

The European Network of Expertise for Rare Paediatric Neurological Diseases nEUroped

Report Workshop: Best Practices for Patient Registries

Conference Day 1

"Building the nEUroped Network for Research and Health"

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Workshop Participants

nEUroped Workshop **Best Practices for Patient Registries**

Brussels, Belgium; 22 November 2010

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Elisa	de Grandis	Scientific Institute G. Gaslini, Italy
Jenny	Denham	Sturge-Weber, UK
Roger	Denham	Sturge Weber UK
Filippo	Franchini	AHC Italy
Laura	Fregonese	European Union Committee of Experts on Rare Diseases (EUCERD)
Barbara	Gnidovec Stražišar	University Children's Hospital, Ljubljana, nEUroped, Slovenia
Christophe	Goubau	University of Leuven, Belgium
Elizabeth	Hernberg-Ståhl	Late Phase Solutions Europe, Sweden
Ragnheidur	Hjaltadottir	AHC Iceland
Francesca	Ingravallo	University of Bologna, nEUroped, Italy
Sigurdur	Johannesson	AHC Iceland
David	Kemlink	Charles University in Prague, 1st Faculty of Medicine, nEUroped, Czech Republic
Roger	Kendall	Epilepsy UK
Monica	Kendall	Epilepsy UK
Tanya	Kepmin	AHC Denmark
Anna	Kole	European Organisation for Rare Diseases (EURORDIS), nEUroped, France

Gert Jan	Lammers	Leiden University Medical Center (LUMC), nEUroped, The Netherlands
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Tom	O'Brien	AHC Ireland
Damjan	Osredkar	University Children's Hospital, Ljubljana, nEUroped, Slovenia
Eleni	Panagiotakaki	Hospices Civils de Lyon, nEUroped , France
Cacha	Peeters-Scholte	Leiden University Medical Center (LUMC), nEUroped, The Netherlands
Nadia	Peppa	European Huntington's Disease Network, UK
Rosa	Peraita-Adrados	Hospital Universitario Gregorio Marañón, Spain
Francesca	Poli	University of Bologna, nEUroped, Italy
Michael	Rotstein	Tel Aviv Sourasky Medical Center, Israel
Monique	Sallaz	Hospices Civils de Lyon, nEUroped , France
Tsveta	Schyns	European Network for Research on Alternating Hemiplegia (ENRAH) , nEUroped, Belgium
Stuart	Tanner	University of Sheffield, United Kingdom
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Rossaria	Vavassori	Italian Patient Association for Alternating Hemiplegia in Childhood (A.I.S.EA Onlus), nEUroped, Italy
Cristina	Villar	Hospital Sant Joan de Déu, University of Barcelona, nEUroped, Spain
Brigitta	von Rekowski	Institute of Human Genetics, Newcastle University, United Kingdom
Tammy	Winkworth	AHC UK
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Workshop Agenda

Best Practices for Patient Registries

nEUroped Conference Day 1: Monday, 22 November 2010

Building the nEUroped Network for Research and Health

Session 1: The Patient's Health, Ethics, and Patient Registries for Rare Diseases in Europe

Session Chairpersons: *Francis P. Crawley, nEUroped Ethics Working Group, Good Clinical Practice Alliance – Europe (GCPA), Belgium*
Alexis Arzimanoglou, nEUroped Coordinator, Hospices Civils de Lyon - France

- 9:00-9:10 Welcome and Background to the nEUroped Project and the Development of a European Patient Registry for Children with Rare Paediatric Diseases
Alexis Arzimanoglou, nEUroped Coordinator, Hospices Civils de Lyon - France
- 9:10-9:35 Ethical Issues Involved in Building, Maintaining, and Using Patient Registries
David Neubauer, University Children's Hospital, Ljubljana, nEUroped, Slovenia [Presented by Francis P. Crawley, GCPA, nEUroped, Belgium]
- 9:35-9:50 Addressing Patient and Public Health Issues in the Design and Implementation of Patient Registries: The Example of the Patient Registry for the Surveillance of Cerebral Palsy in Europe Network (SCPE)
Damjan Osredkar, University Children's Hospital, Ljubljana, Slovenia
- 9:50-10:10 Fitting Patient Registries into Existing Research Strategies for Rare Diseases: Sponsors' Expectations and Contributions
Elizabeth Hernberg-Ståhl, Late Phase Solutions Europe, Sweden
- 10:10-10:40 Plenary Discussion on Merging the Needs of Health, Science, and Ethics in European Patient Registries
- 10:40-11:10 Coffee Break

Session 2: Best Practices for Developing & Using Patient Registries

Session Chairpersons: *Claudio Zucca, IRCCS "Eugenio Medea", nEUroped, Italy*
Jaume Campistol Plana, Hospital Sant Joan de Déu, University of Barcelona, nEUroped, Spain

- 11:10-11:25 Developing Best Practices Guidelines for Patient Registries: The European Challenges and Opportunities
Francis P. Crawley, nEUroped Ethics Working Group, Good Clinical Practice Alliance – Europe (GCPA), Belgium

- 11:25-11:40 Patient Registries As Disease Management Tools: Putting the Patient's Health Central
Stuart Tanner, Coordinator, EuroWilson, University of Sheffield, United Kingdom
- 11:40-11:55 Case Study for Gene-specific Patient Registries in Rare Inherited Neuromuscular Diseases: The TREAT-NMD Patient Registries for SMA and the International Dysferlinopathy Registry
Brigitta von Rekowski, TREAT-NMD Registry Manager, Institute of Human Genetics, Newcastle University, United Kingdom
- 11:55-12:30 Plenary Discussion on European Guidelines for Best Practices for Patient Registries
- 12:30-13:30 Lunch

Session 3: Making Use of the nEUroped Patient Registry for Research

Session Chairpersons: *Michael Rotstein, Pediatric Neurology Unit and Child Development Center, Tel Aviv Sourasky Medical Center, Israel*
Eleni Panagiotakaki, nEUroped, Hospices Civils de Lyon - France

- 13:30-13:45 Report on the Preliminary ENM Workshop: Patients and Researchers Finding Common Ground in nEUroped
Anna Kole, European Organisation for Rare Diseases (EURORDIS), nEUroped, France
- 13:45-14:05 The nEUroped Registry and Its Use for Collaborative Research
Alexis Arzimanoglou, nEUroped Working Party Registry, Hospices Civils de Lyon - France
- 14:05-14:25 Integrating Patient Registries and Biobanks
Filippo Franchini, Italian Patient Association for Alternating Hemiplegia in Childhood (A.I.S.EA Onlus), nEUroped, Italy
- 14:25-14:45 The Initiation of Research Projects Based on Information in Patient Registries: The Projected Contribution of the nEUroped Registry
Arn van den Maagdenberg, Leiden University Medical Center (LUMC), nEUroped, The Netherlands
- 14:45-15:15 Plenary Discussion: Patients, Clinicians, and Scientists Collaborating through the nEUroped Registry
- 15:15-15:30 Summary and Close of Day 1
- 15:30-16:00 nEUroped ENM Conference Reception: Coffee and Cake

Workshop Summary

This Workshop on Best Practices for Patient Registries was carried out on Day 1 of the nEUroped Extended Network Meeting entitled: 'Building the nEUroped Network for Research and Health'.¹ Altogether 43 participants from patient organisations, academic, and research organisations attended the workshop. The workshop examined the accomplishments of nEUroped with regard to developing a European patient registry for rare neurological disorders. It also brought in a wide audience of experts and users of patient registries in Europe to expand the discussion and examine best practices, within the nEUroped project and in collaboration with other organisations. The workshop focused on presentations by experts inside nEUroped as well as invited outside experts, followed by extensive plenary discussion.

Workshop Organising Committee

The workshop was organised principally by the Good Clinical Practice Alliance – Europe (GCPA), with support from the European Network for Research on Alternating Hemiplegia (ENRAH), the European Organisation for Rare Diseases (EURORDIS), leaders of the nEUroped disease specific working groups, and the nEUroped Coordinator's Office. The individual's involved were

Alexis Arzimanoglou	Hospices Civils de Lyon – France (nEUroped Coordinator & RSTES Group Leader)
Francis P. Crawley	Good Clinical Practice Alliance – Europe (GCPA)
Anna Kole	European Organisation for Rare Diseases (EURORDIS)
Brian Neville	Institute for Child Health, University College London, UK (nEUroped Alternating Hemiplegia Working Group Leader)
Sona Nevsimalova	Neurological Clinic of 1 st Medical Faculty of Charles University, Czech Republic (nEUroped Childhood Narcolepsy Working Group Leader)
Monique Sallaz	Hospices Civils de Lyon – France (nEUroped Coordinator's Office)
Tsveta Schyns	European Network for Research on Alternating Hemiplegia (ENRAH)

Workshop Objectives

The principle objective of the workshop was to contribute to the development of best practices for patient registries within the European Union and, in particular, to the nEUroped registry under development for rare paediatric diseases. More specific objectives included the following:

- presenting the nEUroped Projects' work and accomplishments with regard to ethics, GCP and best practices for patient registries;
- developing the nEUroped registry toward the future with regard to its work, organization, sustainability, and extension and cooperation with other networks;
- bringing together the nEUroped network members to review their accomplishments and work toward the establishment of the nEUroped registry;

¹ This Report on the nEUroped Workshop on Best Practices for Patient Registries arises from the project nEUroped which has received funding from the European Union, in the framework of the Public Health Programme (Agreement number – 2007122).

- to educate patients regarding the nEUroped registry and its eventual contribution to their needs and interests;
- to receive input from clinicians and researchers in rare neurological paediatric disorders, particularly in Alternating Hemiplegia in Childhood (AHC), narcolepsy, and RSTES, with regard to the needs of patient registries;
- to examine with the nEUroped consortium and outside experts in patient registries the nEUroped Ethics Working Groups' draft 'European Union Best Practice Guidelines in Ethics and GCP for Networks and Registries', 'An EU Training Course on Best Practices for Developing and Maintaining Patient Registries', and 'A Survey on Ethical Issues in European Patient Registries'.
- to look at core questions relating to European cooperation between the nEUroped registry and other European registries; and
- to achieve a strong foundation for the future development of the nEUroped registry within the European framework for research and health in rare diseases.

Workshop Programme: Session 1

The workshop was divided into three sessions. Session 1 focused on 'The Patient's Health, Ethics, and Patient Registries for Rare Diseases in Europe'. This session looked at the relationship between the conditions of rare paediatric diseases and the design and implementation of patient registries. David Neubauer of University Children's Hospital in Ljubljana, Slovenia & nEUroped presented (in absentia, by Francis P. Crawley, GCPA) an overview of the ethical issues involved in building, maintaining, and using patient registries. The presentation focused on how ethics can contribute to the use of patient registries as a public health tool. It examined topics related to the informed consent and ethical review of patient registries population and use, as well as with regard to the structure and custodianship issues in patient registries. It also introduced for discussion the nEUroped Ethics Working Group's draft 'EU Training Course on Best Practices for Developing and Maintaining Patient Registries' and 'Survey on Ethical Issues in European Patient Registries'.

This was followed by a presentation from Damjan Osredkar from the Department of Pediatric Neurology at the University Children's Hospital in Ljubljana (working under Professor Neubauer) bringing the example of the 'Patient Registry for the Surveillance of Cerebral Palsy in Europe (SCPE)', particularly focused on the challenges to establishing such a registry and what nEUroped could learn from their experience. He also introduced the SCPE European Network to nEUroped and the audience. Elizabeth Hernberg-Ståhl of Late Phase Solutions Europe located in Sweden then presented on how patient registries could be used by researchers, particularly in late phase clinical trials. She focused on the expectations sponsors of clinical trials have for patient registries as well as on the contributions sponsors could bring in the form of research linked to patient registries. She referred to the European orphan drug and paediatric legislations as frameworks for the development of patient registries, particularly that of nEUroped.

Session 1 was concluded by a discussion with the audience. The audience expressed appreciation for the contributions from the speakers as well as the work presented by the nEUroped Ethics Working Group. The discussion concentrated on the need for developing best practice guidance around patient registries and improved communication between patients and researchers on the development of patient registries.

Conclusions of Session 1

There was an expressed need to harmonise European standards on patient registries. Ethics plays an important part in contributing to the development of patient registries, particularly with regard to the involvement and protection of patients and families. Ethics and best practices also provide a good framework for further harmonising European standards and practices with patient registries. Best practices and harmonisation needs to involve multi-stakeholders with an awareness of the variety of purposes served by patient registries. It was emphasised that there is a need for patient registries, not only as a place to gather data, but also as a critical place to increase knowledge and share research on rare diseases.

Workshop Programme: Session 2

The second session of the workshop focused on ‘Best Practices for Developing & Using Patient Registries’. The session opened with a presentation from Francis P. Crawley, GCPA, on the development of best practice guidelines for patient registries. He referred to the general background within Europe and internationally on the increasingly important role registries play in public health and health research. The previous experience of some nEUroped members with the European Network for Research on Alternating Hemiplegia (ENRAH) and other European patient registries has been critical to the discussion within the the nEUroped Ethics Working Group’s development of the draft ‘European Union Best Practice Guidelines in Ethics and GCP for Networks and Registries’, which was presented for discussion. The presentation also outlined the major features of the draft ‘EU Training Course on Best Practices for Developing and Maintaining Patient Registries’. It looked at the roles of researchers and patients in developing registries and examples of how information can be shared for health and research purposes. Focus was given to the custodianship of data.

Stuart Tanner, the Coordinator of EuroWilson at the University of Sheffield in the United Kingdom then presented on patient registries as disease management tools. He focused on the contribution patient registries make to assisting patients, particularly those with rare diseases, to understand and manage their health better. He described the background to Wilson’s disease and explained how patient registries can contribute to the epidemiology, diagnosis, genetic understanding, and treatment of rare neurological diseases, particularly in children. He also introduced the audience to the EuroWilson’s Consortium and its attempts to improve the health of patients suffering from rare neurological diseases.

A presentation was then given on gene-specific patient registries in rare inherited neuromuscular diseases by Brigitta von Rekowski, the Manager of the TREAT-NMD Registry at the Institute of Human Genetics in Newcastle University, United Kingdom. She focused on the TREAT-NMD Patient Registries for SMA and the International Dysferlinopathy Registry. She explained the challenges that these registries had encountered and the current steps they are taking to improve them. She also discussed the need for best practices in patient registries and how increased cooperation and harmonisation at the European level could further the interests of patients and researchers.

Conclusions of Session 2

The session was followed by a lively discussion on the development of best practices for constructing and using patient registries. Patients expressed a need to have their needs and interests expressed in the patient registries, not only for the purposes of science but also to improve their own understanding of disease. It was recognised that there is a growing use of

patient registries by patient organisations, clinicians, and researchers (academic & industry). This leads to a variety of approaches and systems to patient registries without current European standards being established. There is perhaps a need to link the development of patient registries to the increasing standardisation of patient health records, research (clinical trial) registries, and other patient data systems under development in the European Union.

In addition, patient registries contribute to the European public health understanding of diseases, perhaps particularly of rare diseases. They are important tools for collecting epidemiological and demographic data on diseases. Patient registries also contribute to helping us understand the genetic markers of specific diseases as well as the overall way in which they can be diagnosed. These registries can also contribute to physicians' and patients' understanding of how to treat diseases by providing an overview of the interventions currently being used and doses. Finally, these registries are of key importance to promoting research into the diagnosis, treatment, and prevention of diseases. And again this is particularly relevant for rare diseases.

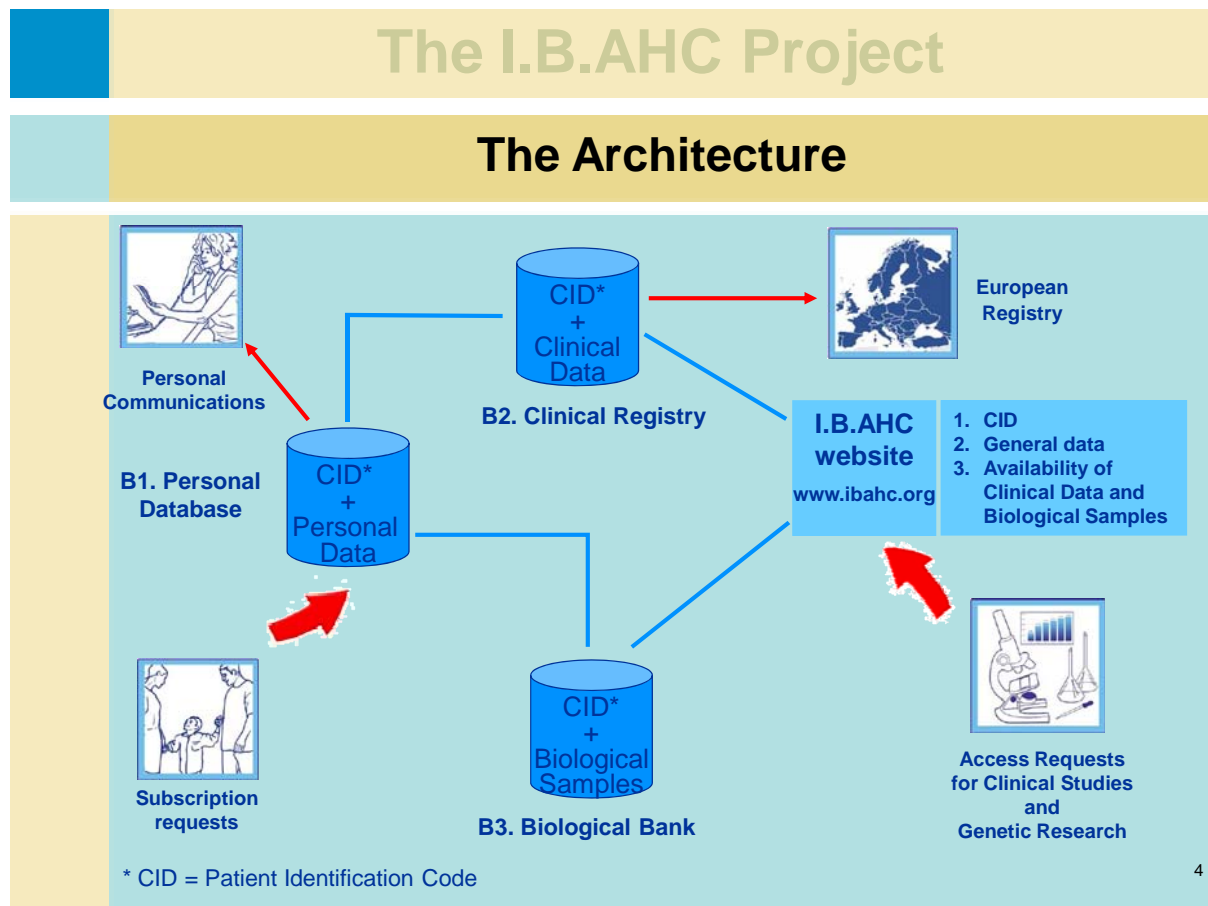
Workshop Programme: Session 3

The final session, session 3, opened with a preliminary report of the previous day's nEUroped workshop on capacity-building and patient network integration. Anna Kole of the European Organisation for Rare Diseases (EURORDIS) discussed the background to the patient's contribution to nEUroped and the steps needed to be taken by patient organisations and researchers to develop more capacity within their organisations and projects to further the development of nEUroped. She focused on the development of EURORDIS as an organisation that was committed to developing improved tools and networks of patients with rare diseases. She stressed how there was a need to further build the capacity of patients to understand the principles of patient registries and find the appropriate role for patient groups in the nEUroped registry. Many of the patient groups came to the meeting less informed of developments within nEUroped and more communication was needed among the patient groups as well as with the researchers. The previous day's workshop had provided the patients with an opportunity to work together in small working groups focused on their diseases. It is necessary to continue this discussion among the patients within the nEUroped disease groups and across the groups.

Alexis Arzimanoglou, the nEUroped Coordinator and Chair of the nEUroped Working Party Registry from the Hospices Civils de Lyon – France then presented the nEUroped Registry and its uses for collaborative research. He discussed the challenges to developing a rare disease registry in paediatric neurology across the European Union. There exists, on the one hand, a complexity of various diseases that have some family resemblance but whose symptoms and underlying disease profiles may differ strongly. On the other hand, there are the challenges of working with limited resources for a defined period of time and without a clear view toward the future maintenance of the consortium and registry. In addition we need to take into account the variety of member states requirements for data protection and ethics, as well as the structure of national patient organisations and European networks.

Filippo Franchini of the Italian Patient Association for Alternating Hemiplegia in Childhood (A.I.S.EA Onlus) a member of nEUroped, and the Project Manager of the Italian Biobank for Alternating Hemiplegia in Childhood (I.B.AHC) introduced the important topic of the relationship between patient registries and biobanks. He stressed three key issues that need to be addressed when integrating patient registries and biobanks: 1. Operational issues need to

be considered with regard to inviting registry participants, data collection, blood samples collection, and follow-ups. 2. Privacy and security issues arise that require coding, anonymising data and samples, and preserving the integrity and flow of data. 3. Ethical issues also need to be contended with in order to ensure that data and samples are treated appropriately with due regard to the needs and interests of the patients. He presented a model approach developed by the Italian Biobank for Alternating Hemiplegia in Childhood (I.B.AHC). This approach is dependent on a strong architecture that clearly relates the various elements (see the slide below):



He emphasised the need for ongoing and persistent work to ensure the appropriate development of such an integration scheme. Patients and their organisations need to work closely with researchers in order to achieve good outcomes.

The last presentation of the session was provided by Arn van den Maagdenberg from Leiden University Medical Center (LUMC) in The Netherlands and a member of nEUroped. He discussed on patient registries contribute to the initiation of research projects and what the expected contribution of nEUroped might be to future research projects on rare paediatric neurological diseases. He focused on how the nEUroped project was designed to improve diagnosis, management, and the dissemination of information regarding rare nervous systems disorders in children. The great value of the consortium approach is that it brings about a multidisciplinary approach at the European level. The critical contribution of a registry is the

development of a European network of patients and researchers. This helps us to join forces and experience to address a large collection of cases. The presentation showed how it is important to combine clinical data for the development of clinical research. He used the example of the research done using the ENRAH registry and a publication that arose from that concerning the natural history of the progression of the disease. He also discussed the relationship between patient registries and basic research looking at basic mechanisms and DNA variations in diseases. Examples from alternating hemiplegia and narcolepsy research were included. By including the three diseases in the nEUroped registry, there was more opportunity to study 1. common pathways in neurological diseases; 2. pathways in rare diseases that may have relevance for common traits; and 3. pathways in brain structures may help us understand pathologies in other diseases.

Conclusions of Session 3

Session 3 and the discussion that followed brought out many of the challenges that face the nEUroped registry as well as patient registries in general. We have already learned a great deal in a short period of time with regard to how to build and use patient registries. Nevertheless significant challenges remain. Greater communication and capacity-building is needed within patient organisations and between patients and researchers in order to improve the value and use of patient registries. This need for communication and capacity-building is felt within nEUroped. There are also challenges regarding the structure of patient organisations within Europe as well as the need to secure ongoing, long-term funding so that the work developed by a project is not lost.

Overall Conclusions

This one-day workshop of patients and experts in rare paediatric neurological diseases focused on best practices for patient registries demonstrated the enormous value disease registries bring to promoting the diagnosis, management, and eventual research of such diseases within the European Union. A clear scientific design supported by ethics and GCP form a basis for developing best practices in patient registries. Patients and their organisations need to be fully involved and committed to the process of building and using registries.

The development by the nEUroped Ethics Working Group of draft ‘European Union Best Practice Guidelines in Ethics and GCP for Networks and Registries’, ‘An EU Training Course on Best Practices for Developing and Maintaining Patient Registries’, and ‘A Survey on Ethical Issues in European Patient Registries’ contribute to both the development of nEUroped as well as greater European understanding and harmonisation on the role patient registries in public health.

Next Steps

The nEUroped registry and the supporting best practice guidelines and training programme need to be further developed taking into account this workshop’s discussion as well as the discussions of the preliminary patient workshop on the preceding day and the following day’s continuation of the Extended Network Meeting.

It is critical that nEUroped continue to develop the disease guidelines in the areas of alternating hemiplegia, childhood narcolepsy, and the Rare Surgically Treatable Epilepsy Syndromes (RSTES): Sturge-Weber, Rasmussen’s, Landau-Kleffner, hypothalamic hamartomas. These guidelines need to form the medical and scientific basis for the data to be

entered into the nEUroped registry. The guidelines should provide a basis for the registry to reflect the symptomatic, clinical, and natural history of the diseases as well as the real life needs of children suffering rare paediatric neurological diseases: medical, behavioural, and social needs.

Patient groups need to understand better the benefits of patient registries so they can better agree to participate in the work. They also have the ability to assist in the recruitment of patients. Both patients and researchers need to work at developing better lines of communication. Networks and consortia such as nEUroped play a pivotal role in assisting in this communication.

There is a need to clarify how data is entered in patient registries as well as how it is maintained and used. More pro-action from patients and their organisations could assist. The structure of the European Union presents strengths to the development of disease consortia and registries that include patients, physicians, and researchers. In particular, the communication, mobility, and financing of such networks and consortia across widely diverse countries is advanced through European projects. At the same time, the need for national approaches remains and can sometimes hinder or appear to duplicate work done at the European level.

The European Network of Expertise
for Rare Paediatric Neurological Diseases
nEUroped

European Union Best Practice Guidelines in Ethics and GCP for Networks and Registries

prepared by the

nEUroped Ethics Working Group

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draft, version 2.0

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1. Forward

These European Union Best Practice Guidelines in Ethics and GCP for Networks and Registries have been developed within the a European Commission funded project aimed at building a consortium and developing a registry for patients and clinicians involved in addressing rare paediatric neurological diseases. The European Network of Expertise for Rare Paediatric Neurological Diseases (nEUroped) has been established by patient organizations and researchers seeking improved therapeutic, diagnostic, and prophylactic interventions for rare diseases in children. These guidelines developed out of several experiences in building European patient, science, and medical registries acting as portals for developing health research into rare paediatric diseases. The Guidelines are developed in collaboration with leading European and international patient registries to serve as a framework for discussion, cooperation, and improving the quality of patient registries in the European Union.²

2. Introduction

The aim of this European Union Best Practice Guidelines in Ethics and GCP for Networks and Registries is to express current existing best practices within the European Union for patients and doctors/clinicians working together on the development of patient registries. An increasing number of patient registries are developed within Europe in order to improve the cooperation between patients and doctors in identifying diseases, identifying patients, identifying doctors and hospitals engaged in treating patients with those diseases, and establishing a database and/or biological samples base for disease identification, diagnosis, best treatment and care strategy, and prophylaxis and prevention, as well as a starting point for new research questions and research projects.

These guidelines reflect best practices based on a European framework of laws, regulation, guidelines, and rules for patient data, biological samples, and research. They express a collective understanding of the current ethical and scientific needs for patient registries and how these registries can be developed to best meet those needs. These guidelines express a collective understanding of best practices, with the intention that they are periodically reviewed and updated according to new understandings borne out of the development of European patient registries as well as the ethics, medicine, and science surrounding those registries.

These guidelines express the most effective approaches to establishing patient and doctor consortia as well as registries to support those consortia. They are not intended to establish required practices; rather they function as a benchmark for which compliance is strictly voluntary.

These Guidelines have been developed against the following ethical values:

- the **respect for (and protection of)** the freedoms, privacy and confidentiality, and rights of all project participants, particularly the patients and families;
- the **security** of all data and biological materials in their collection, storage, transfer, and access; and
- the **high quality** of data included in the nEUroped patient registry.

² This Guideline arises from the project nEUroped which has received funding from the European Union, in the framework of the Public Health Programme (Agreement number – 2007122).

3. Ethical and Scientific Principles Supporting European Patient Registries

When developing a patient and doctor/clinician network that includes and patient registries, the consortium partners agreed on a set of ethical principles and/or values that ensure

- 3.1 the respect for (and protection of) the freedoms, privacy and confidentiality, and rights of all project participants, particularly the patients and families;
- 3.2 the security of all data and biological materials in their collection, storage, transfer, and access; and
- 3.3 the high quality of data included in the nEUroped patient registry.

The commitment to, and promotion of, these values provides a general framework for the network's and registry's engagements and activities.

4. Methodology

The ethical and Good Clinical Practice (GCP) issues have been divided into the following categories:

- 4.1. Clinical Data
- 4.2. Human Biological Materials
- 4.3. Data from Clinical Trials on Medicines and Other Health Interventions
- 4.4. Research Data

5. Operational Principles for Patient Registries

- 5.1. Data and HBMs should be collected at the Patient registries with the informed, free and documented consent of the patient and/or his/her legal representative. The patient's assent should be sought, as appropriate and to the extent possible, in all cases where consent is provided by a legal representative.
- 5.2. An explicit consent for including patient information in the registry should be sought and documented.
- 5.3. Data and HBMs should be collected, stored, and transferred in compliance with the protocol(s) that has received prior independent ethics committee approval/favorable opinion and in accordance with European and national legislation and regulation.
- 5.4. Each individual involved in data and HBMs collection, storage, and/or transfer should be qualified by education, training, and experience to perform his or her respective task(s).
- 5.5. Clinical data should be collected following a protocol established by the network.
- 5.6. HBMs from patients assigned to the registry should be collected at the patient registry for defined purposes.
- 5.7. All collected data and HBMs should be recorded, handled, and stored in a way that shows respect for the persons from whom the data and HBM come, provides for confidentiality, and allows for future accurate reporting, interpretation, and verification.

- 5.8. The confidentiality of records and HBMs that could identify subjects should be protected during all steps of their handling, respecting the privacy and confidentiality in accordance European ethical and regulatory requirement(s).
- 5.9. Data in the registry should be handled according to the rules established by the network as well as respecting the rules of the provider while maintaining an efficient work flow.
- 5.10. Systems for data quality need to be implemented and followed according to Standard Operating Procedures established by the network.
- 5.11. Patients and their families should be kept informed by providing validated information on the results from the studies utilizing the registry.
- 5.12. Patients and their families should also be able to obtain information on the use of their clinical data in research projects making use of the registry.

6. The Roles and Responsibilities of Those Having Access to a Patient Registry

6.1 Patients

- 6.1.1. Patients and their families should be fully informed of the use of their data and HBMs at the time of entering their data and HBMs into the registry,
- 6.1.2. Patients and their families should be kept informed on the current use of their data and HBMs stored or maintained by the registry.
- 6.1.3. Patients and their families should be involved in the process establishing the data parameters of the registry.
- 6.1.4. Patients and their families should be involved in validating the information provided to patients and researchers, and in reviewing the disease treatments recommendations.

6.2 Patient Registries and Clinicians

The members of the consortium should be involved in the process of establishing the data parameters for the registry.

- 6.2.1. A Patient registry should ensure that all persons engaged in data collection and handling are adequately informed regarding the protocol for data collection and management as well as the associated duties and functions.
- 6.2.2. A patient registry should receive ethical review approval prior commencing the collection of data or HBMs for entry into the registry.
- 6.2.3. A patient registry should be able to verify that each subject, or his/her legal representative, has consented in writing for the use of his/her data and/or HBM in the registry.
- 6.2.4. A patient registry should ensure the accuracy, completeness, legibility, and timeliness of the collected data. Data entered into the registry derived from other sources should be consistent with the source documents or the discrepancies explained.

- 6.2.5. A patient registry should ensure that the patient records from which data are entered are stored for at least five years after the data is entered into the registry.
- 6.2.6. A patient registry should share, as appropriate, the collected clinical data with the registry.
- 6.2.7. A patient registry should share information in the registry only with parties who have received an authorization from the network.
- 6.2.8. In case of a patient withdrawing data from the registry, a patient registry should inquire as to the reason(s), when possible, while fully respecting the patient's rights.
- 6.2.9. A patient registry should ensure consistency in labelling data and HBMs for the transfer and exchange of such data and HBMs.
- 6.2.10. A patient registry should have the liberty to decide on the use, transfer, and exchange of its collection of patient HBMs.
- 6.2.11. A patient registry should provide a reference regarding the availability of data and HBMs from its patients.
- 6.2.12. A patient registry should inform the Network in case of sharing of HBMs entered into the registry.
- 6.2.13. A patient registry should share the research data from the use of data and HBMs entered into the registry.

6.3 Researchers Utilizing the Registry and Related HBMs

- 6.3.1. Researchers utilizing the registry and related HBMs should be involved in establishing the data parameters of the registry.
- 6.3.2. Researchers utilizing data and HBMs entered into the registry should publish the results of their research on the registry in a timely fashion.
- 6.3.3. Researchers utilizing data and HBMs entered into the registry are invited to share their research data (including clinical trial data) through the registry.
- 6.3.4. Researchers utilizing data and HBMs entered into the registry should be engaged in the development of research proposals and studies related to the disease treatment.

6.4 Web Registry Provider

- 6.4.1. A web registry platform provider should be an established party, at times certified by the regulatory authority in its country of residence, that provides state-of-the-art web-based tools for developing, maintaining, and using patient registries.
- 6.4.2. A web registry platform provider should work with the consortium to ensure the confidentiality and integrity of data and HBMs entered into the registry, adhering to the technical specifications provided by the consortium.
- 6.4.3. A web registry platform provider should provide an adequate training to the members of the network for accessing, listing, updating, and using data and HBM's contained in the registry.

6.5 Ethics Committees

- 6.4.1. An ethics committee should promote and safeguard the dignity, rights, safety, and well-being of all persons whose data or HBMs are entered into the registry.
- 6.4.2. An ethics committee should obtain the following documents: a description of the registry and its intended uses, the questionnaire used for data collection, the information sheets for patients and their legal representatives; the assent and informed consent forms for patients and their legal representatives.
- 6.4.3. An ethics committee should review a proposed application within a reasonable time and document its views in writing, clearly identifying the documents reviewed and the dates for the approval and/or modifications required prior to its approval or disapproval and/or termination/suspension of any prior approval.

6.6 The Network

- 6.6.1. The network should promote, keep up-to-date, and facilitate the timely and proper use of the data and HBMs entered into the registry for the purposes of promoting patient clinical care as well as promising research into the disease area.
- 6.6.2. The network should promote and facilitate the timely publishing of results from any uses made of the patient information or HBMs contained in the registry.
- 6.6.3. The network should ensure the ongoing maintenance, development, and use of the registry.

7. The Structure of Information in a Patient Registry

- 8.3.1. description of patients
- 8.3.2. clinical data
- 8.3.3. patient family histories: genealogical information
- 8.3.4. images of patients: photos/video
- 8.3.5. information on Human Biological Material (HBM) in the diseases/health conditions represented
- 8.3.6. physical descriptions
- 8.3.7. genetic descriptions
- 8.3.8. images
- 8.3.9. a registry of clinical trials and other forms of research related to the diseases/health conditions represented
- 8.3.10. a protocol database for clinical trials and other forms of research related to the diseases/health conditions represented
- 8.3.11. a results database for clinical trials and other forms of research related to the diseases/health conditions represented

8.3.12. an information centre on scientific, ethical, legal, and other forms of documents related to the diseases/health conditions represented and directed toward patient care and/or research.

8. Custodianship

A European patient registry should be considered a public good housed under the custodianship of a consortium of patients and/or clinicians. Best practices discourages the ownership of data and HBMs entered into the registry, as well as any results arising from research making use of the registry. The consortium should promote the registry as a tool for sharing information and knowledge related to the diseases/health conditions represented for the benefit of the patients and their families.

9. Glossary

Clinical Data

Any information collected by a doctor or healthcare professional in the course of providing normal healthcare to a patient. Clinical data here includes all patient information collected for healthcare purposes by doctors or other healthcare professionals, including data related to a patient's family.

Health Research Data/Clinical Trial Data

Any information collected by a researcher or research organization in the course of carrying out a medicinal or other health intervention research project, including a clinical trial.

Human Biological Materials (HBMs)

Tissues or bodily substances collected from a person for the purposes of healthcare or research.

Research Data

Any information obtained by an investigator for the purposes of clinical or genetic research.

Network

A consortium of individuals or/and organizations that make substantial contributions to the registry, are committed to the responsible sharing of the registry, and are collectively engaged in the custodianship of the registry.

Patient Registry

A collection of patient clinical, genetic, and/or biological material used for the purposes of diagnosis, prevention, treatment and/or research.

10. Supporting References

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(<http://www.wma.net/en/30publications/10policies/b3/index.html>; accessed 11 May 2010)

Appendix 2: Draft EU Training Course on Best Practices for Developing and Maintaining Patient Registries

The European Network of Expertise
for Rare Paediatric Neurological Diseases
nEUroped

An EU Training Course on Best Practices for Developing and Maintaining Patient Registries

prepared by the
nEUroped Ethics Working Group

7 June 2011
draft, version 2.0

www.nEUroped.org

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11. Introduction

This training course is designed for patients, clinicians, and researchers involved with European Union networks of patients and doctors/clinicians and patient registries. The course focuses on developing the understanding, skills, and practices needed to develop, maintain, and share information and human biological materials (HBMs) on a patient registry within the European Union. The course is based on expertise developed within the European Network of Expertise for Rare Paediatric Neurological Diseases (nEUroped) in collaboration with other European networks of expertise in specific disease areas and having experience working with patient registries.³

The course benefits from the expertise of patient organisations and clinicians as well as those involved in clinical trials and other forms of health research. The course is specifically designed to bring together various perspectives from lecturers having differing backgrounds regarding European regulation, best practices, and ethics as related to developing and sharing patient information with the intention of improving patient care and promoting research.

12. Objectives

The primary objective of the course is to develop an understanding of the role and responsibilities of the various parties involved in a patient registry within a Good Clinical Practice (GCP) and ethics setting. In support of this aim, the course also has the following specific objectives:

- to define the needs for patient registries in primary health care and research, including clinical trials: how the needs are determined and how a patient registry is to be constituted to meet the needs;
- to examine both the health, scientific, and ethical backgrounds and expectations from a patient registry;
- to describe the information and format of a patient registry;
- to examine the background needs for patient registry users as well as the avoidance and declaration of potential or real conflict of interest;
- to examine the consortium agreement supporting patient registries, including their content and procedures;
- to develop an understanding of the maintenance and quality assurance standards for a patient registry;
- to understand how to address questions of access and confidentiality for the use and sharing of information on a patient registry;
- to appreciate the expectations others have for patient registries, including members of patients (present and future), clinicians, researchers, ethics committees, pharma & biotech companies, and regulatory authorities; and
- to appreciate public expectations for patient registries.

13. Methodology

The training course is directed at participants with a wide variety in backgrounds. The course is designed to be highly interactive, included in the presentation of standards for best practices and case studies, along with group work, case studies, and open debate on issues.

³ This course arises from the project nEUroped which has received funding from the European Union, in the framework of the Public Health Programme (Agreement number – 2007122).

14. Topics

Part 1: Introduction to Patient and Doctor/Clinician Consortia and Registries

- A. Background to the Development of Disease Consortia and Registries in the European Union
- B. The Perspective of Patients: Their Needs and Expectations from Disease Consortia and Registries
- C. The Perspective of Doctors/Clinicians: Their Needs and Expectations from Disease Consortia and Registries
- D. The Perspective of Researchers: Their Needs and Expectations from Disease Consortia and Registries

Part 2: The Design of Patient Registries

- A. The Various Purposes of a Patient Registry and Their Effect on the Design of the Registry
- B. Identifying the Information to Be Included in a Patient Registry
- C. Designing Fields, Coding, and a Common Language for Use within and across Disease Groups
- D. Validating Data
- E. Developing and Maintaining Standard Operating Procedures for Patient Registries
- F. Establishing Quality Control Systems, Including Audit Procedures
- G.
- H. Maintaining Patient Privacy and Confidentiality in a Patient Registry
- I. Informed Consent Procedures for Patient Registries
- J. Ethical Review Procedures for Patient Registries
- K. Ethical and Regulatory Requirements and Guidelines for Patient Registries

Part 3: The Various Kinds of Data and Uses of Patient Registries

- A. Clinical Data
- B. Genetic Data
- C. Human Biological Materials
- D. Research Data

Part 4: Good Governance of Patient Registries

- A. The Interrelationship between the Consortia and the Patient Registry
- B. Establishing a Governing Board for the Patient Registry
- C. Scientific, Technical, and Administrative Assistants for a Patient Registry
- D. Financing a Patient Registry

Part 5: Access and Transparency Regarding Patient Registries

- A. Ownership versus Custodianship of the Data and HBMs in a Patient Registry
- B. Defining Rules and Privileges for Accessing the Data and HBMs in a Patient Registry
- C. The Sharing of Research Results for Best Practices and New Interventions
- D. Publishing Research Developed in Relation to a Patient Registry

15. Outcomes

The primary outcome of the training course is to ensure that the participants are able to make independent and competent contributions to patient registries, with regard to their needs and interests, as well as the needs and interest of a registry.

16. Rapporteurs

Two participants will be appointed to make a summary overview of the training, including the major topics discussed and the points raised during the discussion.

17. Supporting Documents

Council for International Organizations of Medical Sciences (CIOMS). *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. Revised Edition. Geneva 2002. (<http://www.cioms.ch>; accessed 11 May 2010)

Council for International Organizations of Medical Sciences (CIOMS). *International Guidelines for Ethical Review of Epidemiological Studies*. Revised Edition. Geneva 2005. (<http://www.cioms.ch>; accessed 11 May 2010)

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(<http://www.wma.net/en/30publications/10policies/b3/index.html>; accessed 11 May 2010)

The European Network of Expertise
for Rare Paediatric Neurological Diseases
nEUroped

A Survey on Ethical Issues in European Patient Registries

prepared by the
nEUroped Ethics Working Group

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draft, version 3.0

www.nEUroped.org

Introduction

The aim of this survey is to develop empirical data regarding the ethical issues that arise in the development, maintenance, and use of patient registries in Europe for the purposes of collecting information on patient populations, disease characteristics, and research into diagnostic, prophylactic, and therapeutic interventions. The survey is directed in the first place to the partners in the consortium making up the European Network of Expertise for Rare Paediatric Neurological Diseases (nEUroped). At the same time the survey is addressed to other European Union, Third Country, and international registries. The survey is intended to contribute to the development and appreciation of best practices for building and using patient registries in nEUroped and the European Union.⁴

nEUroped is committed to addressing rare neurological diseases in the European paediatric populations. As such nEUroped has developed this survey against a background of shared values reflecting the needs of patients and their families as well as those of clinicians and researchers. These values include

- the **respect for (and protection of)** the freedoms, privacy and confidentiality, and rights of all project participants, particularly the patients and families;
- the **security** of all data and biological materials in their collection, storage, transfer, and access; and
- the **high quality** of data included in the nEUroped patient registry.

nEUroped's commitment to, and promotion of, these values provides a central framework for its engagements and activities.

This survey addresses ethical issues in patient registries likely to arise in the areas of collecting, storing, transferring, and accessing clinical data, Human Biological Materials (including blood samples and genetic data), and data from clinical trials on medicines and other health interventions.

We appreciate you taking the time to review this survey and return it to the nEUroped Ethics Working Group. The draft survey will be reviewed and discussed at the nEUroped Extended Networking Meeting on 21-23 November 2010 in Brussels, Belgium. From the results and discussion, nEUroped will draft procedures to ensure confidence across consortium members in the sharing of information and data in our collective attempt to better address rare neurological diseases affecting Europe's children. The results of the survey will be made public on the nEUroped website (www.nEUroped.org) and potentially in other publications and fora.

Individuals and organisations are invited to contribute to this survey. The survey may be completed in Word or pdf form as well as through an online survey tool available at this link: www.surveymonkey.com/xxx.

The nEUroped Ethics Working Group thanks you in advance for completing this survey in a conscientious and timely manner.

⁴ This survey arises from the project nEUroped which has received funding from the European Union, in the framework of the Public Health Programme.

Section A. Ethical Issues Arising in nEUroped Related to Patient Registries

1. How important is patient privacy to you and your family?
 - a. a major priority in the patient's care
 - b. a secondary priority to health and research
 - c. of little importance to the patient and our family

2. The clear recognition and identification of your patients' disease is important for the following reasons:
 - a. to ensure appropriate care of the patient
 - b. to achieve support from clinicians
 - c. to achieve support from clinicians
 - d. to gain acceptance, recognition, and support from patient organisations

3. Do you believe that the clinicians and their treatment guidelines are well positioned to address the needs of your patient?
 - a. yes, very well positioned
 - b. yes, well positioned, but this needs to be improved
 - c. no, not sufficiently well positioned
 - d. no, I have lost confidence in the ability of my patient's condition to be addressed properly by physicians and their treatment plans

4. In order for you to contribute data from your patient to a registry, the following is necessary:
 - a. assurance that the collection of the data will contribute to the treatment of my patient
 - b. assurance that the collection of the data will contribute to research on the prevention, diagnosis, and/or treatment of the disease my patient has
 - c. assurance that the collection of the data will not only contribute to the benefit of my patient but also to the benefit of other patients

Section B. Registry-specific Questions

1. Have you or your organisation used a patient registry in the past?
 Yes No

2. If yes to question 1, please identify the patient registry(ies) and the reason(s) for your use of it/them:

Registry Name	Reasons for Its Use

3. If yes to question 1, were you satisfied with your use of the registry(ies)?
 Yes, please explain No, please explain

4. Informed consent should be required for entering information into the registry?
[multiple responses are possible]
- a. for the patient's doctor/clinical information Yes No
- b. for the patient's genetic information Yes No
- c. for the storage of the patient's blood/tissue samples Yes No
- b. informed consent is never needed for storing patient information Yes No
5. Informed consent should be provided by the
[multiple responses are possible]
- a. the patient only (if the patient is an adult)
- b. the patient only (if the patient is a minor)
- c. the patient and the parent/legal guardian (if the patient is a minor)
- d. the parent/legal guardian only (if the patient is a minor)
6. Information in the registry may be shared with [multiple responses are possible]
- a. doctors/clinicians and researchers in the patient's hospital
- b. doctors/clinicians and researchers in the patient's country
- c. doctors/clinicians and researchers in the European Union
- d. doctors/clinicians and researchers around the world
- e. the pharmaceutical/biotech industry
7. Informed consent is required for the sharing information in the registry with third parties outside the registry:
- a. always
- b. always if the information is made anonymous (cannot be traced to the patient)
- c. if the information is shared doctors/clinicians
- d. if the information is shared with the pharmaceutical/biotech industry
- e. informed consent is never required for sharing information in the registry
8. The patient and/or parent/legal guardian should have the right to withdraw his or her information from the registry
- a. always
- b. never
- c. other, please explain
9. The information in the registry should be under the ownership/custodianship of
- a. the patient
- b. the patient's organisation
- c. the patient's doctor/clinician
- d. a consortium of patients and doctors
- e. other, please explain
10. Which ethical principles should guide the development and use of a patient registry?
[multiple responses are possible]
- a. respect for (and protection of) the freedoms, privacy and confidentiality, and rights of all project participants, particularly the patients and families;
- b. security of all data and biological materials in their collection, storage, transfer, and access
- c. high quality of data included in the patient registry
- d. other principles, please list and/or explain

11. Which regulations and/or guidelines should be followed when developing a patient registry in the European Union:
- the European Directive on Implementing Good Clinical Practice (Directive 2001/20/EC);
 - the ICH Good Clinical Practice Guideline (E6);
 - the European Directive on Data Protection
 - other national regulations or guidelines, please list and/or explain
 - other European regulations or guidelines, please list and/or explain
 - other international regulations or guidelines, please list and/or explain

Section C. Respondent's Information

- A. Family Name: _____ Given Names: _____ Title: _____
- B. Organisation: _____
- C. My organisation is
- a patient organisation
 - a hospital/clinic
 - a research organisation
 - other
- D. Current Position in the Organisation
- Chairperson/President Secretary General Member Administrator
 Other
- E. Address: _____
- F. City: _____ State/Province: _____ Postal Code: _____ Country: _____
- G. Telephone 1: _____ Telephone 2: _____ Fax: _____
- H. E-mail 1: _____ E-mail 2: _____
- I. Skype: _____ MSN Messenger: _____ Yahoo Messenger: _____
- J. I agree to my name, title, position, organisation, and e-mail address being made public in the reports of the survey and on the nEUroped and partner websites: Yes No

*Thank you for taking the time to complete this survey.
The nEUroped Ethics Working Group will keep you informed of the results.
We hope to have your further involvement in the development of this important subject.*