

Day one, presentation-session I
Christophe Bérout

How successfully set-up international collaboration and sharing? Lessons learned from the TREAT-NMD experience.

Christophe Bérout (INSERM U827, France)

TREAT-NMD (Translational Research in Europe – Assessment and Treatment of Neuromuscular Diseases) is a European neuromuscular network addressing the fragmentation currently hindering translational research for cutting edge therapies in rare neuromuscular diseases. The TREAT-NMD Work Package 4.2 purpose was to develop and manage patient's supranational databases towards cutting-edge therapies using the Universal Mutation Databases software (UMD). Two specific disorders have first been targeted as new genotype-based therapies were emerging: Duchenne Muscular Dystrophy (DMD) and Spinal Muscular Atrophy (SMA). The primary objectives of this project were: feasibility, planning and recruitment of patients for clinical trials while the secondary objectives were: epidemiology, genotype-phenotype correlations, natural history of the disease, identification of disease modifiers and influence of treatments...

After an initial step to identify partners with existing national registries, various actors (patient's organization, clinicians, researchers and industry) have been contacted to participate to this international project. We first decided: a) to define database content (mandatory, highly encouraged and optional items); b) to identify Legal and Ethical issues related to the development of these databases and make recommendations to partners in order to obtain the appropriate approval/agreements at national levels and c) to set-up "Curators' Training Courses" to insure an homogeneous quality of data. In parallel, a TREAT-NMD patients' registries brochure has been written and translated in various languages to insure the proper information and participation of patients.

Since the beginning, this project has been receiving an unexpected high level of interest and support from around the world. We have thus moved from a EU to an International project with more than 30 countries involved by December 2009. This has been made possible because of: a) the precise definition of goals and database contents in agreement with international legal and ethical issues (participation of layers and the Ethics council); b) the formation and involvement of curators encouraged by a yearly "curators training course" as well as various meetings; c) the definition of a charter and the establishment of an oversight committee (TGDOC) where all partners and collaborators are equally represented; d) a close collaboration with partners from the industry (various clinical trial feasibility studies have already been performed); e) the flexibility of the database systems (each country can have its own system or use the TREAT-NMD toolkit); f) the flexibility of the database content (items can be added or removed after recommendation by the TGDOC) and an easy data transfer procedure and g) the development of specific tools

made freely available to all partners (database software and quality data management system).

In order to protect national interests, only encrypted data are shared with the TREAT-NMD UMD global databases and patients can only be contacted at national levels. The TREAT-NMD global database website also display a limited number of aggregated data. In the near future, links will be established with biorepositories (WP4.1), the registry of outcome measures (<http://www.treat-nmd.eu/research/oms/rom/>) and clinical trial centers (WP5).

Based on this model, other global registries are currently under development for other neuromuscular diseases in collaboration with other networks.



Uniting Rare Diseases

Advancing Rare Disease Research: The Intersection of Patient Registries, Biospecimen Repositories and Clinical Data

Session I Standards, Informatics and Technology

Christophe Béroud
INSERMU827, Montpellier, France

Global Data Aggregation: Case Study/Treat-NMD



What is TREAT-NMD?

- A project funded by the European Union from 2007 - 2011
- Aims to help promising new treatments for various neuromuscular diseases get from the lab to the patient more quickly
- Not a research project but an “infrastructure” project
- Helps different expert centres collaborate better
- Creates the “tools” for clinical trial-readiness in the neuromuscular field
- Helps improve patient care worldwide



21 core partners organization



Imperial College
London





Patient registries: objectives?

- Clinical trials:
Feasibility, Planning, Recruitment of patients
- Research:
Epidemiology; Genotype-phenotype; Natural history of disease; Disease modifiers; Influence of treatments
- Health care:
Planning, Providing services and products
- Politics:
Lobbying, Decision making



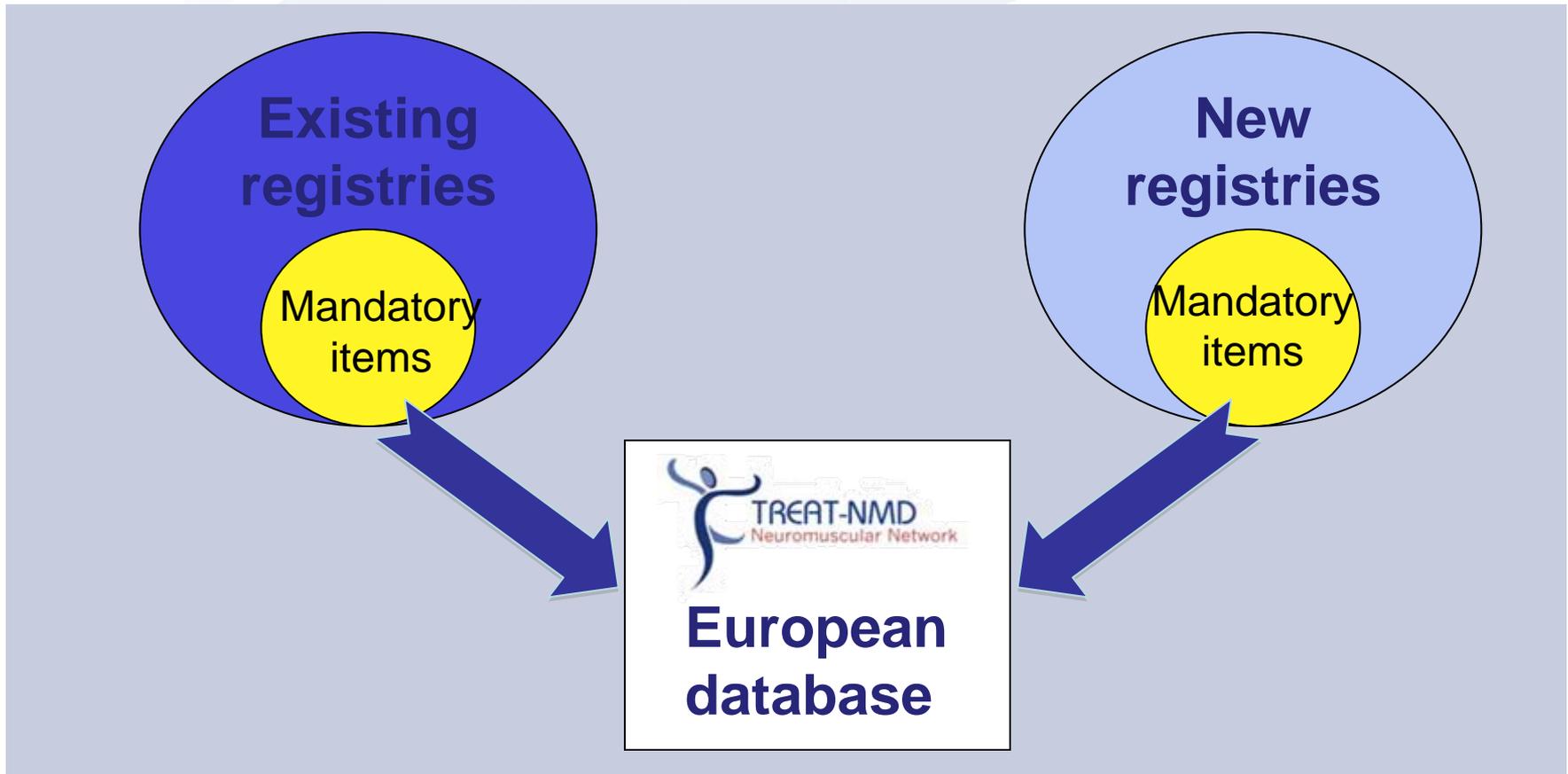
TREAT-NMD databases: first steps & milestones

- Defining the data content for each disease/gene
- Defining the regulatory and ethical framework
- Identifying and analyzing existing national registries
- Informing patients and clinicians
- Training of curators

- UMDs for SMA/DMD starting to operate (M12)
- UMDs for other muscular dystrophy genes starting to operate (M18)



TREAT-NMD patient registries: DMD and SMA





Registries on DMD and SMA: objectives

- Primary: Feasibility, Planning, Recruitment of clinical trials
- Secondary: Epidemiology; Genotype-phenotype; Natural history; Disease Modifiers; Influence of treatments; Standards of care; etc.



Registries on DMD and SMA: content

Items must be

- simple and short enough to ensure participation
- detailed enough to be useful
- **harmonised** internationally
- **standardised** to allow a computerised data analysis:
 - a list of answers is proposed
 - free text is limited
- versatile enough to work with different modes of data collection (professional report, patient report)



SMA patient registry: optional data / modules

- Biobanks
- Outcome measures
- Quality of life
- Standards of care
- Socio-economical consequences of the disorder
- Additional modules should be developed and included!



Data protection in the EU

- EC directive 95/46/EG; implemented by national legislation: very similar level of data protection within the EC!
- Personal data are protected; less requirements for (irreversibly) anonymized data only
- Principles: accuracy of data, minimization of data
- Highly recommended: pseudonymized (encrypted) data
- Required: informed consent

Legal advice by S Geismann and C Roy-Toole!



Legal/ethical best practice for registries

- Feed-Back to the patients
- Possibility of data withdrawal
- Informed consent
- Pseudonymized (encrypted) data
- Frequent updates of data
- Governance and Oversight

Web site

Yes

Yes

Yes

6 months

TGDOC

TREAT-NMD registries will adhere to these principles, which are documented in the charter



Patient registries: national curators

- Collect the data in each country
 - from the professionals (geneticists, physicians)
 - from the patients (self-report)
- Genetics: mutations of SMN1 gene & copy number of SMN2 gene (use the **international mutation nomenclature**: standardization)
- Validate the genetic & clinical data in order to maintain **high-quality** / accurate data
- Feed the medical data into the national and global databases



TREAT-NMD Global Databases Oversight Committee

TREAT-NMD Ethics Council

TREAT-NMD Clinical Trial Coordination Centre

TREAT-NMD Global Database Coordinators

Patient organizations

National registries

Excluded: Industrial partners

Current TGDOC members



Hanns
Lochmüller



Christophe
Béroud



Anna
Ambrosini
(temp.)

Pat Furlong



Sylvie
Tuffery-Giraud



Peter
Van den Bergh



Violeta
Mihaylova



Petr
Vondráček



Jaana
Lähdetie



Sarah
Baumeister



Veronika
Karcagi



Filippo
Buccella



Shin'ichi
Takeda



Anna
Kaminska



M. Rosário
dos Santos



Eduardo
Tizzano



Ian
Murphy



Thomas
Sejersen



Jan
Verschuuren



Serap
İnal



A. Ayşe
Karaduman



Pascale
Saugier-veber



Vitaliy
Matyushenko



Jacqueline
Jackson



Vanessa
Rangel Miller



Kevin
Flanigan



Marie-Christine
Ouillade



Ria
Broekgaarden



Fabrizia
Bignami



Simon
Woods



Ian Max
Huxham



Pierre-Yves
Jeannet



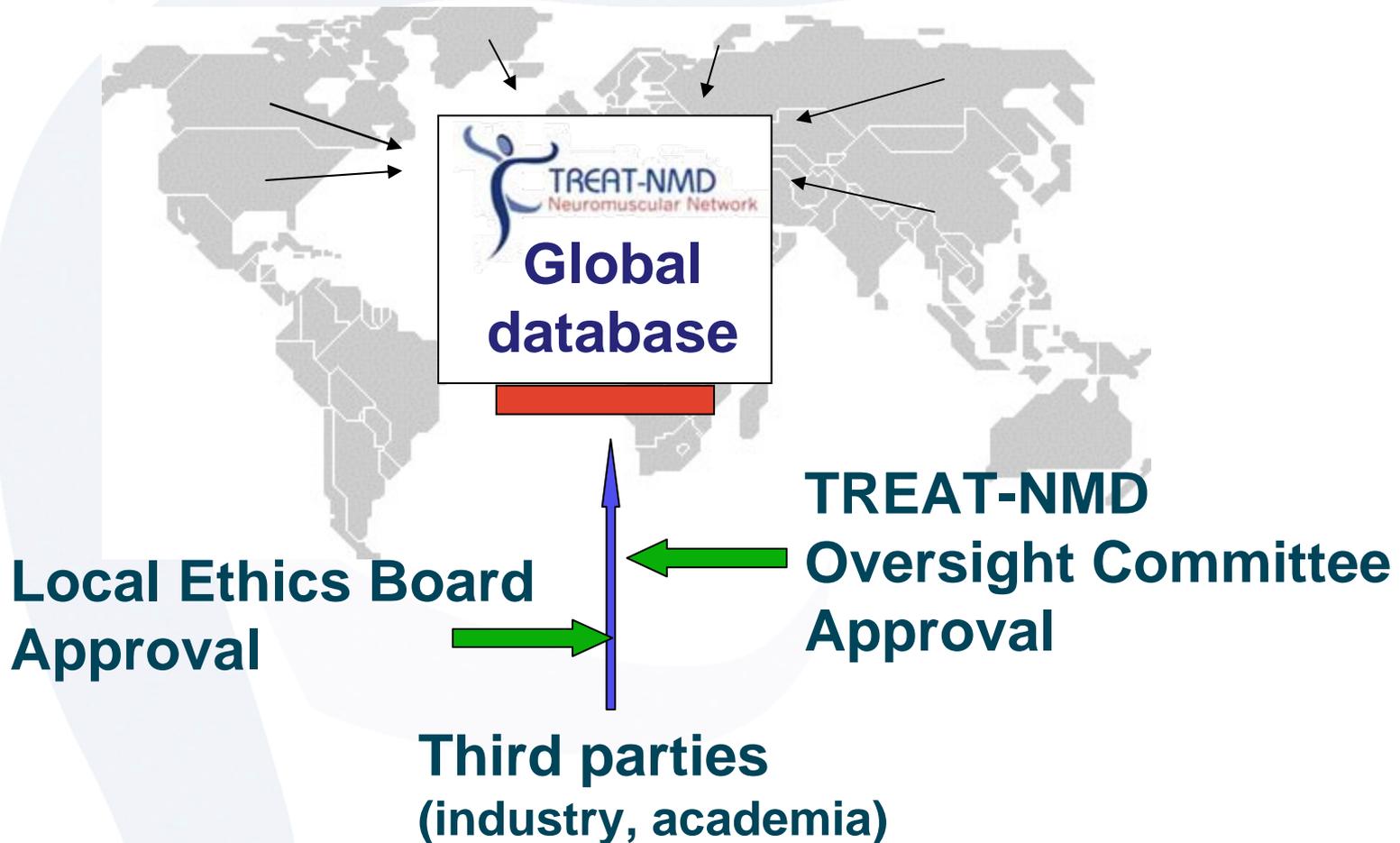
Janbernd
Kirschner



Nick
Catlin

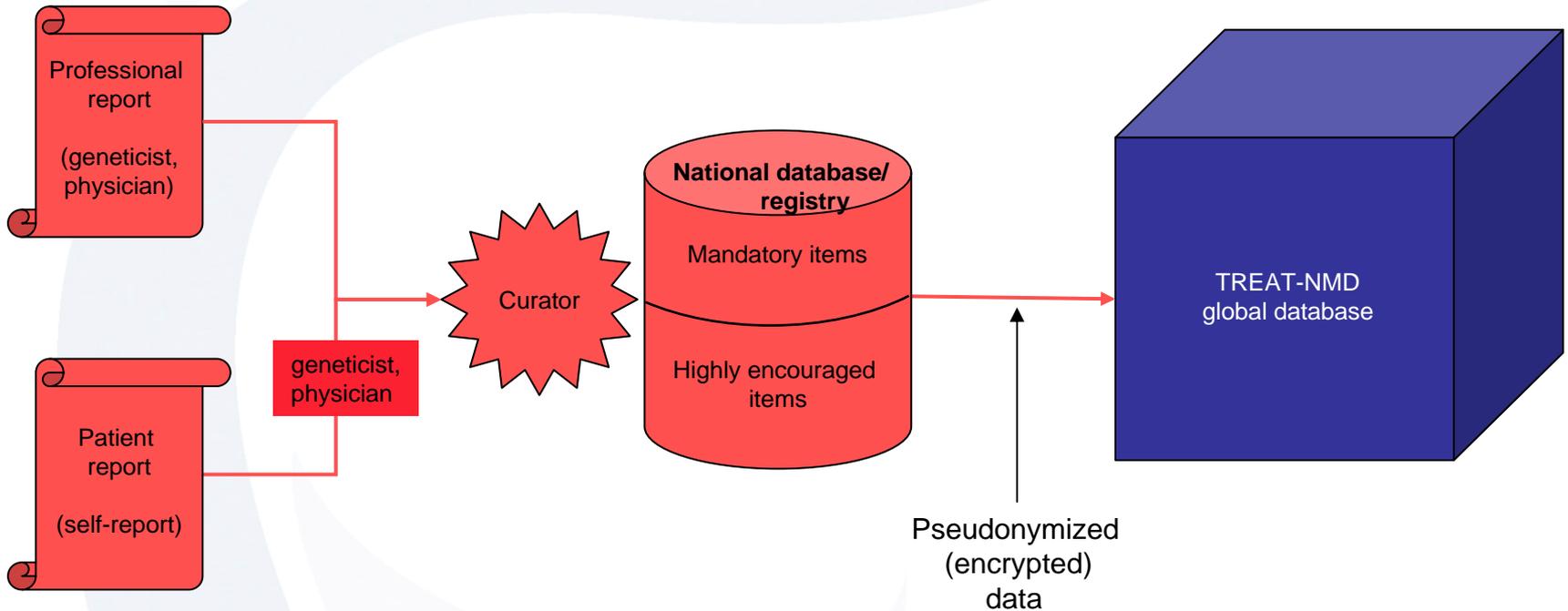


Third party access and participation





Data transfer

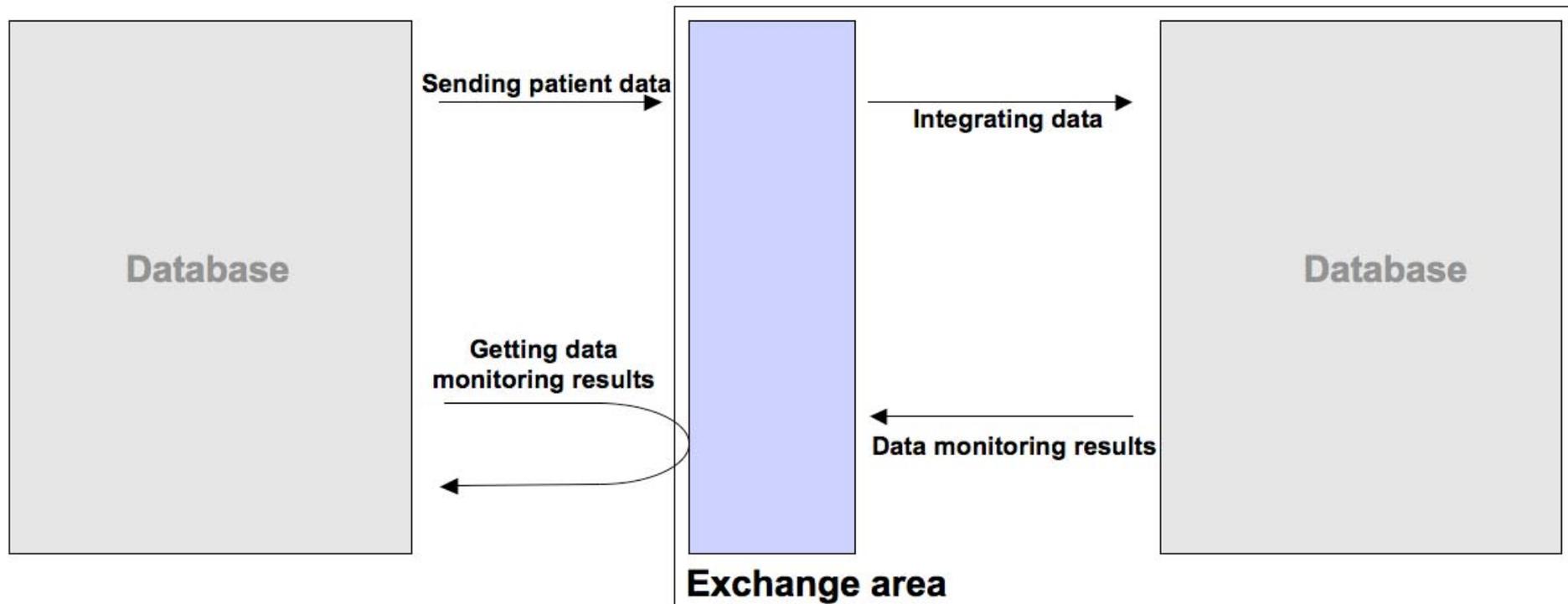




Data transfer

National registries

TREAT-NMD Global registries

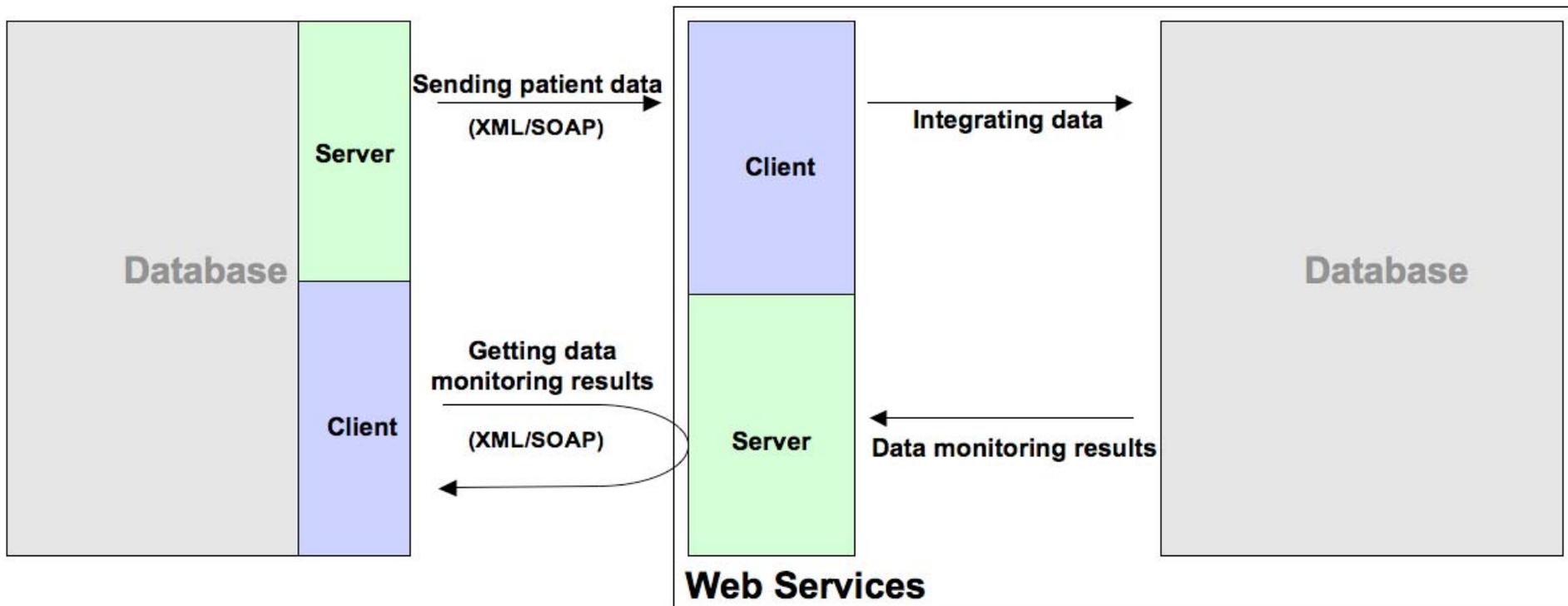




Data transfer

National registries

TREAT-NMD Global registries





Data transfer

- Always use the simplest procedure (sftp)
- Any type of structured data (.csv, .xml, .txt ...)
- Do not require specific skills
- Periodicity: responsibility of the curator (communication)
- Provide data quality checking tools
- The global database controls data (duplicates, quality)
- Send reports to curators



TREAT-NMD curators training courses

First Curators' Training Course (50 participants / 16 countries)

Define database content

Identify existing registries and potential collaborators

Imagine how a worldwide initiative can come to reality

Ethics, charter...

Second Curators' Training Course (60 participants / 20 countries)

Exchange data

Web site

TGODC

Third Curators' Training Course (92 participants / 25 countries)

Extend the network to new partners

Review / Improve quality data

Website

Extend the network to new diseases/genes





Relation with other databases

- Amendment to legal authorizations
 - What (items, objectives)
 - How (protection, withdrawal)
 - Who (ownership, updates)
- Different situations
 - From the global registry (encrypted data)
 - From a national registry (common identifier)*
- Clinical Trial Co-ordination Centre (Freiburg)



Enquiries from industry: the registry is working

AVI BioPharma, Inc., USA:

- Biopharmaceutical company specializing in the discovery and development of novel, *RNA-based drugs* targeting a wide range of important diseases, incl. DMD.
- *Phase 1 clinical trial of AVI-4658 successfully completed (21st Jan.):*
 - ***clinical trial was performed in the UK (national study)*** by members of the MDEX Consortium led by Prof. Francesco Muntoni
 - potential antisense oligonucleotide drug for the treatment of DMD by ***skipping exon 51 in the dystrophin gene***
(to restore reading frame in mRNA sequence, thus restoring dystrophin production)
 - certain types of *exon deletions* in the dystrophin gene are potentially treatable by exon 51 skipping



Enquiries from industry: the registry is working

Prosensa Therapeutics B.V.:

- Biopharmaceutical company specialising in the discovery and development of novel, *oligonucleotide-based drugs* targeting a range of important diseases, incl. DMD.
- *Early phase clinical trial on local administration of antisense oligonucleotides in DMD completed (published in van Deutekom et al., N Engl J Med. 2007; 357: 2677-86).*
- **Currently conducting a clinical trial on systemic administration:**
 - testing a potential antisense oligonucleotide drug for the treatment of DMD by **skipping exon 51 in the dystrophin gene**
(to restore reading frame in mRNA sequence, thus restoring dystrophin production)
 - certain types of *exon deletions* in the dystrophin gene are potentially treatable by exon 51 skipping



Collaboration is key...

“Solutions for patients affected by severe and rare diseases can only emerge if all the actors work together. It is not an option but a prerequisite. This is exactly what TREAT-NMD does: it creates the opportunities to make everyone involved move forward together.”

Dr Ségolène Aymé

Chair of Rare Disease Task Force
Director of Orphanet





Global partnerships







SMA patient registry: registration form

- Personal data of patient (name, date of birth, contact details)

Part I of questionnaire: mandatory items

- Diagnosis (SMA / other)
- Current best motor function (sitting with/without support/walking)
- Best motor function ever achieved
- Wheelchair use
- Use of feeding tube (gastric/nasal)
- Scoliosis surgery



SMA patient registry: registration form

Part II of questionnaire: highly encouraged items

- Family history of SMA or similar symptoms
- Use of ventilation device (non-invasive/invasive)
- Pulmonary function test (FVC value)
- Registration in other SMA registries
- SMA subgroup classification



TREAT-NMD global databases: TGDOC

- Safeguards data access by third parties
- Decision within 14 calendar days upon receipt of the inquiry (streamlined review process)
- Signs confidentiality agreements upon request
- Develops a fee structure
- Protects interests of patients, national registries and TREAT-NMD
- Reports to the TREAT-NMD governing board and to the national registries annually