

# Euro-Histio-Net 2008

## Minutes December 18<sup>th</sup>-20<sup>th</sup>, Paris

### Participants:

**Itziar Astigarraga (IA)**, BIOEF, Spain (Dec. 18<sup>th</sup>-19<sup>th</sup>)  
**Jean Donadieu (JD)**, APHP, France (Dec. 18<sup>th</sup>-20<sup>th</sup>)  
**Lisa Filipovich (LF)**, HS, USA (Dec. 18<sup>th</sup>-19<sup>th</sup>)  
**Riccardo Haupt (RH)**, IGG, Italy (Dec. 18<sup>th</sup>-20<sup>th</sup>)  
**Beth Anne Miller (BAM)**, HAA, USA (Dec. 18<sup>th</sup>-19<sup>th</sup>)  
**Milen Minkov (MM)**, CCRI, Austria (Dec. 18<sup>th</sup>-20<sup>th</sup>)  
**Ulrike Poetschger (UP)**, CCRI, Austria (Dec. 18<sup>th</sup>-20<sup>th</sup>)  
**Richard Price (RP)**, HRT, UK (Dec. 18<sup>th</sup>-19<sup>th</sup>)  
**Abdellatif Tazi (AT)**, APHP, France (Dec. 19<sup>th</sup>)  
**Stefaan Van Gool (SVG)**, Leuven, Belgium (Dec. 19<sup>th</sup>)  
**Leen Vangeebergen (LV)**, Leuven, Belgium (Dec. 18<sup>th</sup>-19<sup>th</sup>)  
**Johannes Visser (JV)**, Leicester, UK (Dec. 18<sup>th</sup>-20<sup>th</sup>)

**Mario Drobics**, IT Company, Austria (Dec. 19<sup>th</sup>)  
**Christope Guitar**, IT Company, France (Dec. 19<sup>th</sup>)

**Eva Schaefer (ES)**, PM Euro-Histio-Net (Dec. 18<sup>th</sup>-20<sup>th</sup>)

### December 18<sup>th</sup>

#### 1. Practical aims of the meeting

JD opens the meeting at 2.15 p.m. and welcomes all participants.

Main aims of the meeting are to conclude required modifications of the consortium agreement draft, to draw the shape for an international data base, to agree on a minimal data set, to define the items for the selection of an IT subcontractor and to agree on an agenda to achieve a common data collection system.

Questions concerning data management and monitoring, generating studies with the Euro-Histio-Net data and the project budget shall not be addressed.

#### 2. General organisation of the project

- **Presentation of backgrounds (JD):**

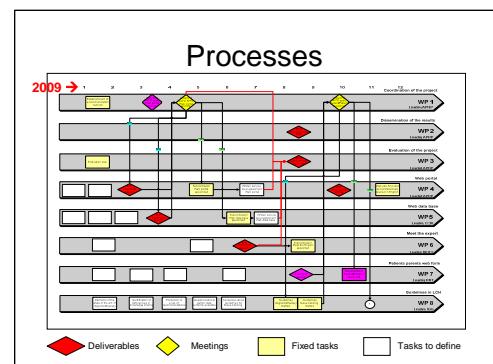
- High diversity of health care organization in different countries but several countries start **public health plans** to coordinate efforts for rare diseases at national level.
- **Rare diseases** have become a public health issue, due to the work of patients/parents associations and internet technology. Two EU directions are committed at EU level (DG sanco and DG research), orphan drug systems have been

set up (EMEA and COMP), rare diseases networks are supported and generic projects tend to ameliorate the situation (ORPHANET and EURORDIS).

- It has to be considered that **LCH** is not only a very rare disease but in addition is very specific due to its **various manifestations**. To date only 15 % of the LCH patients have been included in clinical trials; observational studies are useful. The Histiocyte Society has already managed to federate efforts, to improve communication and to define references. Nevertheless the commitment of public institutions and hospitals in the EU should be improved by means of Euro-Histio-Net.
- Annex I of the EU grant agreement gives a detailed description of the **objectives of Euro-Histio-Net** which aims to be a network of referent centres and therefore a tool to facilitate communication and research concerning the diseases.
- An amount of 72,000 EUR is available to realise the **IT part** of the project and will be administered by the CCRI.
- An amount of 80,000 EUR serves to pay a **project manager** for organising the work. The position will be located in Paris (AP HP).
- An amount of 36,000 EUR is available for **travel and other costs** and will be distributed according to Annex II of the EU grant agreement.
- Proposition of the following members for the **External Audit Committee**: S. Aymé, M. Egeler, Y. Le Cam.
- The **tasks of the project manager** will be: Collecting scientific information to report to the European commission, coordinating the work between the partners, the coordinator and the European commission, cooperating with the AP-HP administrator for the financial statements, delivering different support documents (time sheets/ financial reports etc.), convening meetings and writing minutes, ensuring that material on the web-site is up-to-date and relevant.

- **Presentation of timing and processes (ES):**

- In order to accomplish the deliverables in due time according to the time schedule defined in Annex I of the EU grant agreement, several **interdependences** have to be considered.
- Within January 2009, ES will send to all associated partners an **illustration of the processes** showing the time limits and the ways of decision defined in Annex I.
- The associated partners will be asked to give a **detailed description** of the work needed to fulfil their working packages and the planned workflows.



- **Questions and remarks:**

- **External Audit Committee (EAC):**  
A potential conflict to be a member of the EAC at the same time as a collaborating partner is not critical: The Executive Agency for Health and Consumers has agreed and the main task of the EAC is rather to survey the progress of the project than to give scientific or medical advices.
- **Further financial resources:** If there was a need of additional financing to realise the project or to maintain it, there would be different possibilities. An FP 7 grant can be applied for if basic scientific work will be done with involvement of laboratories. The international histiocytosis associations could be asked to help raising funds. Histiocytosis specialists could also be asked to do some fundraising. The amount needed has to be fixed in advance.

- **Project budget:** To inform the associated partners in detailed form about the sums which will be distributed and the dates of distribution as well as about the formal procedures of proving payments, a describing document shall be sent out by JD and ES.
- **Conclusion:**
  - **External Audit Committee – Members to ask:**  
Dr Ségolène Aymé (Director of orphanet)  
Prof R. Maarten Egeler (Paediatric hemato-oncology, University of Leiden, The Netherlands; former President of the Histiocyte Society; present President of the International Society of Paediatric Oncology),  
Yann Le Cam (Chief Executive Officer of Eurordis)  
[Decided unanimously by the associated partners.]

### 3. Consortium agreement

- **Objectives of the Consortium agreement (JD):**
  - Define the different levels of project participation as well as the relation and communication between the partners:
    - Coordination including managing and distributing the budget, reimbursing collaborating partners and reporting
    - Involvement as associated partner that is responsible for fulfilling working packages
    - Involvement as collaborating partner that participates to the project.
  - Define the entry of new Consortium partners.
  - Define the financial issues according to Annex I and II of the EU grant agreement: applicants' contribution, budget distribution in four parts and feasible additional contributions resp. amendments to the contract.
  - Find a solution for the enduring maintenance of the Euro-Histio-Net web portal.
- **Presentation of the draft (ES):**
  - **Partners:** 5 associated partners plus numerous collaborating partners to optimise knowledge input.
  - **Purposes:** Improve knowledge about the disease, create a web portal for LCH professionals and patient/parent organisations, improve quantity and quality of knowledge exchange, produce guidelines, set up an international data base.
  - **Duration:** The project is limited to 3 years. After that time, histio net has to be maintained. Long-term intension should be to extend histio net to other histiocytic diseases and to further international participation.
  - **Communication:**
    - Personal or paper with receipt acknowledgment (if „formal“ is required)
    - Any other communication like telephone, email, ... (if „formal“ is not required)
    - Any change of the Consortium address list has to be notified immediately.
  - **Governing bodies:** Coordinator, steering committee, advisory board and external audit committee
  - **Steering Committee:** Composed of associated partners; defined decisions plus numerous according procedures; meetings or telephone conferences; validly decides (with absolute majority), if 2/3 of members are present or represented
  - **Advisory Board:** Composed of all associated partners and collaborating partners.
  - **Technical provisions:** Fulfil EU contract and respect time schedule

- **Financial provisions:** Up to now defined by the grant agreement.
  - **Ownership of web portal and table structure (software):** For the future, ownership could be assumed by a new founded association. Full membership should be open to health professionals (histiocytic disorders), legal entities representing histiocytosis experts and legal entities supporting scientific development concerning histiocytosis
  - **Ownership of patient data:** Without prejudice to any property rights of patients concerned, ownership will remain the property of the data supplier. **Data entry:** Entry in histio net CRF without own data base or merging data from a compatible data base. Compliance with regulations for data inclusion will be reviewed.
  - **Access and user rights:**
    - Guidelines: public access
    - Meet the expert website: health care professionals
    - Patients/parents website: public access
    - Data base – patient data:
      1. Owners: unlimited
      2. Association members: on demand
      3. Third Users: formal request
      2. + 3. Supervised
 Owner of data can veto access and use of its own data.
  - **Data modification rights:** Each owner has the right to modify its own data; veto of surveying committee is possible in case of non-compliance with regulations of data inclusion.
  - **Confidentiality:** Legal regulations of data confidentiality have to be kept. Concerning own data, confidential will be what is designated by the owner to be confidential.
  - **Dissemination:** Dissemination has to be announced to the surveying committee. In any case where patient data is concerned, a prior formal notice to the owner of the data is required.
- **Questions and remarks:**
    - **Advisory Board:** If the Advisory Board shall vote and give binding advices, it should be composed of fewer members with high qualification. If it shall act on demand and give advices that can be considered by the associated partners, there is no need for a formal voting process.
    - **Owner, collector and supplier of data** are difficult formulations due to the fact that there could be various combinations and there should not be an obligation to guarantee access to the patient data to each patient or physician that is owner of patient data, but only an obligation to delete patient data in case of information referring to this. “Data controller” is the legal term used in UK for the one who must have access.
    - **Data modification:** For any modification of data, retraceability of the modifier should be secured.
    - **Data confidentiality and patient consents:** It has to be checked whether all data stored in the database have to fulfil the highest level of legal regulations of all participating countries or all data have to fulfil the level of the patient’s own country. In some countries, different consents are needed concerning participation in a clinical trial and saving data in a database.
    - **Quality control processes:** Data entry has to be monitored as well as data use, e.g. the question of publishing data of patients included in a clinical trial before the trial has been closed.
    - **Association:** In the future, the web portal including the data base (excluding the patient data) could be owned by an association. Big advantage of an association would be the much better possibility to raise funds, due to the extended long-term nature. Disadvantage for the first three years would be a possible conflict with the interests of the associated partners, concerning the fulfilment of the EU grant

agreement. The concept for an association should contain a clear structure of the level and the purpose of an international or worldwide histio net and should be considered when formulating the constitution of the association. In the long term, the association could be the Histiocyte Society or the group of those who contribute to the maintenance of the project.

- **Conclusions:**


- As far as possible, the **project shall be extended** to other histiocytoses and to international partners.  
[Decided unanimously by all participants of Dec 18<sup>th</sup>.]
- **Signature** of the Consortium agreement will be done by the legal authorities that have signed the EU grant agreement. In addition, the representatives for all associated partners will be listed on page 3 of the contract.  
[Decided unanimously by the associated partners.]
- **Advisory Board:** Delete the sentence concerning votes (page 8, 4.3).  
[Decided unanimously by the associated partners.]
- French **law** (page 8, 5.1).  
[Decided unanimously by the associated partners.]
- The **financial plan** is defined by the EU grant agreement (page 8, 6.1).  
[Decided unanimously by the associated partners.]
- **Special provisions** concerning ownership, data entry, access rights, user rights and data modification rights (page 10):  
The paragraph has to be reformulated completely: The 5 associated partners shall assume ownership of the web portal, the data base software and the table structures (use has to be guaranteed for Histiocyte Society clinical trials); the future association shall not be mentioned; “scientific committee” shall be replaced by “steering committee”.  
[Decided unanimously by all participants of Dec 18<sup>th</sup>.]
- **Consortium agreement:** Revised draft of the contract will be sent out by JD and ES mid January. If possible, the contract shall be agreed to be signed on the occasion of the LCH IV study group meeting in Vienna, March 20<sup>th</sup> 2009.  
[Decided unanimously by all participants of Dec 18<sup>th</sup>.]
- **Sustainability by means of an association:** Until mid May, BAM and ES will formulate a concept for an association that could secure the long-term maintenance of the project. The concept will be the basis for further discussions.  
[Decided unanimously by all participants of Dec 18<sup>th</sup>.]

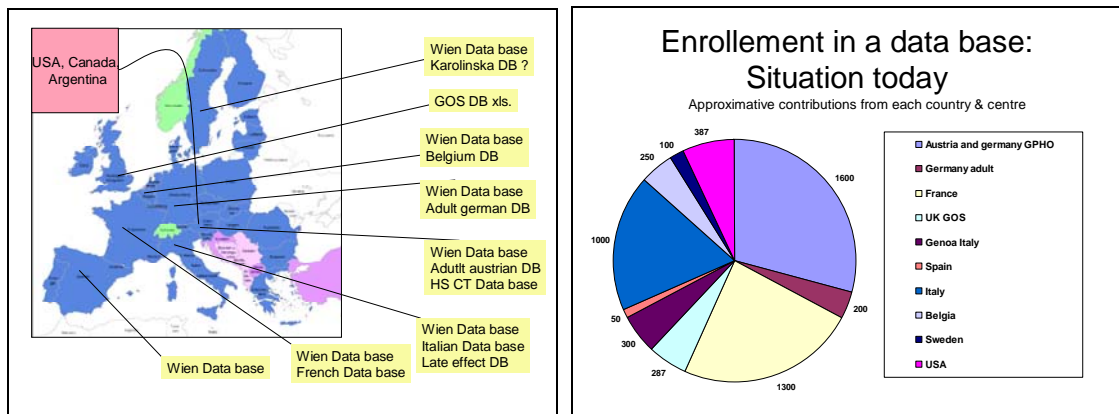
## December 19<sup>th</sup>

### 4. Web portal including database

- **Data base in Langerhans cell histiocytosis (JD):**

- In the best case, **monitored data collections** lead to a continuous process of medical care improvement: Statistic analyses of data collections enable definition of evidence based medical guidelines which help to improve treatments. The outcomes of clinical expertise based on more effective treatments can be a basis for further data collections.
- **Databases** are basically necessary to collect clinical experience and to allow for studies of epidemiology, natural disease history and therapeutic outcomes. Therapy may be evaluated by therapeutic trials as well as by observational studies.

- **Different purposes require different data:** For some kinds of studies there is a need of very simple, basic data whereas other approaches necessitate sequential data of different visits, data of long-term observations or very detailed data. LCH as a potentially multisystemic disease with various presentations is more difficult to describe than other diseases. A well elaborated and optimised database could be a swiss knife of clinical research in LCH, i. e. a very useful instrument. 
- **Situation of databases in EU:** There are a lot of different databases currently used in the EU in which almost 5,500 patients are registered, many of them twice. The data base systems range from single excel table systems to relational access data bases with 51 tables. One web based system is already realised in Italy, two more web solutions are in progress in Austria (HSCTCB) and France.



- Basis for a **common case report** form should be a general structure containing simple core data concerning demography to identify a patient, sequential data of each patient visit, examination data for specific purposes (e.g. CNS involvement) and therapy data.
  - An agreement on the **principle of subsidiarity** could help to solve the problem of varied commitments and capacities in different institutions or countries. Subsidiarity would mean to allow each partner to participate following its possibilities, interests and means within a defined frame and general structure of the common database. (Hematological involvement for instance is considered very differently in the EU databases. There is a range from a few items - commonly accepted as specific for a haematological dysfunction - up to several sheets containing comprehensive blood data.)
  - **Establishing a priority** for the data to be collected could define *mandatory* information, information to collect *with priority* due to its use for therapeutic evaluation and information *only for specific studies* for teams that are interested in detailed data.
- **Questions and remarks:**
    - **Mandatory data:** There should be an obligation for data entry in each mandatory field to force that the aspect has been considered (e.g. no 'collective' "no" for organ involvement). For all historic patients all mandatory data – including follow-ups and visits - should be entered to the new database.
    - **Data entry:** Raw data should be collected as far as possible to avoid the problem of future changes of limit definitions.
    - **Case report forms:** CRF depend on the purpose of the study and should therefore be specially designed and not defined in advance.
    - **Pseudonomisation:** Data shall be pseudonomised and not anonymised to ensure the possibility to add follow-up information to registered patient data. All fields for data

that have to be pseudonomised should contain a remark stating that these data will never be passed to anyone. Pseudonomisation has to be done systematically according to an approved procedure.

- **Integration of 'old' patient data:** The problem of differing past definitions can be solved by different ways, e.g.
  - prospect thinking by finding up-to-date definitions and accepting mistakes in former data (a note referring to this should be contained)
  - integrating only core data into the new system and preventing a solution to track former data.
- Key issue for the **quality of the database** is a good data monitoring.
- Some issues can be **regulated at IT level** (e.g. patient consent for clinical trials) by means of defining mandatory fields.
- If the existing data bases are retained, the **compatibility** of the different systems could allow for exchange of data.
- **Advantages of a common database:**
  - The more long-lasting and extensive the system the better fundraising can be done.
  - Especially for small databases, costs and efforts to maintain the system could be foregone if the common database was created in a manner that allows the use in a restricted way.
- **Imaging data (e.g. MRI):** The meet-the-expert area of the webpage should provide contacts to experienced radiologists for a consultation in difficult cases. Very big data volumes make the integration difficult due to the time needed to upload the images (most often, the data are sent on CD-ROMS) so all the imaging functionality will be optional.
- **Validity checks** should be integrated in the database. (If for instance a haematological involvement is declared, the system should automatically verify the entry of pathologic blood data.)
- **Units of data** should be asked for in mandatory fields to avoid incorrect data entry.
- **Organ involvement:** The definition of organ involvement should be given in the guidelines (paper: "basic definitions in LCH"). Therefore, only "yes/no" should be requested including a specification, if organ involvement is affirmed. To produce internationally accepted definitions, there should be a process of work-sharing. For each organ, all available literature should be reviewed, graded, categorised and summarised as a basis for scientifically established definitions.
- A **call for tender** following EU public market rules has to be launched for the selection of the subcontractors building up the web portal and its contents (in particular the web data base and the meet-the-expert tool). There is a possibility to choose different subcontractors for each part. For some parts, software solutions may already exist that can be bought.

- **Conclusions:**

- **Concept of the new database:** A catalogue of data shall be collected which will be very comprehensive. It will contain data defined to be mandatory for all users of the data base as well as data for special projects only. Case report forms will be defined on the basis of the principal catalogue and must contain all mandatory data. Definition of the CRF will be done by a project team responsible for a clinical or epidemiological study.  
[Decided unanimously by all participants of Dec 19<sup>th</sup>.]
- **List of mandatory data:** Saving of a patient registration will not be possible without information in the following fields.

Last Name  
 First Name  
 Date of Birth  
 Gender  
 Unique patient number (assigned by the system)  
 Agreement of patient to store data according to national law  
 Date of diagnosis = date of biopsy OR date of clinical diagnosis (describe basis of diagnosis)

**For all following information: Yes, No or Not available.**

LCH  
 HLH  
 Erdheim Chester  
 Juvenil Xanthogranuloma  
 Rosai Dorfmann  
 Other histiocytosis

Date of the initial evaluation

Organs involved: **For all following information: Yes, No or Not available.**

Bone  
 Skin  
 Lung  
 Liver  
 Spleen  
 GI  
 Hematology  
 Pituitary  
 CNS  
 Soft tissues  
 ENT  
 Genital mucosis or anus  
 Mouth  
 Others; if "other" specify

Therapy:

Treated/Not treated

If treated: Treated following study protocol (specify) / Not treated following study protocol

Follow-up (Recommendation: yearly):

Date of the visit

Status: Alive / Dead

If dead, date of death and specification disease or therapy related

If alive, disease status: Active disease / Non-active disease

If disease active: organs involved (see list)

Sequels: Yes / No

[Decided unanimously by all participants of Dec 19<sup>th</sup>.]

- **Catalogue of data for the database:** A catalogue of all data currently collected in EU databases concerning LCH shall be compiled, amended if necessary and concluded on the occasion of the LCH IV study group meeting in Vienna, March 20<sup>th</sup> 2009. The catalogue must be extendable.

Agenda to finalize this catalogue:

- Catalogue of data → mid January (Raw data as much as possible)
- Merging the 'LCHIV CRF' and the French proposal: MM, JD and ES until end of January
- Comments and adding of all meeting participants: in February
- Comments to all national LCH IV study coordinators: end of January
- Formal approval: March 20<sup>th</sup> in Vienna

[Decided unanimously by all participants of Dec 19<sup>th</sup>.]



- **Explicit standard definitions:** For the variables contained in the principle catalogue, a definition of the standard has to be available (e.g. what is diabetes insipidus, organ involvement, disease activity ...).  
[Decided unanimously by all participants of Dec 19<sup>th</sup>.]
- **Call for tender:** The call for tender can be based on a former document of Nicole Grois and has to comply with the EU regulations.  
[Decided unanimously by all participants of Dec 19<sup>th</sup>.]

## December 20<sup>th</sup>

- **Presentation of the outcomes – first summary (JD)**
- **Agreement on a first summarising document (Outcomes.ppt)**
- **Conclusions:**
  - Any **information** given under the Consortium agreement has to be given to all associated partners, important information will be given to all collaborating partners (page 5, 3.4 of the Consortium agreement).  
[Decided unanimously by all participants of Dec 20<sup>th</sup>.]
  - **Attachment 2** shall be deleted (collaborating partner); none of the collaborating partners will have to sign a document concerning confidentiality.  
[Decided unanimously by all participants of Dec 20<sup>th</sup>.]

JD closes the meeting at 11.30 a.m.

These minutes arise from the project *Euro-Histio-Net 2008 - A reference network for Langerhans cell histiocytosis and associated syndromes in EU* which has received funding from the European Union, in the framework of the Public Health Programme. Sole responsibility for the content of this document lies with the authors. The Executive Agency is not responsible for any use that may be made of the information contained therein.

