ROUND TABLE: STUDY AND DEVELOPMENT OF DRUGS FOR RARE HAEMORRHAGIC DISEASES

NETWORKS FOR HEMOPHILIA CARE IN ITALY

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The UK[1,2] and American[3] guidelines state that hemophilia care should be centralised in designated hemophilia treatment centres (HTCs) and provide detailed requirements for these HTCs.

The main requirements are:

- Providing care for at least 40 patients with severe hemophilia A or B (FVIII/IX <2%).
- Availability of multidisciplinary comprehensive care teams.
- Availability of specialised services, e.g. prenatal diagnosis, orthopaedic surgery and genetic counselling.
- Organization and availability of home-treatment for patients.
- Participating in a National Registry.
- Doing research to improve care.

These main goals were recently confirmed by a publication from the USA[4] and a review from the United Kingdom.[5]

Several studies describe the large effects of improved hemophilia care on life expectancy. Starting with the availability of clotting factor concentrates and the increase in their consumption, life expectancy for patients with severe hemophilia increased from 19 years in the 1930s to 71 years in 2001.[6,7] This trend is also observed in developing countries: the ratio of the adults/ children younger then 13 years increases from 0.35 in countries with a GNP of less than $ 2000 per capita to 3.7 in countries with a GNP over $ 10,000 per capita.[8] The implementation of home treatment provides better access to treatment, but also reduces direct medical costs.[9]

Care in specialized centers improves outcome, both in developing[8] and Western countries. Soucie et al reported a reduced mortality rate in US patients treated in hemophilia treatment centres.[10] In addition, several studies have reported improved short-term outcome as a result of specialized care and have been summarised by Baker *et al*.[4] Main parameters used were hospital visits, hospital admissions and unemployment rates. Unfortunately, no studies have reported long-term effects of specialized hemophilia care on more important parameters such as joint status and disability.

In Italy the network of hemophilia centers provides a focus for the provision of safe concentrates, effective allocation of resources, collection of data on concentrate usage, recording of adverse reactions, sharing of developments in care and coordination of research. In geographically small areas with dense populations a centrally located model of health care delivery with links radiating out to smaller peripheral centres (*hub and spoke*) may be appropriate (see the example of the Emilia Romagna region). Different solutions may be preferable where distances are large, or where the population is scattered or concentrated in very few areas.

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VON WILLEBRAND DISEASE, ITS BLEEDING TENDENCY, AND ANEMIA

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Von Willebrand disease

Von Willebrand disease (VWD) is an autosomally inherited bleeding disorder with a high prevalence in general population.[1,2] The diagnosis is based on the presence of bleeding symptoms, a low von Willebrand factor (VWF) level and a family history of low VWF with bleeding symptoms (except in subtypes with recessive inheritance).[3]

There are three main types of VWD. Type 1 is caused by a quantitative deficiency of the VWF, often without a definite proof for mutations in the VWF gene, type 2 by missense mutations producing dysfunctional VWF in plasma and type 3 by a virtual absence of VWF, usually associated with inheritance of two null alleles (4). Type 2 is further divided into types 2A, B, M and N depending on the nature of the functional defect[4] (Table 1).

Despite the fact that the history of the disorder dates back to 1926,[4] there are still open questions about diagnostic criteria, laboratory methodology and clinical history. It is general experience that patients with type 3 show the most severe bleeding tendency, while for the other subtypes the possible correlation of a given phenotype/genotype with severity of bleeding has still so far poorly investigated. Until recently, no quantitative description of bleeding symptoms in VWD has been available. This represents a diagnostic problem, since normal subjects may self-refer hemorrhagic symptoms quite frequently (Table 2)[5,6] and thus discriminating between a significant bleeding history and trivial symptoms could help in designing a *risk profile* for VWD. The number and the perceived severity of symptoms, as reported by the patient, may be influenced by his/her education, family background (e.g., some symptoms may be underreported by subjects belonging to a bleeding family) and personality, but also by the type of data ascertainment. For instance, using a self-reported questionnaire, Friberg et al found that as much as 23% of Swedish girls reported three or more hemorrhagic symptoms.[7] To overcome these problems, recently a physician–administered bleeding questionnaire has been developed to produce a severity score for each symptom.[8] By this approach, less than 1% of normal controls reported three or more hemorrhagic symptoms compared to 50% of obligatory carriers of type 1 VWD.[8] Furthermore, it appeared that the presence of 3 bleeding symptoms or a bleeding score of 3 in males and 5 in females was very specific for the bleeding history of type 1 VWD.[8] Within the MCMDM-1VWD Project, it has been also demonstrated that bleeding history, as assessed by a modification of the original developed physician-administered questionnaire, was more severe in index cases than in affected relatives[9] and its severity is probably greater in affected relatives with some multimeric abnormalities (but not typical for type 2 VWD) compared with those having normal VWF multimers in plasma.[10]

The bleeding tendency of von Willebrand disease

To date, only few extensive descriptive reports of symptoms in VWD have been provided and only in one has differentiation according to the subtype been taken into account. Table 3 shows the relative frequency of bleeding symptoms in three large series of patients with VWD diagnosed at specialized centers. Notably, in the Scandinavian experience, post-partum bleeding percentage overlaps with that observed in normal females. Interestingly, the distribution of different types of bleeding (apart from joint bleeding) is roughly similar among the different subtypes. However, it should be borne in mind that the severity of bleeding manifestations (for example menorrhagia or gastrointestinal bleeding, often requiring substitutive treatment) is more prominent in type 3 VWD,. Furthermore, these studies do not provide data about the frequency of the single symptom in a given patient.

Clinical expression of VWD is usually mild in type 1 with slightly reduced VWF levels, with increasing severity in type 2 and type 3. However, in some families variable severity of bleeding manifestations is evident, underlying the different molecular basis responsible for the diverse phenotypes of disorder and its variable penetrance. In general, the severity of bleeding correlates with the

Table 1. Classification of von Willebrand disease.

Quantitative deficiency of VWF	
Type 1	Partial quantitative deficiency of VWF
Type 3	Virtually complete deficiency of VWF
Qualitative deficiency of VWF	
Type 2	Qualitative deficiency of VWF
A) Type 2 A	Qualitative variants with decreased platelet-dependent function associated with the absence of high-molecular-weight VWF multimers
B) Type 2 B	Qualitative variants with increased affinity for platelet GPIb
C) Type 2 M	Qualitative variants with decreased platelet-dependent function not caused by the absence of high-molecular-weight VWF multimers
D) Type 2 N	Qualitative variants with markedly decreased affinity for factor VIII

degree of the reduction of FVIII:C, but not with the magnitude of BT prolongation or with ABO blood type of the patient. Mucocutaneous bleeding (epistaxis, menorrhagia) is a typical, prominent manifestation of the disease and may affect the quality of life. VWD may be highly prevalent in patients with isolated menorrhagia. Females with VWD may require treatment with antifibrinolytics, iron supplementation or estroprogestinic pill to control heavy menses. Home-treatment with nasal spray or subcutaneous desmopressin frequently occurs in these women. Bleeding after dental extraction is the most frequent post-operative bleeding manifestation. Since FVIII:C is usually only mildly reduced, manifestations of a severe coagulation defect (hemarthrosis, deep muscle hematoma) are rarely observed in type 1 and 2 VWD and are mainly post-traumatic, whereas in type 3 the severity of bleeding may sometimes be similar to that of hemophilia. Hemarthrosis is rare in type 1 and 2 while in type 3 it is rather frequent and some patients requires prophylactic treatment with FVIII/VWF concentrates to avoid long-term arthropathy. Bleeding after delivery in type 1 is rarely observed since FVIII/VWF levels tend to correction by the end of pregnancy in mild type 1 cases. A few cases, however, do not show significant increase of FVIII/VWF levels and need prophylaxis with DDAVP or Factor VIII/VWF concentrates before delivery (14,15). Type 2A and B and type 3 females usually need replacement therapy post-partum to prevent immediate or late bleeding. Post-operative bleeding may not occur even in more severely affected type 1 patients, whereas in type 3 prophylactic treatment is always required. Gastrointestinal bleeding is uncommon in VWD and these episodes are mostly due to the commonly reported causes observed in patient without bleeding disorders (peptic ulcer, hemorrhoids, varices etc.)

Table 2. Frequency of hemorrhagic symptoms, as reported by Wahlberg *et al.*[5] and Mauser- Bunschoten *et al.*[6]

Investigated Symptom	*Frequency*
Profuse menstruation	44%
Nosebleeds	5%-36%
Bleeding at delivery	19.5%-23%
Bleeding after tonsillectomy	2%-11%
Bleeding after surgery	6%
Bleeding from small wounds	2%
Various symptoms (1 or more)	40-50% in men 50-60% in women

A few patients however may have angiodysplastic lesions, often unrecognized, which can cause catastrophic bleeding episodes. A recent international survey in 4,503 VWD patients demonstrated that these episodes occur more frequently in type 2 (especially type 2 B) and type 3 and particularly in acquired VWD (AVWD) (16). In almost all these cases, the larger multimers of plasma VWF are absent. A relationship with older age appeared also evident. A variety of treatments have been tried in these cases (oestrogen and progesterone, octreotide, thalidomide, Immunoglobulins in AVWD, surgical resection etc), but due to the rarity and peculiarity of these episodes no definitive therapeutic guidelines can be provided for this clinical entity (17).

Table 3. Incidence (%) of bleeding symptoms in patients with VWD and in normal subjects (adapted from ref. 11-13).

Symptoms	*Iranian VWD*	*Italian VWD (n = 784)*			*Scandinavia*	
	Type 3 (n = 348)	*Type 1 (n = 168)*	*Type 2 (n = 550)*	*Type 3 (n = 66)*	*VWD (n= 264)*	*Normals (n = 500)*
Epistaxis	77	61	63	66	62	5
Menorrhagia	69	32	32	56	60	25
Post-extraction bleeding	70	31	39	53	51	5
Hematomas	N.R.	13	14	33	49	12
Bleeding from minor wounds	N.R.	31	35	56	36	0.2
Gum bleeding	N.R.	31	35	56	35	7
Post-surgical bleeding	41	20	23	41	28	1
Post-partum bleeding	15	17	18	26	23	19
Gastrointestinal bleeding	20	5	8	20	14	1
Joint bleeding	37	3	4	45	8	0
Hematuria	1	2	5	12	7	1
Cerebral bleeding	N.R.	1	2	9	N.R.	0

Treatment of anemia in von Willebrand disease

In addition to the specific treatment to control bleeding (desmopressin, antifibrinolytics, FVIII/VWF concentrates), some patients may require transfusional support in presence of acute and severe bleeding manifestations (gastrointestinal bleeding, menorrhagia at menarche, bleeding post-partum), especially in older age. Furthermore, recurrent bleeding (menorrhagia, epistaxis in young patients) usually requires iron treatment. Treatment modality is similar to what is usually adopted for iron deficiency in patients without bleeding tendency. The goal of therapy is to supply iron to repair the hemoglobin deficit and replenish iron stores. Oral iron is the treatment of choice. Parenteral iron is restricted to those patients unable to absorb or tolerate oral iron or due to increased needs (e.g. recurrent bleeding) which can not be met by oral treatment, since the risk of adverse reactions. Ferrous iron salt is the preferred formulation and should be taken apart from meals to assure adequate absorption. A total 150 -200 mg daily of elemental iron is the dose for adults and 3 mg/kg in children. If treatment is adequate, mild reticulocytosis begins within 3-5 days, is maximal after 8-10 days, then declines. An increase of hemoglobin concentration ≥2 g/dL after 3 weeks of treatment is considered as adequate therapeutic response (18). After anemia is corrected, oral iron should be continued to replace storage iron, for at least 3 months or until plasma ferritin is 50 μg/L. Obviously, if bleeding recurs frequently (e.g., untreated menorrhagia), treatment should last longer, mainly on empirical basis.

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RESEARCH AND DEVELOPMENT ON DRUGS FOR RARE DISEASES

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Rare diseases are defined in Europe as being severe and disabling and having a prevalence of fewer than 5 cases per 10,000 inhabitants. There are more than 5000 such rare diseases, affecting any organ or function, and amounting to more than 10% of total diseases. Patients with rare diseases not only sum up against difficulties in obtaining a diagnosis but also have little hope of finding the right treatment. The cost of developing a new drug dampens the pharmaceutical companies' enthusiasm because of the scant demand and poor return.

With considerable delay compared to other countries, the European Union activated a system of incentives to promote the development of orphan drugs in the year 2000. The system, based in the European Medicines Agency (EMEA) in London, works through a committee (COMP) that grants the designation of orphan drug in response to organizations that submit an application. When the drug is approved by another EMEA committee (CHMP) it has the privilege of ten years' exclusivity, regardless of the patent situation.

Now the system has been in place for seven years it is worth analyzing the results. Thirty products have been approved, with different types of documentation. In general, however, clinical trials have had small numbers of patients, even considering they refer to rare diseases, poor methodology, short treatment, and use of surrogate endpoints. It is worth noting the lack of orphan drugs for neurological diseases, which account for a large proportion of rare diseases. The present status of the development of orphan drugs will be examined in detail during the round table presentation.

One of the problems afflicting interest in orphan drugs is the lack of funding. Although the European law on these drugs establishes the need to support research and to allow fiscal incentives very little has been done, except some limited backing through the various EU Frame Work Programs. The Italian Agency for Drugs (AIFA)'s initiative to support independent research is therefore worthy of note.

A recent Italian law requires all pharmaceutical companies operating in Italy to pay a fee each year of 5% of their promotional expenses, except salaries. This money must be utilized to support independent clinical research in three areas: efficacy of orphan drugs, head-to-head comparison of drugs with the same indications, studies of outcome and pharmacovigilance. Studies are aimed at collecting data not usually provided by pharmaceutical companies, but which may be important for decisions related to the admission or maintenance of drugs for NHS reimbursement.

To implement this law a ten-member committee has been set up, half nominated by AIFA and half by the Regions. This committee, after consultations with the technical committee of the AIFA and other scientific institutions, launched a call for proposals in July 2005 indicating topics of interest. The selection was made in two steps. First, the committee checked that the projects presented were consistent with the aim of the law. Out of 404 letters of intent, 98 were selected to present a full proposal. These proposals were made available to three international study groups that made a written evaluation, then met in Rome for three days and drew up a list of priorities, using a scoring system. In March 2006, 54 projects were approved for a total cost of about 35 million Euro. For Italy this offered an unprecedented independent evaluation for public financing of research. In July 2006 all the contracts were signed and work could start.

At the same time AIFA approved a second call for proposals, which was launched after consultation with interested parties. Other topics were covered, in the same three areas. This second call attracted encouraging participation from Italian clinicians. Out of 454 letters of intent 104 projects were selected and are currently being evaluated by the study groups; the results will be available at the end of March. The third call is in preparation.

The projects approved and topics considered by the calls for proposals are listed on the web-site (*www.agenziafarmaco.it*).

Out of the first 54 projects approved, 20 were related to orphan drugs. Examples of projects concern studies of efficacy of treatments of phenylchetonuria, amyotrophic lateral sclerosis, juvenile dermatomyositis, Kaposi sarcoma, thalassemia, scleroderma and others.

The Mario Negri Institute has been instrumental in arousing awareness of rare diseases and orphan drugs. In 1992 the"Aldo e Cele Daccò" Clinical Center for Research on Rare Diseases in Ranica, near Bergamo, started work, to serve as a model for the field. The main aim is to provide information, an orphan area itself, on rare diseases.

Up to now over 10,000 cases have been collected and catalogued concerning more than 800 rare diseases. This data-base is available to clinicians interested in organizing clinical studies. A staff of physicians is available to answer questions, and this has attracted considerable interest from patients and physicians.

The second aim is to coordinate the network of clinical centers involved in research on rare diseases in the Lombardy Region. The Daccò Center also maintains a listing of Italian associations dealing with patients with rare diseases. A special program has been set up for contacts with families with patients with very rare diseases for which there is not specific patient association. Finally, the third aim is to conduct clinical research and trials relating to renal, hematological and vascular rare diseases.

It should be mentioned that in all the Mario Negri Institute sites there is considerable interest in developing *in vitro* and *in vivo* models of rare diseases, with the aim of clarifying their pathophysiology and developing remedies. Rare diseases and orphan drugs is a growing field that will, it is to be hoped, dose up the gap between patients' needs and biomedical research.

RARE DISEASES AND ORPHAN DRUGS IN EUROPE

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Rare diseases are diseases affecting a limited number of people. On a European level, a disease is defined as rare when it occurs in not more than 5 patients in 10,000 inhabitants. While this number seems small, it translates to approximately 230,000 considering 25 out of the 27 Member States of the EU.

It is estimated that between 5,000 and 8,000 distinct rare diseases exist, affecting between 24 and 36 million people in the European Community. Eighty percent of rare diseases have genetic origins, others are the result of infections and allergies or are due to degenerative and proliferative causes.

Rare diseases are almost always:

- serious chronic, degenerative and usually life-threatening diseases;
- disabling diseases, where quality of life is compromised;
- diseases for which no effective cure exists, but where symptoms can be treated.

Rare diseases are characterised by a broad diversity of disorders and symptoms that vary from disease to disease and from patient to patient suffering from the same disease.

Despite the progress made over the last ten years, many challenges still exist:

- delay in and failure of diagnosis,
- absence of information about their disease,
- lack of referral to qualified professionals,
- lack of availability of quality care and social benefits,
- poor co-ordination of in- and out-patient care,
- difficulty reintegration into working, social and family environments.

For the vast majority of rare diseases no protocol exists for good clinical practice and the segmentation of medical specialities is an obstacle to the comprehensive care of a patient.

Families and health care workers frequently complain also of the difficulty of the administrative procedures required to receive social benefits.

Major and arbitrary disparities exist between countries and even regionally within a country in the allocation of financial aid, income support and reimbursement of medical costs. Treatment costs incurred are often higher than they are for other diseases because of the rarity of the disease and the limited number of specialised centres. A significant proportion of these expenses is born by the families.

The focus on rare diseases is a recent phenomenon due to the new and global approach to rare diseases. Addressing and developing public health policy for each rare disease is impossible, grouping many morbid conditions, which differ among themselves both clinically and aetio-pathogenetically, into a unique category called “rare diseases”, give great advantages.

Considering the healthcare-related difficulties which these disorders have in common, it is likely that a lower cost-benefit ratio would results from a strategic approach in public health which deals with rare diseases as a group rather than as individual pathologies.

Application of these kinds of strategies began in the USA, which in 1983 adopted the Orphan Drugs Act (ODA) to promote the development and marketing of these products. During the same year, and again in the USA, the activity of NORD National Organization for Rare Diseases began. This organization brings together all the volunteer associations involved in the support of those affected with a rare disease.

In April 1999, the European Parliament and Council set forth Decision No. 1295/1999/EC adopting a programme of Community action on rare diseases within the framework for action in the field of public health (1999 to 2003).

Again, at the European level, in 2000 Regulation No. 141/2000 of the European Parliament and of the Council was published. This regulation concerns orphan medicinal products and lays down the provisions for Community procedure for the designation of a medicinal product as an orphan medicinal product (OMP). In compliance with this regulation the Committee for Orphan Medicinal Products (COMP) was set up within the context of the European Medicines Agency (EMEA).

An orphan medicinal product, or “orphan drug”, is a product that is potentially useful in treating a rare disease but does not have a market sufficient to cover the costs of its development. It is called an orphan medicinal product, because the pharmaceutical industries are not interested in investing in a product which serves only a few patients in spite of its utility toward public health. The medicinal product is therefore without a sponsor, or orphan.

According to the regulation (Regulation (EC) No. 141/2000 of the European Parliament and of the Council the criteria for the designation of a medicinal product as “orphan” are:

a) that the medicinal product be intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand persons in the Community, or

- that the medicinal product be intended for the diagnosis, prevention or treatment of a condition that is life-threatening, seriously debilitating or a grave and chronic condition in the Community and that, without incentives, it is unlikely that the marketing of the medicinal product within the Community would generate sufficient return to justify the necessary investment

b) that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition

The status of orphan application since the establishment of the COMP is reported in Table 1.

At January 2007 31 OMP received the EU marketing authorisation.

The European Organisation for Rare Diseases (EURORDIS) undertook a survey on orphan drugs availability and pricing in EU member states. Eurordis carried out a survey (2002-2003) on the first five orphan medicinal products (OMP) that received the EU marketing authorisation: Fabrazyme, Replagal, Glivec, Trisenox, Tracleer).

The availability of orphan drugs vary greatly among EU

Table 1. Status of orphan application (2000 – January 2007).

	2000	*2001*	*2002*	*2003*	*2004*	*2005*	*2006*	*2007*	*Total*
No. of applications submitted	72	83	80	87	108	118	104	0	652
Positive COMP Opinions	26	64	43	54	75	88	81	6	437
Commission Decisions	14	64	49	55	72	88	80	0	422
Final Negative COMP Opinions	0	1	3	1	4	0	2	0	11
Withdrawals	6	27	30	41	22	30	20	3	179

countries. The 5 OMP surveyed were available only in 5 member states: Austria, France, the Netherland, Portugal and the UK. Only two were available in Ireland, and one in Belgium and Luxemburg.

Market availability delays is highly variable per OMP (mean delay: Glivec 26 days, Trisenox 99 days, Tracleer 156 days, Replagal 158 days, Fabrazyme 160 days) and also from one member state to another: from 35 days mean national delay in Germany to 212 days in Portugal.

The price of orphan drugs in the EU member state also varies greatly:

- the mean OMP national price was twice higher in Luxemburg and Greece than in Portugal and Spain
- the mean price for a specific OMP in different EU countries can vary by as much as 250%

With regards to rare diseases, in 2005, in collaboration with the Rare Diseases Task Force (RDTF), a survey explored the status of rare diseases at European level. The results of the survey showed that the situation on rare disease at European level is very non-homogenous:

- Different policy attitudes with regards to rare diseases
- Few countries have public funded structures dedicated to rare diseases
- Few countries have national plans
- Few countries have a system to collect data on rare diseases

A summary of the results follow:

- National Plans/National Centres: Denmark, Spain, Italy, France
- National Networks/National registries: Denmark, Spain, Italy France
- Public funded structures on rare diseases (specific rare diseases or groups): Belgium, Denmark, Spain, France, Italy Netherlands, Sweden, UK
- Steering Committee on rare diseases: France, Italy
- Database on rare diseases: Spain, France, Italy, Netherlands, Sweden

At European level, the Decision No. 1295/1999/EC, the Regulation No. 141/2000, the establishment of the RDTF, currently involved in the discussion on Centres/networks of reference to tackle the problem of rare diseases management, show: 1) a growing commitment of EU decision-makers toward rare diseases and 2) an increasing awareness of the added value of tackling rare diseases at European level.

Despite the progress made over the last ten years, a main effort still remain to keep rare diseases a priority in the political agenda, to strengthen collaboration among EU member state and to foster research on rare diseases as the knowledge on rare diseases is still very limited.

INTRODUCTION TO RARE HEMORRHAGIC HEREDITARY DISEASES NORTH AMERICAN LEGISLATION ON RARE DISEASE

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Rare disease is defined as a condition affecting fewer than 200,000 patients in the United States. The National Institutes of Health estimates there are 6,000 rare diseases affecting 25 million Americans. Millions of dollars are invested each year to fund research, novel treatments and drug development for common diseases. Treatment options, drug development and funding are limited for rare disease. The Orphan Drug Act of 1983 was enacted to provide incentives that would encourage orphan drug research and help all afflicted with a rare disease.

Patient advocacy groups are non-profit voluntary agencies, such as the HHT Foundation International, and they primarily serve as the central source for education, information, referral and support for patients, families, and health care professionals. The mission of the advocacy organizations in the United States is to work to increase identification, treatment, education and research for rare disorders. The primary funding for the advocacy organizations come from membership dues and grants. The organization's focus is to provide programs and services to support patients and families.

Advocacy organizations have been at the forefront in proposing legislation for specific disorders in order for a rare disorder to be recognized as a true national health care problem. Rare disease organizations have become legislative experts in maneuvering the legislative process to obtain increased funding for rare disease research and initiatives. The process includes obtaining House and Senate Champions on specific legislative committees to sponsor Congressional language. Rare disease organization' members and families must educate and engage their elected representatives to obtain support from Congressional districts and states across the United States. Advocacy organizations must learn how bills become laws and how best to navigate the steps necessary for successful funding for the rare organization's initiatives. Organizations must work concurrently with specific federal agencies such as the Centers of Disease Control and the National Institute of Health to identify and obtain agreement from the agencies to establish the programs and fund the research as identified by the United States Congress.