows in IHTCs, there is a risk that the expertise that such fellows acquire is not applicable in their local country. It would therefore be sensible to establish haemophilia training centres within countries. For instance, Vellore could operate in India, in order to train laboratory skills and management of haemophilia which is relevant to local resource and customs. Similarly, in Turkey, Ankara could act as a training centre within Turkey. The First National Haemophilia Congress took place in Ankara, Turkey, 5-7 May 1997 and a Turkish National Haemophilia Registry has been set up, which has identified a total 1438 patients from 20 institutions nationwide. However, it is significant that only 579 of this total number of patients remain in follow - up, which probably reflects the cost of medical care and therefore the inability of such individuals to access it. It is also significant in such a population that 25-30% of the population enter consanguineous marriages. As a result there is a higher proportion of the rarer bleeding disorders, such as factor V, VII and XIII than one would encounter in a western practice.

6. THE TWINNING PROGRAMME

The Twinning Programme was conceived by Professor Guglielmo Mariani [56] and was proposed as a means of implementing an action of the WFH strategic plan 'to recommend plans for initiating and maintaining programmes in those countries or locations not meeting basic standards'. The twinning programme now provides a cost effective way of transferring expertise and resources between both centres and WFH National Member Organizations (NMOs).

6.1 Aims

The aims of the Twinning Programme are:

(a) to develop more advanced and efficient care programmes using existing capabilities
(b) to create and develop a network between co-operating haemophilia centres and NMOs in the developed world and haemophilia centres and NMOs in the developing world. The programme was approved in October 1993. Spontaneously created or, in many cases, pre-existing partnerships were the first to be officially recognized. These were the product of historical, linguistic, cultural and political affinities. In the initial stages of the programme, centres recognized by the WFH IHTC Committee were involved and provided the first partnerships. Subsequently, other haemophilia care centres were invited to participate.

A number of minimum requirements for the developing world institution were considered necessary. There was to be a key person working in the field of haemophilia, a working blood transfusion service and the level of care for people with haemophilia must have been well below the minimum acceptable standard.

The programme's objectives focus on the creation of a continuous stream of scientific and organizational assistance to the haemophilia centres in the developing world by the developed world partner.

6.2 Activities

The following activities were initially suggested:

- improving access to scientific information on new developments in haemophilia care (books, articles, journals, abstracts, meeting proceedings), since attending at meetings and other scientific events is difficult and sometimes impossible for professionals in the developing world
- rapid consultation on special cases and issues
- provision of clinical and laboratory protocols and methods
- donation of reagents, standards, diagnostics, substrates, instruments
- donation of therapeutic materials for emergency cases.

In essence, anything that could improve the diagnosis and treatment of haemophilia and related clotting disorders is included.

Once a partnership is officially recognized, a small but significant financial allocation (Canadian $1000) for each year of activity is provided to fund communication between the centres, partial support for travelling expenses and short training periods. This entitles WFH to carry out periodic checks to ensure that the partnership is communicating and working well. This audit, which is carried out at least once a year, also enables the Federation to take note of the activities of the partnerships and publicize them as suggestions for other participants. Each year, on the basis

of the report submitted by the participants in the programme, a plaque is awarded to the most active partnership.

The number of recognized partnerships is only dictated by the finance available through the Federation. It is intended that partnerships be financed for no more than three years, both in the hope that ties between centres will then be sufficiently strong to allow the relationship to continue and to allow finance for the creation of new partnerships. The national member organizations of WFH, together with local haemophilia associations or chapters, have an important role in supporting the partnerships, and personal ties between those with haemophilia treated in twinned centres, are highly valued; they offer further opportunities to strengthen the partnership and to stimulate common activities in non-medical areas as well.

7. OPERATION IMPROVEMENT

7.1 Aim

Numerous countries in the developing world have not yet reached a state of economic development to sustain comprehensive care programmes for many chronic diseases including haemophilia. These countries do, however, provide various aspects of care for these diseases and would benefit from assistance programs that make incremental step improvements in basic infrastructure necessary for haemophilia care.[12] The specific goal of Operation Improvement is to assist these countries in making significant and long-term incremental improvements in one or more aspects of haemophilia care such as treatment skills of medical teams, development of a Registry and information systems, improvement in diagnostic and laboratory skills, organization of national comprehensive care system plans, and provision of educational programs for patients and their families. It is hoped this operation can produce an environment in which programmes such as Operation Access may be implemented.

7.2 WFH activities

In addition to obtaining and administrating the resources necessary for the programme and selecting countries for participation, WFH performs the following activities and functions of Operation Improvement:

(a) develops small training teams of four or five WFH volunteer haemophilia specialists who will spend 8-10 days in selected countries giving on-site training to haemophilia care workers, and providing technical assistance for the country to achieve its objectives for the project
(b) funds travel costs for volunteers, education material adaptation, translation, and photocopying
(c) provides WFH fellowships in one of the WFH International Haemophilia Training Centers to qualified candidates
(d) promotes a partnership between a treatment centre in the project country and a more established one in another country (the "twinning program") to provide ongoing consultation and assistance for the medical care of haemophilia patients
(e) promotes the "twinning program" between the local haemophilia society (a WFH national member organization) and a well established haemophilia association to interchange ideas and provide other assistance
(f) provides technical assistance in preparing proposals to bilateral institutions
(g) evaluates the progress of the programme.

7.3 Activities of participating country

The activities of the participating country in Operation Improvement are:

The participating country assesses its overall needs for haemophilia care, develops long-range goals suited to its culture and level of medical practice, and then considers and selects projects that can realistically be accomplished and which work toward achieving the long-range goals. The participating country conducts the project and thus is responsible for its local organization and administration. To be awarded the project, the participating country must:

(a) develop a project objective and write a proposal that meets the selection criteria of Operation Improvement
(b) agree to provide funding for local transportation, lodging, and meals of the participants
(c) provide project meeting sites
(d) assist in the evaluation of the program.

Operation Improvement is open to all countries with per capita gross national product less than US$10,000 with the exception those already participating in an Operation Access project (see below). There should be substantial support from the medical establishment and/or the haemophilia association in the project. A national leader must be chosen to direct the project locally and to maintain relations with WFH. Finally, the country should have a total population greater than two million inhabitants.

7.4 Choice of country

Three basic criteria are used to assess the quality of the application. Of primary importance is the public health impact, that is, the extent of improvement in care for haemophilia patients which results from the project and the long-term impact on haemophilia care within the country. Second is the quality of project's organization and content. This is judged by the qualification of the local person responsible for implementation of the project, the feasibility of developing the project, its ease of implementation, and its simplicity. Also important is the level of coordination between the individuals and institutions involved in haemophilia care. Third, but not least, is the level of involvement of key participants including the medical establishment, the haemophilia association, and the Ministry of Health.

8. OPERATION ACCESS

8.1 Aim

Countries with a sufficient level of economic development can actively develop health care programmes for chronic diseases. Generally, these countries have good medical care infrastructure, strong public health programmes and a strong haemophilia association working toward improvement of haemophilia care. Operation Access is designed to provide the catalyst for these countries to achieve a rapid transition to a national health care system for haemophilia patients.[7] The specific goal of this program is to assist these countries in developing a national infrastructure for haemophilia treatment which is self reliant and self supporting. To achieve this goal, WFH provides three years of technical assistance including educational programmes, on-site management assistance, and clotting factor necessary for treatment. The elements of this programme are designed according to the needs and financial capacity of the Ministry of Health of each participating country.

8.2 WFH activities

Activities of WFH in Operation Access are similar to those in Operation Improvement. WFH negotiates with the government of the selected country regarding the responsibilities each will have in developing and implementing the program. Although these responsibilities vary and are specific to each participating country, WFH activities include:

(a) obtaining and administrating the resources necessary for programme elements external to the country
(b) evaluating and selecting the candidates for the programme
(c) providing technical assistance to the participating country for planning, project goals and objectives, establishing time lines, organizing and implementing strategies, developing education, training and evaluation plans
(d) providing donated clotting factor for the national care plan for a period of 3 years
(e) providing two training fellowships per year, organizing training programmes, and providing international experts and teams to fulfil the programme needs
(f) supporting a "twinning" process between the health-care providers in the participating country and a developed training centre in another country and between the haemophilia association of the selected country and that of a well developed haemophilia association
(g) providing technical assistance in evaluation of program outcomes
(h) monitoring the distribution of clotting factor to assure its proper utilization and distribution.

8.3 Activities of participating country

In Operation Access, the participating country has more organizational, administrative, and co-ordinating responsibilities than those required for Operation Improvement. Extensive planning is necessary to achieve an effective interaction of the various elements necessary for a network of haemophilia care facilities in the country. At a minimum, the participating country:

(a) plans national goals and organizes, implements, and evaluates a national programme of comprehensive care for haemophilia patients
(b) provides funding for transportation, storage, and distribution of clotting factor concentrates to haemophilia patients in conjunction with the national care programme
(c) develops funding resources for long-term haemophilia care following the 3-year project duration
(d) provides funding for training and education of health-care providers and patients needing haemophilia care
(e) implements a data collection system to evaluate clinical outcomes and the impact of the project on the health care of the patients
(f) conducts a comprehensive evaluation of the programme.

8.4 Choice of country

Selection of qualified countries for Operation Access is one of the most important tasks in achieving project success. Experience to date indicates that several criteria are important for programme success and are used to identify countries which will be successful in achieving the programme goals:

(a) the participating country should be able to make a long-term commitment to the health-care needs of the haemophilia population including provision of a continuing supply of blood products for treatment

(b) the national health agency must make a commitment to designing a national comprehensive care program for haemophilia, including available funding
(c) the gross national product must be increasing rapidly to ensure that the country will be able to either contract fractionate or purchase concentrate at the end of the three years of technical support
(d) the national haemophilia association should display a strong interest in the programme and a commitment to working with the medical community and government to achieve the project outcome. The medical provider community should also display a strong interest in the programme
(e) less than 10% of the clotting factor used to treat haemophilia patients in the country should come from commercial sources. This requirement is in order to meet the conditions of donations of clotting concentrate from manufacturers.

9. GENETIC TESTING

Carrier detection and prenatal diagnosis were the subjects of the second Joint WHO/WFH Meeting on the Control of Haemophilia in 1992[3]. Much of this document is still highly relevant to the provision of genetic services for haemophilia world-wide and should be studied with the following update, and with the full paper by Antonarakis in the Supplement to Haemophilia.

9.1 Polymorphism based gene tracking

Further information has been obtained in relation to the use of polymorphisms within both the FVIII and IX gene, but the basic information regarding their use and usefulness is unchanged from that given in the 1992 report. With regard to the FVIII gene polymorphisms it is now clear that the intron 13 and 22 repeats are in linkage disequilibrium as are all the other diallelic intragenic FVIII polymorphisms. In reality, when looked at together the two repeat polymorphisms will be informative in about 70% of haemophilia A families world-wide even though the distribution of alleles varies between ethnic groups. Advances in technology now mean that these repeats can be analyzed on ethidium bromide or silver stained gels (so removing the need for radioactivity), or by automated techniques utilizing automatic DNA sequencers. Interestingly, the XbaI RFLP within intron 22 of the FVIII gene, which can only be detected by Southern blotting, can be detected by the same probe that detects the intron 22 inversion mutations (see overleaf).

9.2 Mutations within the factor VIII and IX genes

Increasing use of rapid mutation detection methods is leading to the identification of a large number of causative mutations within the FVIII and FIX genes of individuals with haemophilia. These mutations are now recorded on databases accessible through the Internet (FVIII data base:- http://europium.mrc.rpms.ac.uk. FIX database:- http://www.umds.ac.uk/molgen/). In the UK, Sweden and New Zealand projects have been started to identify and catalogue mutations in all families with haemophilia B and similar proposals are in hand for haemophilia A. There are no apparent "hot-spots" for mutations within either gene apart from an increased incidence for cytosine to thymine (C to T) mutations at CpG dinucleotides as seen throughout the genome.

However, 40-50% of cases of severe haemophilia A are caused by unique inversion mutations of the tip of the X-chromosome resulting from intra chromosomal recombination between homologous regions of DNA found within intron 22 of the FVIII gene (1 copy) and a region close to the telomere of the X-chromosome (2 copies). These recombinations between the intron 22 copy and either the distal or proximal telomeric copies result in complete inactivation of the FVIII gene and severe disease. These events appear to occur with similar frequencies within different

haemophilic populations around the world and can be readily detected by a Southern blot procedure utilizing a probe specific to the homologous regions. Analysis of families with sporadic haemophilia A caused by the intron 22 inversion has shown that 96% of mothers are carriers, and that in the majority of cases the mutation has arisen in the grandfather's germline. Methods using non-radioactive probes are being developed to detect this mutation but PCR based methods are difficult to establish since the regions involved are highly homologous.

9.3 Strategies for genetic tests in haemophilia

For genetic studies in families with haemophilia A, if the condition is severe then the presence of the intron 22 gene inversion should be investigated. As indicated above, this will be found in 40-50% of severe haemophilia A patients world-wide. If the inversion is not present then gene tracking utilizing the intron 13 (CA)n and intron 22 (GT)n (AG)n repeat polymorphisms should be performed. If neither of these multiallelic polymorphisms are informative then the most common diallelic polymorphisms in the local population should be tried. In general, only when none of the above are helpful should mutation detection be considered because, as a result of the size and complexity of the FVIII gene, this is a costly and technically demanding procedure. However, with the recognition that small amounts of FVIII mRNA can be obtained from leucocytes, reverse transcription and subsequent PCR of the cDNA (RT-PCR) followed by DNA mismatch analysis and sequencing has significantly increased the mutation detection rate.

Attention should be paid to possible misdiagnosis of type 2N von Willebrand disease (VWD) as mild haemophilia A. The phenotype of a homozygote (or compound heterozygote) with this condition, which is caused by mutations in the FVIII binding domain of von Willebrand factor (VWF), is very similar to mild haemophilia A. Levels of plasma FVIII are reduced, but VWF is quantitatively and qualitatively normal, unless its binding to FVIII is assessed in a specific FVIII binding assay. Thus a male with type 2N VWD with no family history will appear as a sporadic case of mild haemophilia A, unless further tests are performed. Clearly the inheritance of type 2N VWD (autosomal recessive) is entirely different from that of haemophilia A, and it is recommended that all sporadic cases of mild haemophilia are tested by the VWF/FVIII binding assay.

In families with haemophilia B the range of intragenic polymorphisms previously described will allow for accurate carrier detection and prenatal diagnosis in up to 90% of families of Caucasian origin where there is a family history of the disease. This figure is lower for other ethnic groups but could be enhanced by the method described in a recent report in abstract form from Japan indicating high informativeness when two newly described 5' flanking region RFLPs are used in conjunction with the 3'HpaI RFLP.

All the FIX polymorphism methods are PCR based and therefore well standardized. In families where these polymorphisms are non-informative, or where there is no family history of the disease and haemophilia cannot be excluded by polymorphism analysis, then mutation detection is necessary to provide accurate information. Indeed, mutation detection has replaced polymorphism based gene tracking completely in some centres where the methods are well established. Mutation detection is clearly the method of choice because where it is being used mutations are identified in practically all patients with haemophilia B. The disadvantages of the methods are solely related to cost and availability of equipment.

Finally, it should be remembered that it is essential to store down DNA from people with haemophilia in order to facilitate future genetic diagnoses in families[33].

10. CONCLUSIONS AND RECOMMENDATIONS

Haemophilia is an inherited disorder of blood clotting characterized by severe, recurrent spontaneous bleeding, and chronic, painful joint deformities. Without treatment most people with haemophilia die in childhood or early adult life.

With correct treatment haemophilic bleeds are controlled, and arthritis and premature death prevented. People with haemophilia with access to adequate treatment may lead normal lives as productive members of society.

In reaching their conclusions the experts recognized that any planning of haemophilia programme development must take into account the fact that each country is unique in its needs and culture. The elements of a proposed haemophilia programme should therefore always be graded to meet the capacity, special needs and health care goals of the developing country, using the accepted WHO/WFH Guidelines for the Development of a National Programme for Haemophilia, published in 1996[31] (this publication is available from either WHO or WFH).

Certain approaches are important to all successful self-improvement programmes for haemophilia care. Essential issues to be addressed are:

- identification of needs
- establishment of goals with objectives
- prioritization
- organizational structure
- co-ordination of planning
- financing
- follow-up and evaluation of results

Any national government invited to support a haemophilia programme must be satisfied that measures proposed are rational, cost effective and designed for the long term care of people with haemophilia and their families. To this end five main areas of haemophilia care were *recommended*:

- overall national strategy
- implementation of programmes
- transfusion services
- quality assurance
- prevention of haemophilia

10.1 Overall national strategy

It is *recommended* that the provision of care of haemophilia in a developing country be approached as an issue of public health. This is because of the nature of comprehensive care for people with haemophilia and their families, which involves close teamwork within medical, paramedical and social disciplines.

For this reason it is further *recommended* that responsibility should be assigned by the Ministry of Health to a co-ordinating agency with the remit of ensuring the integration of haemophilia care into the national health system. Such a body should be able to delegate authority to link relevant services and organizations.

It was considered that, in order to allow for the proper planning and development of health services, the establishment of a National Registry of people with haemophilia is essential. It is therefore a *recommendation* that priority be given to the identification and diagnosis of affected people and their families and to the central registration of individuals with haemophilia and related disorders. In order to be successful, such a scheme must guarantee confidentiality and respect for human rights.

10.2 Designing programmes to implement strategy

It is *recommended* that:

A step-by-step, outcome-based plan of action be developed in order to establish the care of people with haemophilia and other bleeding disorders throughout the country using existing WHO/WFH Guidelines, recommendations and educational material.

Resources should be put into programmes for the control and prevention of haemophilia, which are result-oriented, economically effective, and which plan sustainable and defined outcomes.

Programmes should be designed to be flexible. They should evolve from planning within a country, and be appropriate to that country's culture, economic position, expectations and needs.

Whenever possible haemophilia programmes should be linked with other social or cultural health care programmes which support the development of the individual.

Programmes should include recommendations for the development of National treatment protocols appropriate for the proper management of bleeding disorders including haemophilia.

Several programmes have already been developed in order to assist countries design their own integrated support programmes and health care infrastructure. They contain culturally sensitive educational material, and detail the resources needed to sustain self-reliant programmes for people with haemophilia. Examples of such WFH programmes include "Operation Improvement", "Operation Access", the International Haemophilia Training Centre Network (IHTC) and the Twinning Programme; (information on these programmes is available upon request to WFH).

10.3 Transfusion services

It is *recommended* that, within any national health system, haemophilia services be an integral part of haematology and transfusion medicine.

The World Health Assembly Resolution No. 28.72, 1975 recommended that Member States

- promote the development of national blood services
- enact effective legislation governing the operation of blood services and take other action necessary to protect and promote the health of blood donors and of recipients of blood and blood products
- take steps to develop good manufacturing practices specifically for blood and blood components in order to protect the health of both donors and recipients.

In keeping with this Resolution it is *recommended* that, as an essential component of its Health of the Nation plan, each Ministry of Health establish a Blood Transfusion Committee and Regulatory Authority.

The remit of this committee is to enact effective legislation governing the operation of blood services and to take other action necessary to protect and promote the health of blood donors and of recipients of blood and blood products.

In keeping with this remit, it is *recommended* that the functions of the Committee include the procurement and equitable distribution of blood and blood products for the treatment of people with transfusion dependent disorders including haemophilia. It is particularly important that the Committee allocate sufficient funds to ensure that people with haemophilia receive, as a minimal level of care, adequate treatment for their bleeding episodes, and to cover essential surgery.

The role of desmopressin (DDAVP) in the treatment of patients with mild haemophilia A, or most of those with von Willebrand disease, should be emphasized. The use of desmopressin in these cases prevents patient exposure to blood products and saves valuable resource for others.

It is *recommended* that an integral part of the work of such a committee be the development and audit of policies designed to provide the maximum possible level of safety for blood and blood products.

10.4 Quality assurance

The accurate diagnosis of haemophilia and related inherited bleeding disorders is the essential prerequisite to appropriate, cost effective treatment.

As a minimum requirement it is *recommended* that laboratories be capable of differentiating between severe and moderately severe haemophilia A and B.

It is further *recommended* that, in order to enable the correct assessment of other patients presenting with abnormal bleeding, including some carriers and females with menorrhagia, the World Federation of Hemophilia Laboratory Science Committee publish redefined laboratory guidelines for developing countries. Criteria for one of the basic clotting tests, the Activated Partial Thromboplastin Time (APTT), should be included within these guidelines. Whilst recognizing that APTT reagents vary considerably, they should be sufficiently sensitive to allow detection of mild abnormalities of factors VIII and IX.

At present both WHO and WFH administer External Quality Assurance (EQA) schemes for participating laboratories. It is *recommended* that a possible merger of these schemes be explored and expanded to include genetic tests.

Whilst participating laboratories should be funded from local health service sources, much additional help and support is available from both the present schemes. It is *recommended* that this be expanded through advice, encouragement and training options, to allow participants to improve specific tasks or overall laboratory performance.

It is further *recommended* that participation and support to assist developing countries set up and monitor laboratory performance involve all relevant WFH programmes including IHTC Fellowships, Workshops and Operations Access and Improvement. In particular, WFH IHTC laboratories assign the target values for EQA and are thus expected to participate fully in the scheme.

10.5 Prevention of haemophilia

Tools are available which allow families a choice in any decisions they make with regard to the health of future children. Using appropriate technology females who carry the haemophilia gene may be identified and, if they so wish, they and their partners can take preconceptual and prenatal decisions.

For these reasons it is *recommended* that, as a minimum requirement, the factor VIII gene inversion that is present in 45% of patients with severe haemophilia A should be diagnosed. For reasons of safety the laboratory method used, Southern blot analysis, should preferably be non-radioactive, and the development of a Polymerase Chain Reaction (PCR) based detection of the inversion is encouraged.

For those people or families without the factor VIII inversion, indirect detection of the mutant gene by DNA polymorphic markers is *recommended*. Choice of appropriate markers will depend on the frequency of polymorphic alleles in a given population. Non radioactive detection of polymorphic alleles is encouraged.

The detection of the majority of point mutations will await the development and the availability of low cost, high yield diagnostic tests. Until then storage of DNA from individuals is *recommended*. DNA should only be stored with informed consent, taking into account confidentiality, non-discriminatory guidelines and protection of genetic individuality.

The transfer of genetic information and related counselling should be part of the diagnostic programme. It is *recommended* that individuals with knowledge of both the haematological and the genetic aspects of haemophilia should be involved in this counselling. It is also *recommended* that the opportunity to repeatedly counsel about the risks to individuals and families be available, and that haemophilia education of physicians involved in preconception and fetal diagnosis be encouraged.

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