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► **To cite this version:**

Nathalie Duchange, Sylviane Darquy, Diane D'Audiffret, Ingrid Callies, Anne-Sophie Lapointe, et al.. Ethical management in the constitution of a European database for leukodystrophies rare diseases.. European Journal of Paediatric Neurology, Elsevier, 2014, 18 (5), pp.597-603. <10.1016/j.ejpn.2014.04.002>. <inserm-00995366>

**HAL Id: inserm-00995366**

**<http://www.hal.inserm.fr/inserm-00995366>**

Submitted on 23 May 2014

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## **Ethical management in the constitution of a European database for leukodystrophies rare diseases**

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**Original article**

**Word count – 3735**

## **ABSTRACT**

**Background.** The EU LeukoTreat program aims to connect, enlarge and improve existing national databases for leukodystrophies (LDs) and other genetic diseases affecting the white matter of the brain. Ethical issues have been placed high on the agenda by pairing the participating LD expert research teams with experts in medical ethics and LD patient families and associations. The overarching goal is to apply core ethics principles to specific project needs and ensure patient rights and protection in research addressing the context of these rare diseases.

**Aim.** This paper looks at how ethical issues were identified and handled at project management level when setting up an ethics committee.

**Methods.** Through a work performed as a co-construction between health professionals, ethics experts, and patient representatives, we expose the major ethical issues identified.

**Results.** The committee acts as the forum for tackling specific issues tied to datasharing and patient participation: the thin line between care and research, the need for a charter establishing the commitments binding health professionals and the information items to be delivered. Ongoing feedback on the database, including delivering global results in a broad audience format, emerged as a key recommendation. Information should be available to all patients in the partner countries developing the database and should be scaled to different patient profiles.

**Conclusion.** This work led to a number of recommendations for ensuring transparency and optimizing the partnership between scientists and patients.

### **Keywords**

rare disease, leukodystrophy, health database, ethics committee, ethical management

## MAIN TEXT

Patient registries and databases are key tools for the development of biomedical and clinical research — particularly in the field of rare diseases which faces specific challenges tied to small patient populations and variations among disease sub-types. Gathering information on a large scale has considerable potential for helping to improve diagnosis and treatment, promote the development of clinical trials, and facilitate recruitment,[1, 2].

One aim of the EU LeukoTreat program ([www.leukotreat.eu](http://www.leukotreat.eu)) is to develop a supranational database geared specifically to leukodystrophy (LD) — the LeukoDataBase (LeukoDB). Collecting clinical data on LD patients will improve understanding of the natural history, epidemiology and genotype–phenotype correlations of these disorders. The challenge is to connect, enlarge and improve pan-European databases on LDs and other genetic diseases affecting the white matter of the brain. Addressing this challenge entails organizing the collection and management of clinical and biological data, including genetic information. The objective is to foster the emergence of innovative therapeutic strategies as part of translational research designed to accelerate the clinical application of fundamental research results.

LDs are a group of rare genetically inherited neurodegenerative diseases of the white matter and its main component, myelin. LDs predominantly affect young children but can also hit adults, causing cognitive deficits and potential loss of autonomy. The overall prevalence of LDs is approximately 1 in 10,000 of the population, with around 1,000 new cases every year in Europe. Despite great strides forward made over the past decade in terms of advance in each individual LD, there is currently still no curative therapy (see,[3,4] for review).

LeukoTreat has placed ethics issues high up the agenda by pairing the participating LD expert research teams with experts in medical ethics and LD patient families and associations. The overarching goal is to apply core ethics principles to specific project needs and ensure patient rights and protection in research addressing the context of these rare diseases. The ethical approach was integrated right from the project's outset to handle the sharing of medical information at a European level in the context of LD patients, which are a heterogeneous population characterized by variable clinical expression and age of appearance. This approach also considers the harmonization of information and consent on existing practices in national databases.

This paper looks at how ethical issues were identified and handled at project management level during the project lifetime.

## **SYNERGY BETWEEN AN ETHICS COMMITTEE AND AN ETHICS RESEARCH GROUP**

Before starting LeukoTreat, the proposal first received approval from the EC ethics review board, which is an integral component of the research evaluation procedure under FP7,[5]. The EU report singled out the plan to form a project-long ethics committee as a positive. Indeed, a stand-out feature of LeukoTreat was that it attached a LeukoTreat Ethics Committee (LEC) to the ethics research group involved in the project.

The LEC is composed of two categories of members: project members (clinicians and the ethics research group) and independent non-project members, including international experts in medical ethics, human sciences and law professionals as well as representatives of patient organizations. The LEC was put together in accordance with EU recommendations for ethics review panels,[5]. The LEC is dedicated to the LeukoTreat project and is thus a separate entity to Institutional Review Boards (IRB) or Research Ethics Committees (REC) whose role is to review research proposals involving humans. The LEC is responsible for the ethical management and follow-up of the project during its lifetime. Its role is to help identify specific issues and facilitate discussion and awareness among project partners, especially those involved both in care and research. The LEC is a forum for discussion and debate: one of its main objectives is to offer guidance to LeukoTreat partners on the issues addressed in the project and on other issues that the Committee may identify over the course of the project. One of the LEC's first tasks was to produce recommendations and documents framing the database. Together with the ethics research group, the Committee carried out evaluations in the existing national-level procedures with a dual objective: 1) to elaborate ~~a core charter~~ rules governing data-sharing within the database, and 2) to harmonize information and consent documents.

The work was performed as a co-construction between health professionals, ethics experts, and patient representatives relaying patient expectations. The standpoints and expectations of patients and families were also concurrently investigated via a survey led with French families participating in the annual meeting of the European Leukodystrophies Association (ELA), where 55 questionnaires were returned and analyzed (unpublished results). This approach resulted in the production of a charter defining the binding commitments and responsibilities of health professionals in terms of the preservation, use and sharing of participants' data. Based on international texts and recommendations issued by international organizations,[6-10], the charter develops the main principles on data privacy, regulation of potential value and the exploitation of data, as well as issues tied to consent, information and release of results. The charter anchors transparency as a core functional requirement and an

essential tool for answering patients/families' questions on individual elements included in information and consent documents. Indeed, McCormack *et al* highlighted that a particular concern and possible source of anxiety for patients and families is ownership of the registry/database and the data contained, as it defines who controls how the data is used,[11]. The charter is accessible on the dedicated LeukoTreat website (<http://www.leukotreat.eu/leukodatabase-ethics.php>).

## **DATA SHARING IN LEUKODB**

The primary concern of the LEC was to establish ethical rules governing the sharing of data. The database gathers sociodemographic and medical data extracted from patient records, including biological, radiological, electrophysiological data, genetic studies and cognitive evaluations. The data is collected and processed in LeukoDB by the referent Clinical Centers in charge of the patients. In the context of biomedical research, the aim of building a European database is to gather data for the largest number of patients in order to optimize:

- epidemiological knowledge on the various forms of the disease,
- genotype–phenotype correlation,
- knowledge of the natural history and evolution of these diseases,
- the development of therapeutic approaches and recruitment in future clinical trials.

Ethical principles are defined in LeukoTreat to ensure that each participating entity in the different countries has obtained approval from their local data protection and ethics authorities and guarantees the same level of data protection and security, in accordance with Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995,[6] on the protection of individuals with regard to the processing of personal data. -Confidentiality is ensured in accordance with the right to privacy of life, as defined by the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine,[7]. In LeukoDB, data is secured and cannot be used to stigmatize and/or discriminate the people concerned, in accordance with the International Declaration on Human Genetic Data,[10]. Data for research purposes is coded and rendered anonymous for researchers, i.e. it is impossible to identify an individual participant. Only the physicians in charge of the patients can combine clinical data with personal data. The data is accessible to researchers engaged in the LeukoTreat program. For researchers not engaged through the LeukoTreat agreement, access is provided through a specific request procedure. Publications on the basis of the data will always be anonymous.

Finally, participants have the right to access their personal data, in compliance with Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the

protection of individuals with regard to the processing of personal data,[6]. LeukoTreat members and partners are committed to respect these principles, as listed in the leukoDB charter, and must include them in the informed consent for participants.

## **SPECIFIC ETHICAL ISSUES IDENTIFIED**

### **A lack of frontier between care and research: what impact?**

The ethical framework governing biomedical research revolves around the dichotomy between care and research. However, in rare diseases like LDs, research and care are very often intertwined, as diagnostics or therapies are often only available at the research stage. Furthermore, the sense of urgency in diseases with no effective therapies is particularly conducive to therapeutic misconception,[12]. With the focus on implementing the European database on LDs in LeukoTreat (LeukoDB), the lack of a clear distinction between care and research has been a recurrent subject of discussions within the LEC.

The database is partly built from clinical data collected from patients as they present for care. It was thus recognized that confusion could occur for a number of patients/families being unaware that their medical data was being shared for research purposes, even though they had signed a consent form for this purpose. In practice, the only approach available to the patient or to his/her representative is to give consent for his/her medical information to be used for research purposes. Furthermore, medical acts such as lumbar puncture, blood tests or MRI can be realized at the same time for both care and/or research goals. The upshot is a risk of trivializing certain research procedures for clinicians and researchers — procedures that patients would then perceive and experience as acts of care. If the information given to patients does not make a clear distinction between the processes of care and research, then patients may find themselves in a situation where consent is not fully informed.

The LEC thus responded by addressing two main issues. First, what does it mean for a patient to participate in a database? Second, what do information and consent mean in this context?

Patient conceptions of biomedical research usually revolve around technical and drug trials involving interventions on human beings. The LEC and the research group both felt that the fact that patients' data would be used for research was an important message to deliver. Indeed, there was the feeling that patients did not have a clear enough perception about the need to be informed and protected in this kind of research that they do not consider research as there is no intervention on the human body. Care professionals reported that patients' main fear is that samples might be taken without being justifiable within a strict 'care' framework. The LEC thus concluded on the importance of communication to patients on all the aspects

and facets involved in the protection of human subjects in this kind of research.

**Participation in the database: what information?**

The challenge is to ensure that registry/database participants receive adequate information to make an informed decision. Participation in a database or a registry is somewhat different from participation in clinical trials. However, the LEC stressed the importance of obtaining individuals’ consent to use their health information for research purposes as a fundamental ethical consideration as regard to the principle of respect for persons participating in registries and databases,[1, 13, 14]. Debate as to what the consent process should be and what information content should be delivered is an ongoing process, as it depends on the context in which data and specimens (or links to specimens) is collected, stored and used,[15-17]. The LEC held dedicated meetings addressing the ethical issues encountered in the LeukoDB setting. Aside from well-established principles such as information on scientific goals, privacy and security, and rights to access, rectify and delete personal data, the LEC also made a number of specific recommendations as described below and presented in Table 1. These recommendations are made available to all database participants (patients and families) via the project website.

Table 1. Specific points considered by the LEC for patient participation in the database (LeukoDB)

- Information should help make the distinction between care and research
- Need for a charter establishing the binding commitments of health professionals
- At the time of consent, information should specify:
  - the nature and origin of data collected (‘genetic’ information should be specified)
  - the conditions for datasharing, and the existence of a charter
  - data preservation continuing *post-mortem*
- Age and mental ability should be taken into consideration by establishing different models of consent.
- After inclusion, ongoing information should be delivered:
  - regularly, on an annual basis,
  - including non-results information on the database and aggregated research results.
- Individual results should only be delivered by physicians, and only once the merits have been weighed up.



### *Data description*

The patient should be informed that data are derived from all elements included in his/her medical file and that biospecimens issued for care may be used for research, although specific consent is requested before taking each different kind of sample. A clear description of the data collected and shared within the database should be provided. For example, LeukoDB includes clinical data (the Leukoclinical database), mutation data (the Leukomutation database), and a listing of existing biospecimens most often collected during care. The database collates personal, socio-demographic, psychological, and familial history elements derived from consultation and from everyday life, plus biological and medical imaging data.

### *Length of data conservation*

For public health and scientific research interests, long-term data preservation is crucial, especially in rare diseases where data are scarce, heterogeneous, and take a long time to collect,[13, 14]. Each patient's data is precious information for studying the natural history of the disease and for research. Thus, patients should be informed about the interest of being able to conserve data with no limits on time. The LEC has integrated this key data conservation concern, as the choice was made for LeukoDB to keep data even after the participant's death, except if an opposite choice was expressed during the patient's lifetime. In this case, the irreversible anonymization of the data already collected and stored is considered. Although patient representatives participating in the LEC agreed on these points, they underlined that families and patients may have other wishes during their lifetime. Thus, the recommendation was that these questions should be clearly stated to patients/families at the time of consent in order to allow them to express potential opposition.

### *Adapting information to patients' clinical situations*

Given that a major percentage of LD patients are either minors and/or cognitively-impaired individuals, the LEC stated the necessity to adapt information on a case-by-case basis. EU regulations on minors or incapacitated adults unable to give legal informed consent require that all persons are given information geared to his/her capacity of understand it,[18], but there still appears to be room for improvement in the delivery of written information in pediatric research,[19]. The LEC established recommendations in terms of personalized information and template documents, but insisted on the fact that clinicians in reference centers should take ownership of these documents and adapt them to the individual situations they encounter. Recommendations were made to improve the involvement of children in

health research,[20]. Documents should be re-drafted in a simplified language, and drawings or cartoons may prove helpful for supporting the information given by the medical team and parents alike. Such a document for children illustrating the participation to the LeukoDB was produced in the form of a storyboard (available on the LeukoTreat website). For patients with partial mental impairment, the LEC proposed the development of simplified materials to complement the document submitted to the legal representative. In addition, the LEC recommended that in all cases, oral information should be delivered adapted to the patient's profile.

Having the adolescent and their parents counter-sign consent is often considered an option. Furthermore, the LEC recommended that once when the minor becomes adult, they should be given the occasion to reconsider research participation, after first receiving exhaustive information.

#### *Patients already included in national databases*

The gathering of data at pan-European level raises the question of information for patients already included in the national databases. Is the initial consent signed for inclusion in national databases still valid for the transition to the pan-European database? The LEC proposed to examine existing information sheets and consent forms at national level. It was decided that if those were conform to the requirement criteria established by the LEC, then there was no need to have the participants sign a fresh consent. However, if the gap between the initial documents and the recommendations is judged too wide, a procedure should be launched to seek new informed consent. For the three countries responsible for starting the inclusions, i.e. Germany, Italy and France, the LEC arbitrated to validate that the initial consents were consistent with the new criteria. Two recommendations were made by the LEC: first, every patient included in the future should sign a harmonized consent according to the model established, and second, patients having signed initial consents should benefit from information about the evolution of the national databases enabling them to give properly-informed ongoing consent.

#### *Ongoing information*

For the autonomy principle to be effective and for participants to be able to continue their participation, they need to have access to information after the time of inclusion. It is logical to expect new elements to emerge over time, whether at the organizational, scientific or human level. Indeed, this is a condition for ongoing consent,[21], and is particularly important in long-term studies, as we previously emphasized for HIV cohort participants,[22].

Note that follow-up information also offers an opportunity to get patients involved in research and create partnerships with health professionals, as well as to increase the sense of community surrounding their disease. Patient registries and databases are of great importance to rare disease patients and patient organizations who are actively engaged and involved in their setting and development,[23].

Finally, giving ongoing information also offers a framework to respect the fundamental right of participants to withdraw from research at any time.

Thus, the LEC's recommendation was that all research shareholders, clinician-researchers, health professionals and patient organizations should collaborate on delivering regular information bulletins, at least one a year, via a newsletter released in paper-print and online at the dedicated LeukoTreat website and on patient organization websites. Printed documents are essential as they are the primary medium for communication in the reference centers, where the information content can be explained and expanded upon if necessary.

As to the content of ongoing information, the LEC stressed the importance of delivering general information on the database, its evolution (number of patients included, evolution of participation in different countries and centers, etc.), the scientific project developed, and any new orientations adopted — all of which is deemed 'non-results information',[24]. The newsletter should also integrate aggregated research results, once validated and written in an accessible form, with the whole process relying on the interaction with patient organizations. As concerns individual research results, the recommendation in Leukotreat was that they should only be communicated in a clinical perspective, leaving it to the physician to decide whether it was relevant to communicate them and whether the patient was ready and/or able to discuss their significance results and the potential incidence on their care,[25–27].

## **EXPERIENCES IN OTHER CONSORTIA**

Registries and databases gathering trans-national patient data are recognized as high priority tools in the field of rare diseases. However, their regulation is considered to be in its early stages in most European countries where legal requirements are not always the same,[23]. Most publications reporting on database management tend to focus on technical aspects, the way data is collected, data quality and use. The way ethical aspects tied to patients' rights and information are handled is rarely described in detail, even though some projects make ethical documents publicly available on their websites. This is the case for the database for primary immunodeficiencies developed by the European Society for Immunodeficiencies (ESID),[28]. The documents describe how to enter and access patient data in a secure decentralized way, the need for documenting centres to obtain permission from local data protection and ethics

authorities, and the duty to conform to European Directive 95/46/EC[6]. Patients are informed that data is shared between different centres and may be used for research purposes. Documenting centres must obtain patient informed consent before entering data. Models of patient consent forms are also available on their website. a paper by Holland *et al*,[29] on the Prader-Willi database describes the database objectives and organization scheme and underlines the need for ethical management and follow-up. The paper also stresses the importance of this kind of database for many researchers, thus implying the need to decide who owns the data, who has access, and for what research purposes. Bergin *et al*,[30] on the EpiNet epilepsy database, which gathers data from thirteen countries, points to how data transmission is regulated in other countries. Approval was granted by the relevant authorities in all thirteen countries from which data were transmitted, and in all cases the ethics committees and institutional review boards were satisfied that patient information was secure and confidential, that the encryption processes used in the transmission of the information were adequate, and that transmission of the data was justified.

The LeukoTreat project also relies on the principle of ethical approval by national committees but goes further to insist on the necessity to harmonize practices as far as is practicable and to harmonize the content of patient information collected in different countries for participation in the database. To achieve this objective, an ethics steering committee (the LEC) was adjoined to the project. This was considered an added value in terms of database management . For the LEC, it is important that participants in national databases are informed of the existence and purpose of data sharing between European countries and of the conditions under which data is shared and secured. We recommend that all these information items be made available on a public-access website. Emulating the European muscular Treat NMD network,[31], LeukoDB describes the responsibilities and engagements of the different stakeholders in a publicly available charter. We also propose reflexion on the provision of continuous information to participants to keep them up-to-date on the evolution of the database, the orientations of the research performed, and its results.

## **CONCLUSION**

This paper reports on experience shared by healthcare professionals, ethics experts and patient representatives on ethical issues management in the setting of a European database on leukodystrophies. The LeukoTreat Ethics Committee established at the outset of the 3-year project acted as a forum for optimizing ethical procedures geared to the rights and expectations of participants.

In this context of a database on rare diseases, patients and families are most often committed by conviction, leading to a strong participation, especially as the risks linked to participation appear low. However, as data are often derived from medical records, participants may be unaware that their data is being used for research purposes.

Given that therapies are mostly inexistent at the present time, research progress harbors great expectations, which means the information process must be thought out as a long-term process. The right to be informed after the initial time of consent (ongoing consent) is a key element, as participants may duly expect feedback. Ongoing feedback on the database, including delivering global results in a broad-audience format, thus emerged as a key recommendation. The delivering of information should be built on a partnership with patient organizations. This information should be made available to all patients in the partner countries developing the database and should be scaled to different patient's profiles.

The LEC recommendations help better organize and structure the information to be delivered, and to optimize the scientist–patient partnership that helps build efficient databases.

### **Acknowledgements**

**LeukoTreat ethics committee (LEC) members:** Lazare Benaroyo (University of Lausanne, Switzerland); Marie-Claude Blondeau (Leuko Reference Center, AP-HP, Bicêtre Hospital, France); Odile Boesflug-Tanguy (Paris Diderot University, Robert Debré Hospital, France); Ingrid Callies (Paris Descartes University, France); Jean-Christophe Coffin (Paris Descartes University, France); Diane d'Audiffret (Paris Descartes University, France); Nathalie Duchange (Paris Descartes University, France); Gaël de Miomandre (ELA Belgium); Marc Dupont (AP-HP, France); Béatrice Godard (University of Montréal, Canada); Ella Haven (X-ALD Association, The Netherlands); Anne-Sophie Lapointe (VML Association, France); Boris Loeve (Paris Descartes University, France); Marie-Laure Moutard (AP-HP, Trousseau Hospital, France); Grégoire Moutel (Paris Descartes University, France); Roger Picard (Huntington Espoir, France); Sylvie Séguret (AP-HP, Necker, France); Marie Louise Vendeville (Leuko Reference Center, AP-HP, Robert Debré Hospital, France).

**Competing interests:** None

**Funding:** This work was funded by the EU program FP7 under the Leukotreat Grant Agreement no.241622.

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