International networks and DMD registries

Hanns Lochmüller, Newcastle University

Why have a network?

- Rare diseases - no one country is enough
- To tackle issues that can be settled more effectively collaboratively than alone
- To provide a platform to support and accelerate translational research with opportunities for collaboration and cooperation
- To add value to the research aims of individual groups

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Collaborative NMD and RD research projects (from 2007)

TREAT-NMD

- 10M EUR "network of excellence" for rare inherited neuromuscular diseases

Neuromics

- 12M EUR research project on nextgen omics approaches to neuromuscular and neurodegenerative disease

RD-Connect

- 12M EUR RD infrastructure: central global hub connecting registries, biobanks and clinical bioinformatics

EUCERD Joint Action for Rare Disease

- Implementing RD policy and national plans across Europe

NMD-Chip

- High throughput sequencing (gene chips) for NMD diagnostics

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- Implementing care standards for DMD across Europe, in particular Eastern Europe

Rare Bestpractices

- Infrastructure for best practice sharing across rare diseases

SCOPE-DMD

- Clinical trial for antisense oligonucleotide exon skipping in DMD - Prosensa

BIO-NMD

- Identifying and validating pre-clinical biomarkers for diagnostics and therapeutics

LGMD2I, 2B natural history studies

- Collaborations with Jain Foundation and LGMD2I research fund

OPTIMISTIC

- Natural history and exercise therapy clinical study in myotonic dystrophy

SKIP-NMD

- Clinical trial for antisense oligonucleotide exon skipping in DMD - Sarepta

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International networks in neuromuscular and rare disease

RD Connect

IRDiRC
INTERNATIONAL
RARE DISEASES RESEARCH
CONSORTIUM

NeuroOmics

TREAT-NMD
Neuromuscular Network

IRDiRC

INTERNATIONAL
RARE DISEASES RESEARCH
CONSORTIUM

Co-operation at international level
to stimulate, better coordinate & maximise output
of rare disease research efforts around the world

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The EU: A major player in funding health research in rare diseases

- Over two decades of investment in the area
- Over € 430 million invested in current programme
- More than 80 collaborative research projects launched in FP7
- Continued strong investment through the next funding programme foreseen

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Research challenges related to rare diseases are too big to master alone

- Huge unmet medical needs for patients across the globe
- Scarce research resources
- Small patient populations
- Scattered knowledge
- Limited harmonisation of information and data

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IRDiRC – the International Rare Disease Research Consortium

- Harmonised research funding initiative launched by the European Union and US NIH – other countries invited to join
- Goals: Diagnosis for all rare diseases and 200 new therapies for RD – by 2020
- Governed by Executive Committee made up of representatives from each member organisation
- Now has 32 committed members from Australia, Canada, China, European Union, France, Germany, Ireland, Italy, Netherlands, Spain, UK, USA (+ others joining)
- Each member commits to spending min. 10 million USD over 5 years on research projects contributing to IRDiRC objectives
- Scientific input via 3 scientific committees (diagnostics, therapies, and interdisciplinary) and working groups consisting of experts from funded projects

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IRDiRC vision and 2020 goals in rare diseases research

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200 New Therapies

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Means to Diagnose Most Rare Diseases

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IRDiRC – basic principles

- Teams up public and private organisations investing in rare diseases research
- Research funders with relevant programmes >$10 million US over a 5-year period can join
- Small funders may form a group of funders
- Each organisation funds research its own way
- Funded projects adhere to a common framework

32 committed members

Europe

- E-RARE Consortium (EU)
- European Commission (EU)
- EURORDIS (EU)
- French Association against Myopathies (FR)
- French National Research Agency (FR)
- German Federal Ministry of Education and research (DE)
- Italian Higher Institute of Health Research (IT)
- Italian Telethon Foundation (IT)
- Lysogene (FR)
- Netherlands Organisation for Health Research and Development
- Prosensa (NL)
- Shire (IE)
- Spanish Carlos III Health Institute (ES)
- UK National Institute for Health Research (UK)

IRDiRC

INTERNATIONAL RARE DISEASES RESEARCH CONSORTIUM

Australia

- Western Australian Department of Health

China: BGI

North America

- Canadian Institutes for Health Research (CA)
- FDA Orphan Products Grants Program (US)
- Genome Canada (CA)
- Genetic Alliance (US)
- Mendelian Disorders Genome Centres (US)
- National Centre for Translational Therapeutics (US)
- National Cancer Institute (US)
- National Institute of Neurological Disorders and Stroke (US)
- National Institute of Arthritis and Musculoskeletal and Skin Diseases (US)
- National Institute of Child Health and Human Development (US)
- National Eye Institute (US)
- NORD (US)
- Office of Rare Diseases (US)
- Sanford Research (US)
- PTC (US)

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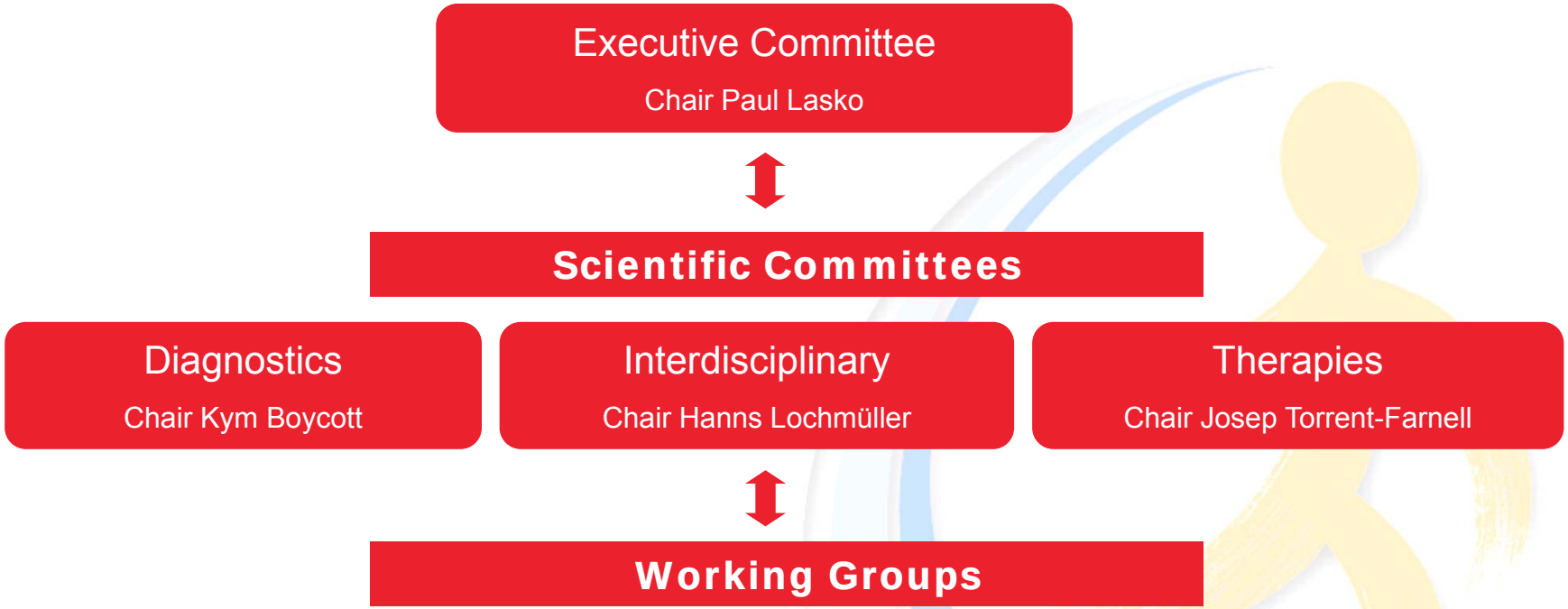
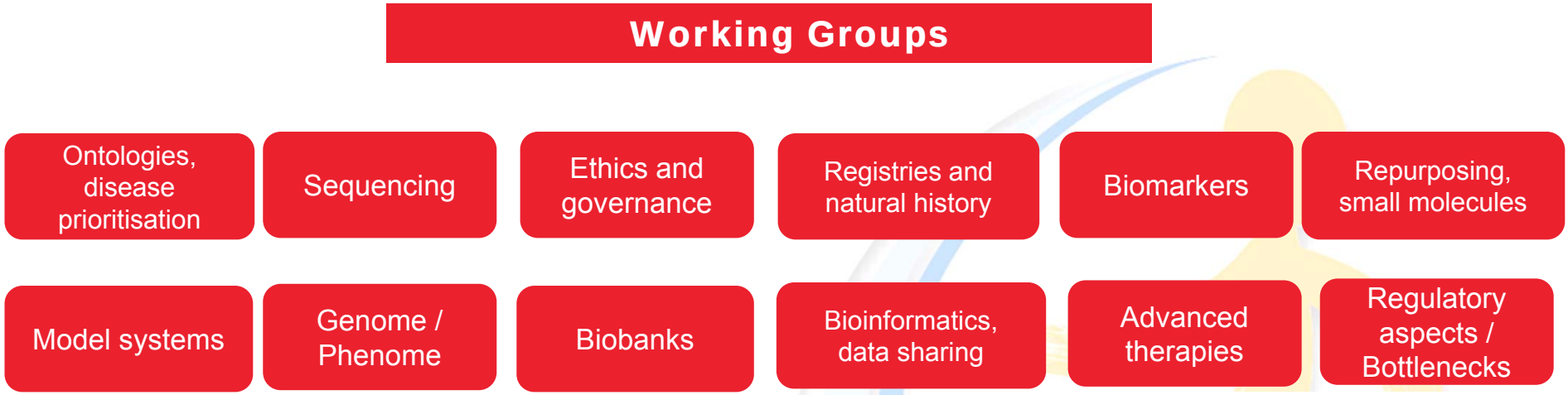
IRDiRC Governance Structure



IRDiRC Working Groups



FP7-funded SUPPORT-IRDiRC provides organisational support for Scientific Committees and Working Groups

Coordinator: Prof. Ségolène Aymé, INSERM

IRDiRC
INTERNATIONAL RARE DISEASES RESEARCH CONSORTIUM

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RD-CONNECT: An integrated platform connecting databases, registries, biobanks and clinical bioinformatics for rare disease research

(Hanns Lochmüller, Newcastle University, UK)

RD-Connect objectives

Overarching objectives:

- Contribution to the IRDiRC objectives of delivering 200 new therapies for rare diseases and means to diagnose most rare diseases by the year 2020
- Development of an integrated, quality-assured and comprehensive hub/platform in which complete clinical profiles are combined with -omics data and sample availability for rare disease research, in particular IRDiRC-funded research.

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RD-Connect objectives

- Harmonisation and development of common standards for databases and patient registries for rare diseases by collaborating internationally to implement common registry infrastructure and data elements across a federated system.
- Harmonisation and development of common standards and a common catalogue for rare disease biobanks that collect and provide standardised, quality-controlled biomaterials for translational research.
- Development of a suite of clinical bioinformatics tools, including data mining and knowledge discovery tools for analysis and integration of molecular and clinical data to discover new disease genes, pathways and therapeutic targets.

RD-Connect objectives

- Development of an integrated platform to host the processed data from Neuromics, EuRenOmics and future IRDiRC projects.
- Development of best ethical practices for balancing patient-related interests associated with rare disease research using databases/registries, biobanks and omics databases, engaging with relevant stakeholders, including patient organisations, clinical and research networks, legislators and policymakers and the pharmaceutical industry
- Development of a proposal for an expedient regulatory framework for linking of medical and personal data related to rare disease on a European and global level.
- Ensuring access to project results and broad and global impact in science, diagnostics and translational research including industrial collaborations.

Workpackage overview

WP1: Coordination

Hanns Lochmüller
Newcastle and TREAT-NMD

WP2: Patient registries

Domenica Taruscio
ISS and EPIRARE

WP3: Biobanks

Lucia Monaco
Fondaz. Telethon & EuroBioBank

WP4: Bioinformatics

Christophe Béroud
INSERM Marseille

WP5: Unified platform

Ivo Gut
CNAG Barcelona

WP6 Ethical/legal/social

Mats Hansson
Uppsala

WP7: Impact and innovation

Kate Bushby
Newcastle and EUCERD/ EJARD

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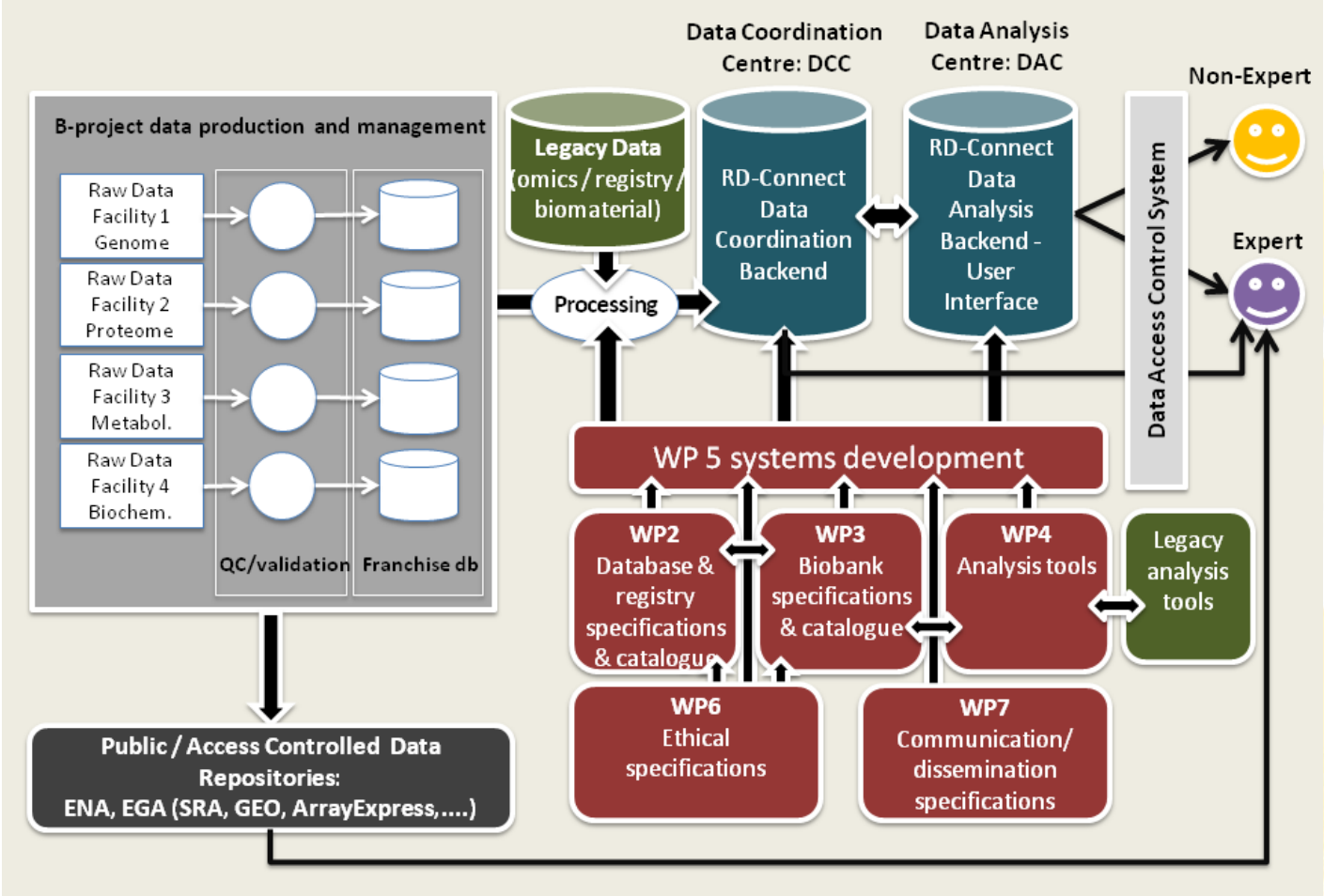
Platform and data exchange



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NEUROMICS: Integrated European Project on Omics Research of Rare Neuromuscular and Neurodegenerative Diseases (Olaf Riess, Institute of Human Genetics, University of Tübingen)

NeurOmics

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Neuromics overview

- FP7 funded, 5 year project involving 21 international centres, all experts in their field
- Working towards the IRDiRC goals
- Operating in close interaction with RD-Connect, EURenOmics and Support-IRDiRC
- Overall aim of improving patient diagnosis, care and therapy and facilitating more clinical trials for a group of 10 NMDs and NDDs in line with IRDiRC's goals
- Makes extensive use of the latest, cutting edge Omics technologies
- NEUROMICS expertise and findings may be transferrable to a wider range of related conditions

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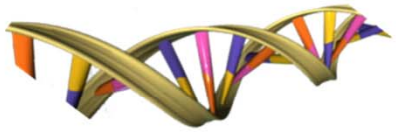
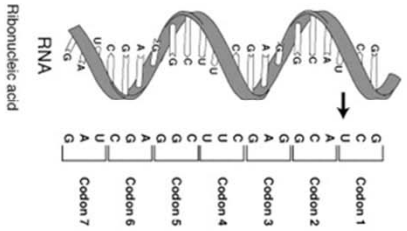
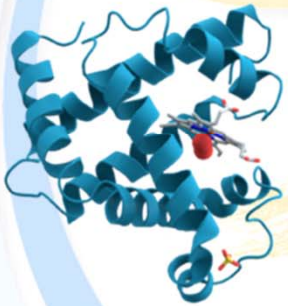
Omics technologies

Analysing the genome	Analysing RNA	Analysing the proteins made	Analysing metabolites
Genomics	Transcriptomics	Proteomics	Metabolomics







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Deep phenotyping –
extending phenotypes into much greater detail

- In Neuromics, Omics approaches will be combined with **deep phenotyping**
- This is a detailed, **comprehensive** and precise description of a patient's phenotype, describing its different components
- Allows more sensitive and useful **sub-grouping** of patients

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Diseases and disease groups

Sarah Tabrizi

Alexis Brice

Ludger Schoels

Thomas Klockgether

Brunhilde Wirth

Vincent Timmermann

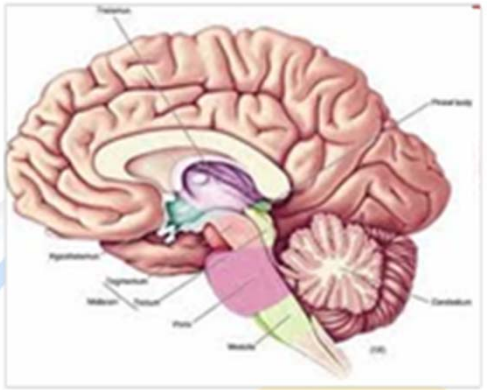
Hanns Lochmüller

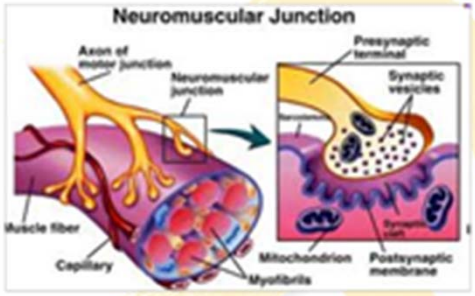
Francesco Muntoni

Gert-Jan van Ommen

Mike Hanna

- Huntington disease (HD)
- Fronto-temporal lob dementia (FTLD)
- Hereditery spastic paraplegia (HSP)
- Ataxias (ADCA, ARCA, CA)
- Spinal muscular atrophies & lower motoneuron diseases (SMA, LMND)
- Hereditary motor neuropathies (HMN)
- Congenital myastenic syndrome (CMS)
- Congenital dystrophies & myopathies (CMD, CMY)
- Muscular dystrophies (DMD, BMD, FSHD, LGMD)
- Muscular channelopathies (MCP)





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TREAT-NMD: a network of excellence for rare inherited neuromuscular disorders

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TREAT-NMD overview

- A “network of excellence” initially funded by the European Union (but with global collaborations)
- Aims to help promising new treatments for neuromuscular diseases make the transition from the lab to the patient
- Not a research project but an infrastructure project
- Creating the “tools” for trial-readiness in the neuromuscular field
- Helping researchers and expert centres collaborate better
- Improving patient care worldwide
- ***Sustained beyond 2011 as TREAT-NMD Alliance***

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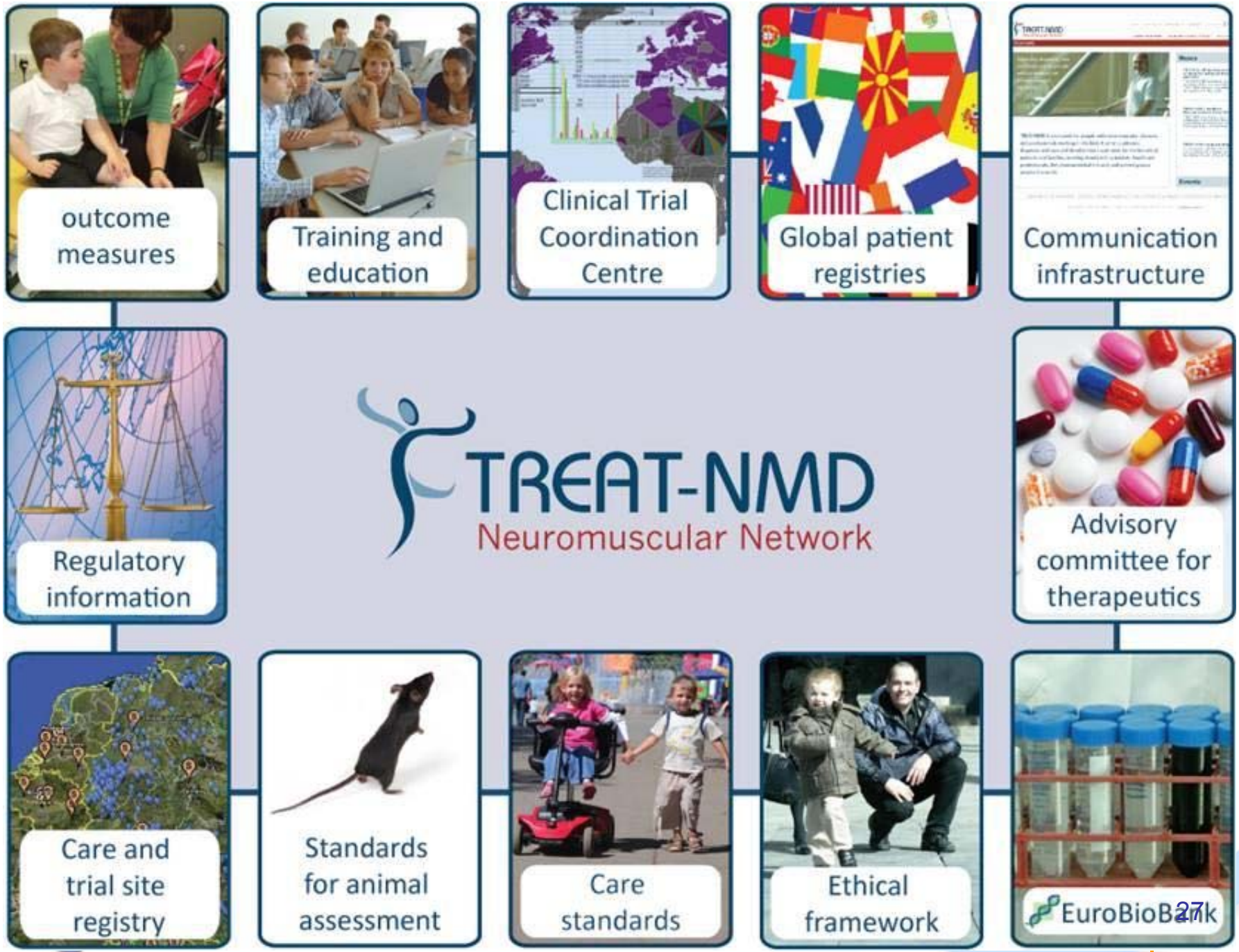

outcome measures
Training and education
Clinical Trial Coordination Centre
Global patient registries
Communication infrastructure
Regulatory information
TREAT-NMD
Neuromuscular Network
Advisory committee for therapeutics
Care and trial site registry
Standards for animal assessment
Care standards
Ethical framework
EuroBioBank

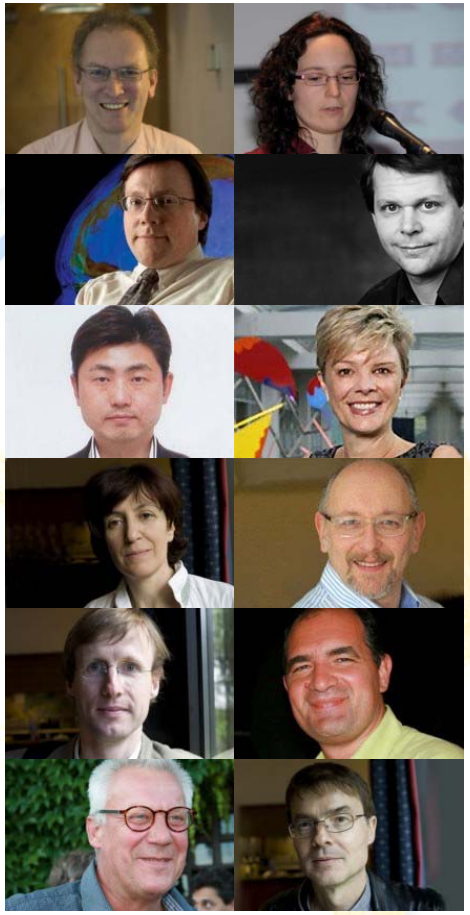
TREAT-NMD new developments

- 2007-2011: Network funded by the European Union

- 2012 onwards: TREAT-NMD Alliance funded through multiple funding streams and with global partners
  - Led by an elected Executive Committee
  - Supported by academic advisory board (“task force”) of NMD leaders
  - 3-year “action plan” of key areas where global collaboration is required
  - Newly funded research projects
  - New Alliance charter and membership
  - New focus on additional neuromuscular conditions

TREAT-NMD Alliance Executive Committee

- 12 members, global representation (Europe, USA, Australia, Japan)
- Clinicians, researchers and patient representatives
- Chair: Hanns Lochmüller, UK; vice-chair: Annemieke Aartsma-Rus, NL
- Monthly teleconferences
- New Alliance charter (September 2012)



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TREAT-NMD Academic Task Force

Membership

Membership of the new Alliance was opened in 2012.
Now:

- Individual members = 220
- Organisational members= 80
- Total = **300**

- www.treat-nmd.eu/membership

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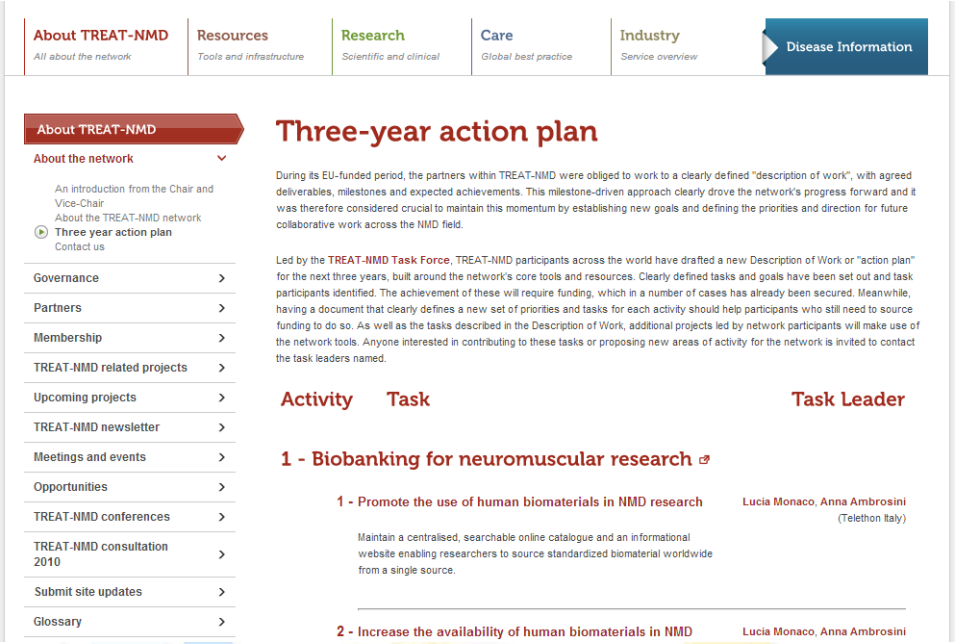
Three-year work plan

- Led by Task Force
- Designed to maintain progress by retaining a milestone- and deliverable-driven approach
- Split up into tasks which could seek individual funding
- Published on TREAT-NMD website



www.treat-nmd.eu/action-plan

Patient registries for trials: the TREAT-NMD model

- Standardized genetic and clinical data necessary for trial recruitment – “minimal” dataset for “maximal” uptake
- Many benefits to registered patients
  - Feedback on standards of care and new research developments
  - Feeling a sense of “belonging” to a broader community
  - Not being left behind as clinical trials develop
  - A link to the research community
- Many benefits to industry
  - Easy access to patient community
  - Clear concept of target market
  - Feasibility and planning of clinical trials
  - Recruitment of patients into clinical trials

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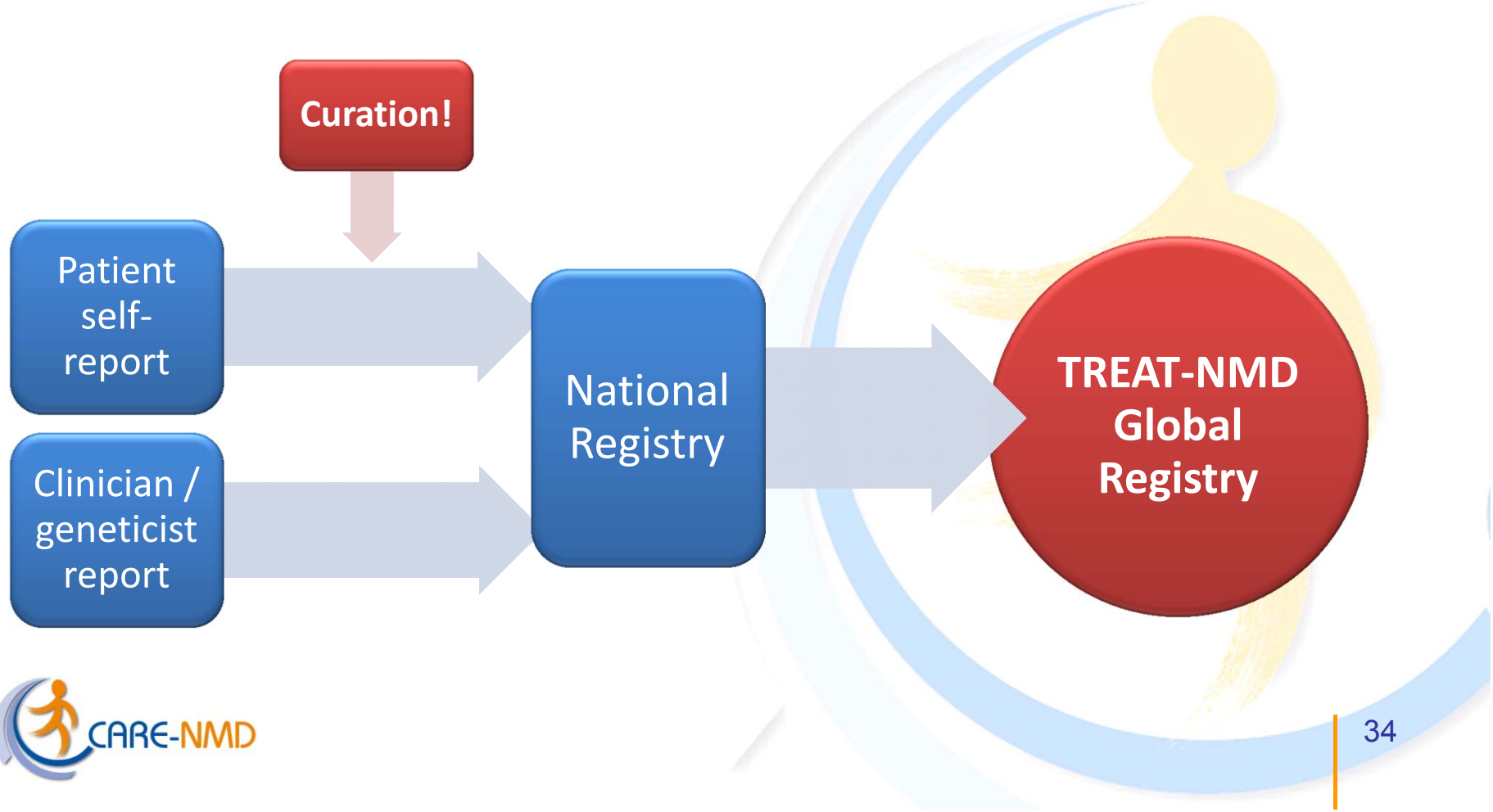
Patient registries for DMD



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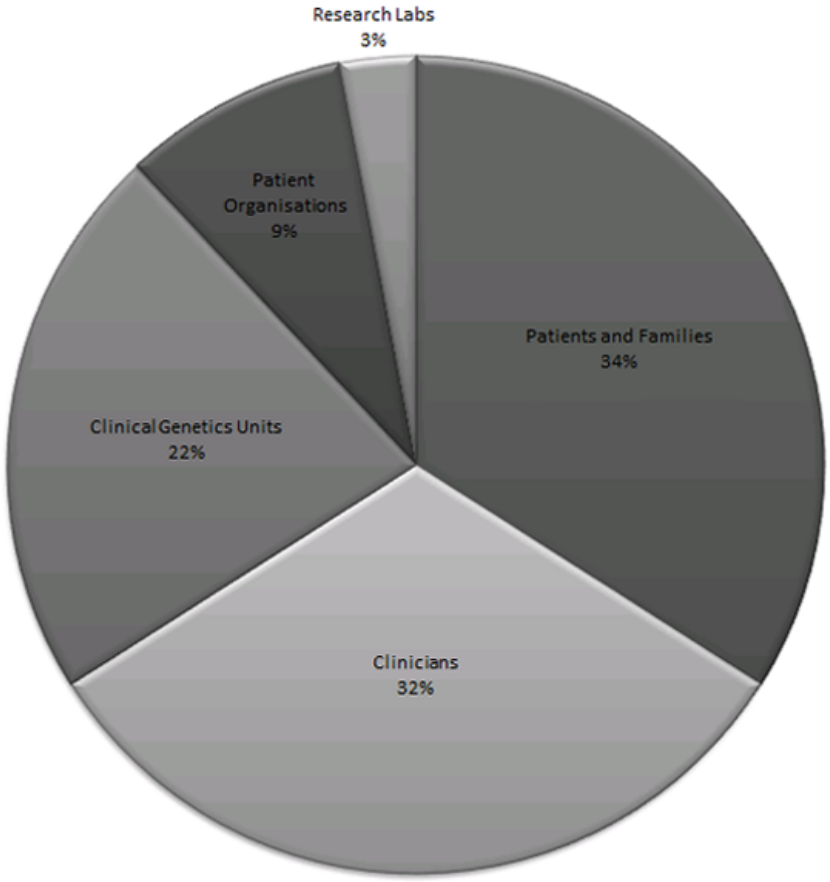
Types of data providers and data entry methods

a



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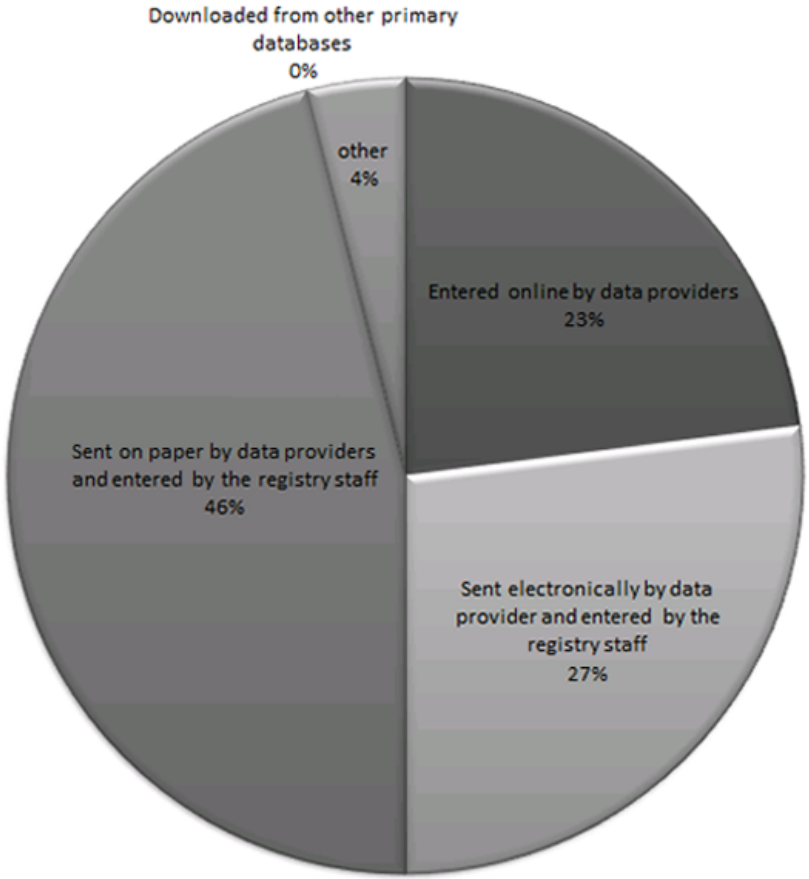

88% of the registries reported an annual update.

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TREAT-NMD patient registries

- Mandatory dataset and means to share core global data
  - Single entry point for information
- Interface with patients can be variable from country to country
  - Depending on local situation, involvement of clinical and patient groups, funding availability, size of disease group
- Focus on reliable information that will be needed for clinical trials
  - Strict curation of mutation data and annual training of curators
  - Mandatory annual update of data
- Ensure ethical and governance best practice
  - Regulated by TREAT-NMD registry charter
  - Oversight committee approves all registry requests

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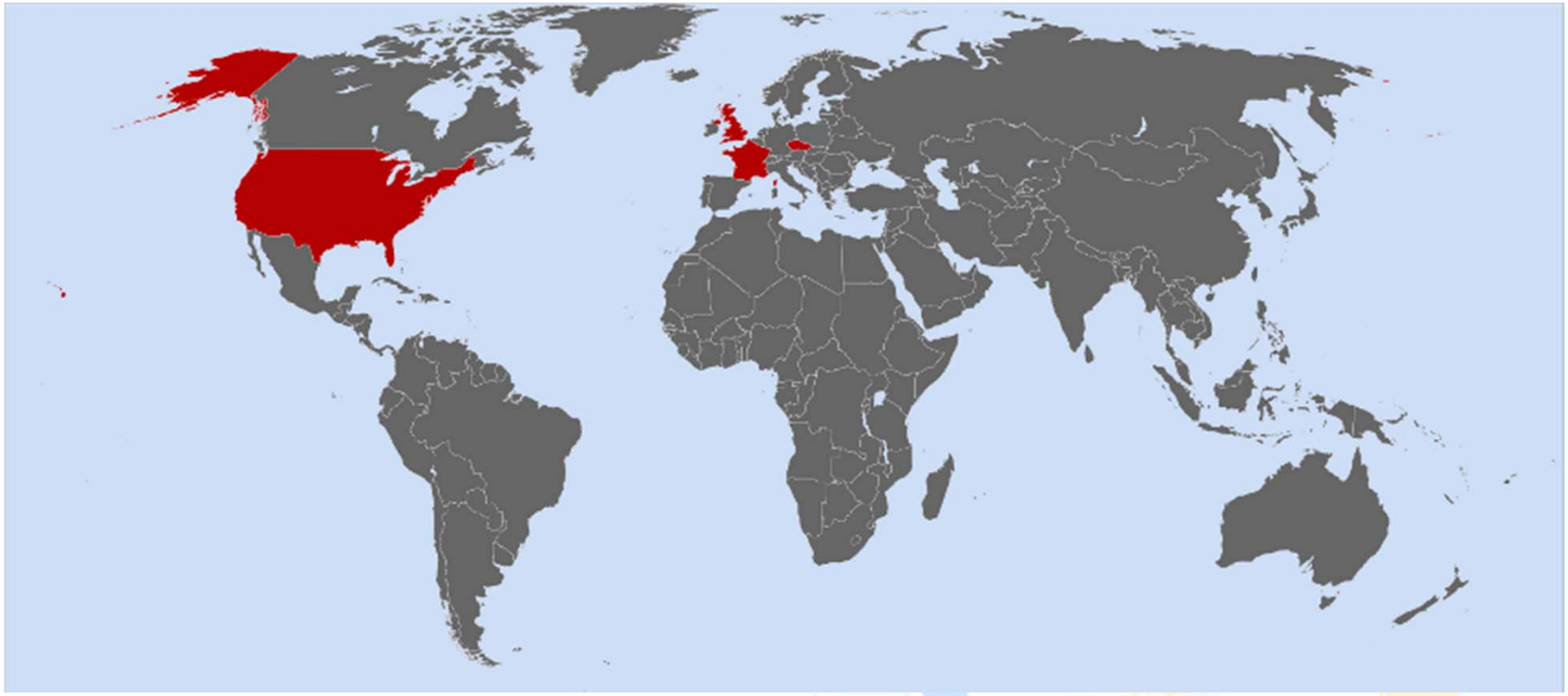
DMD Registries before TREAT-NMD



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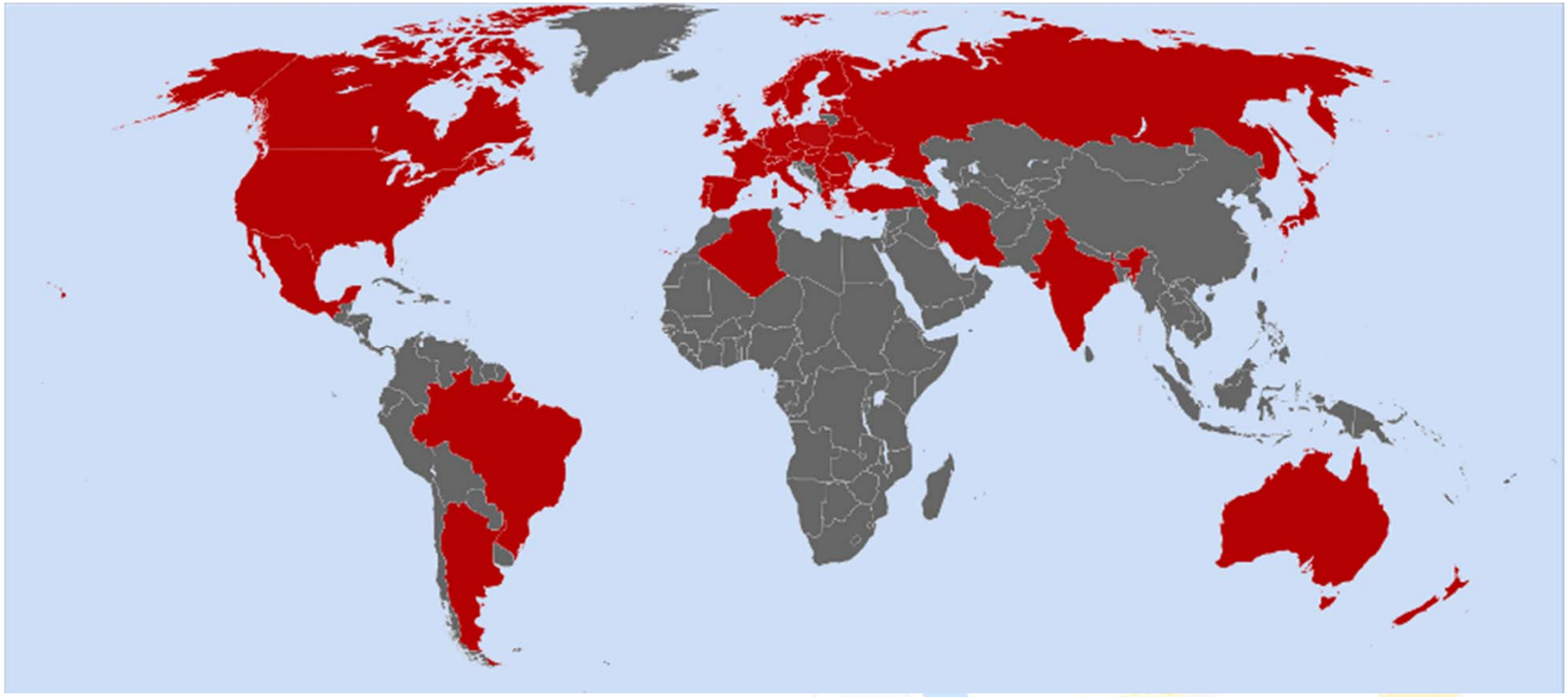
DMD Registries Today



> 10,000 patients in 30+ countries – global data for multicentre trials

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Annual registry funding

Annual funding	
No annual funding	28%
50,000€ or less	25%
51,000–100,000€	19%
101-200,000€	5%
201,000-500,000€	5%
501,000-1M€	3%
Donations/benefactors	5%

Table 1. Summarises annual funding of the registries.

The total amount of annual funding for all of the registries for one year was in excess of 1,610,000€.

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Utilisation of the registries (industrial liaison)

There was a clear split between the use of the registries at the national and international levels.

Nationally, the registries were used mainly for academic and internal purposes.

At the international level, there was a clear trend in the registries being involved in industrial applications.

Year	Feasibility Enquiry	Recruitment Enquiry	Other (including trial site enquiries)
2009	1		2
2010	5		
2011		1	1
2012			1

Table 2. Summarises the enquiries made to the DMD registries from industry (2009-2012).

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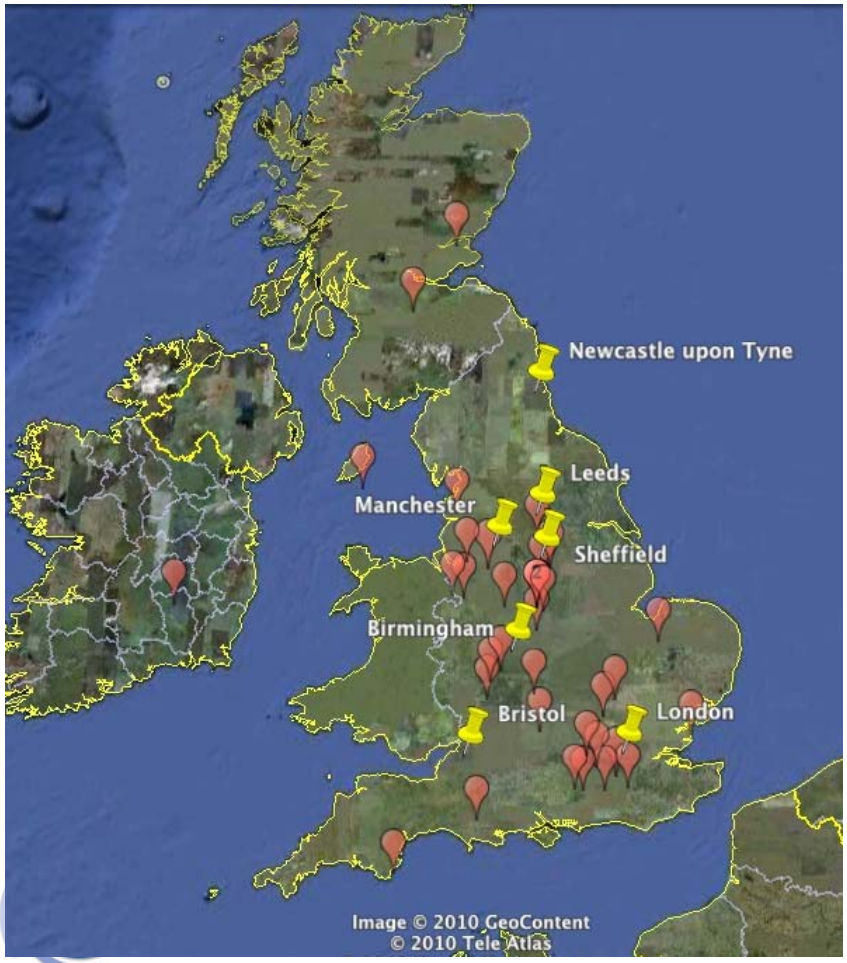
Trial feasibility: where can we run the trial?



- Registry data can be combined with trial site data to assist trial planning and centre selection
- Patients filtered by inclusion criteria can be matched to trial sites and recruited via the registry

Trial recruitment: where are the patients?

Yellow pins:
German and Austrian
trial sites (16)

Blue pins:
DMD & BMD patients
in German/Austrian
patient registry (693)

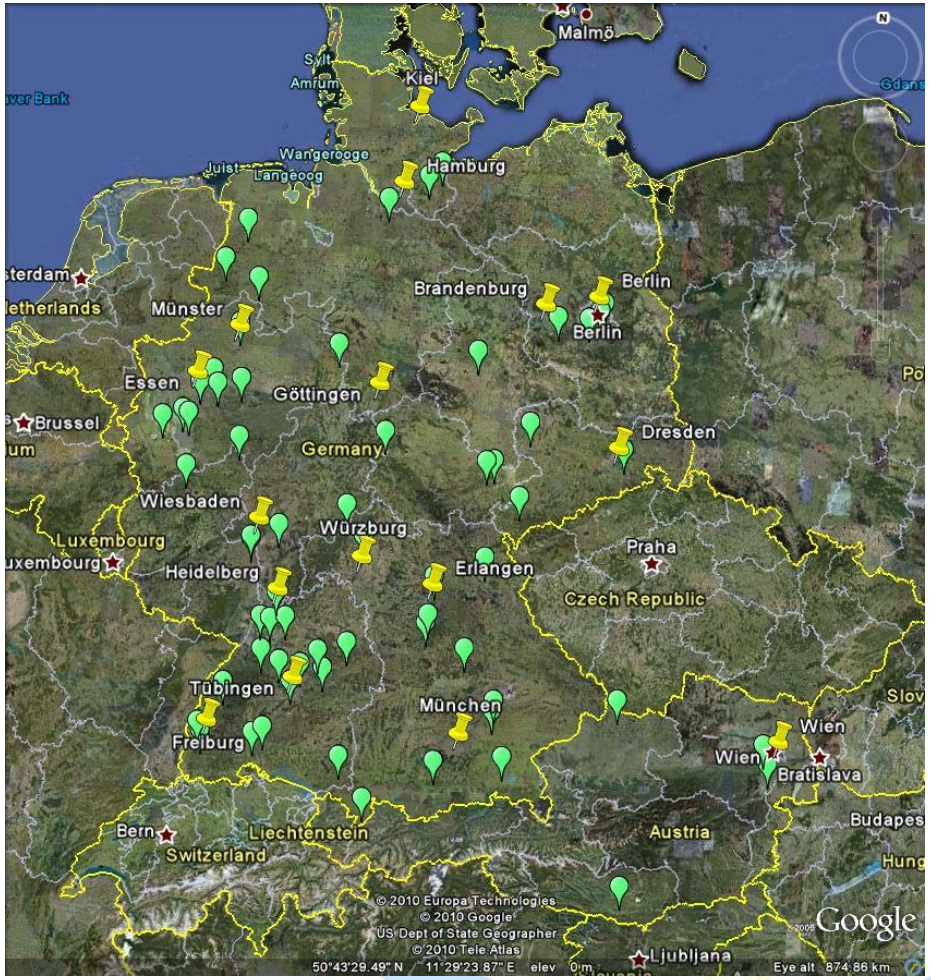
May 2010

Trial recruitment: where are the patients?

Yellow pins:
German and Austrian
trial sites

Green pins:
Patients meeting basic inclusion
criteria for trial (67)

May 2010



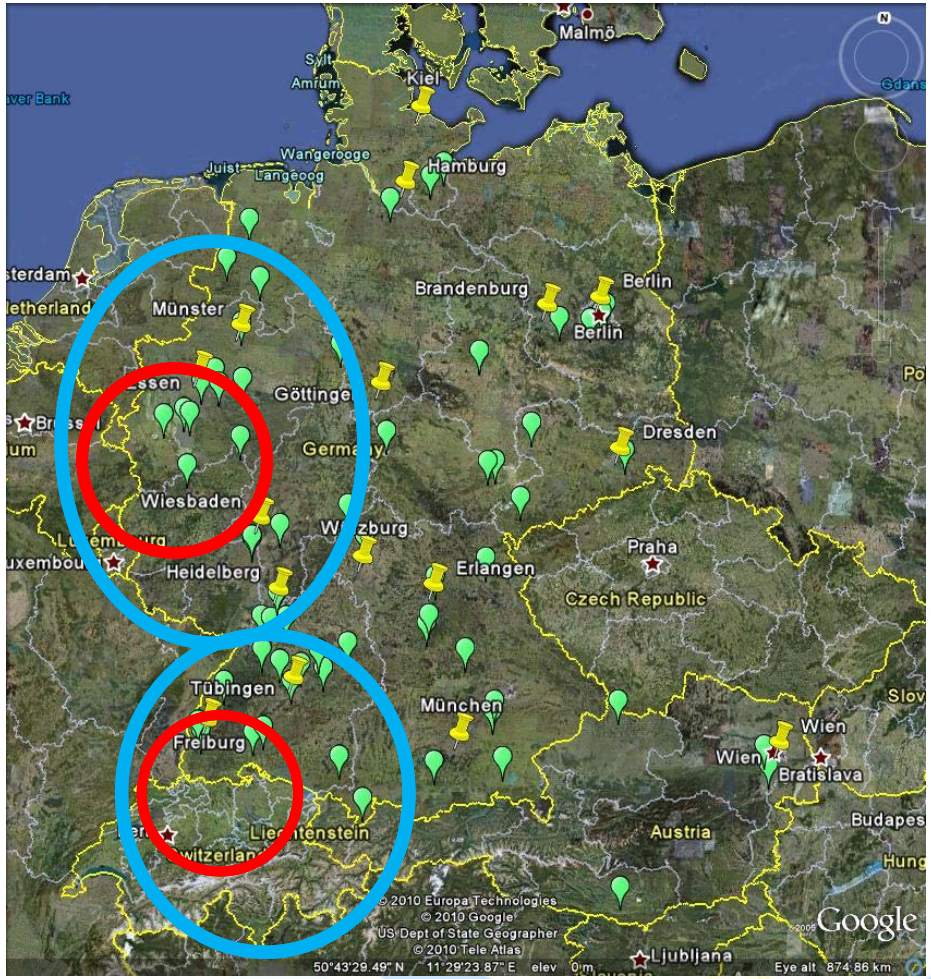
Trial recruitment: where are the patients?

Yellow pins:
German and Austrian trial sites

Green pins:
Patients meeting basic inclusion criteria for trial(67)

Red circle:
Under the care of Freiburg (4) and Essen (9)

Blue circle:
Recruitment potential (within 2 hours reach)
Freiburg (15) and Essen (15)

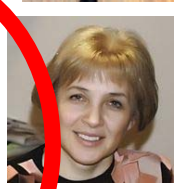



Hanns

Christophe Béroud





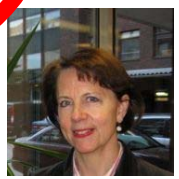





Vedrana Milic Rasic | Ludo van der Pol | Isabela Tudorache | Hugh Dawkins | Svetlana Artemieva | Alexander Baranov | Ole Gredal | Lawrence Korngut | Pat Furlong | Anna Ambrosini










Sylvie Tuffery-Giraud | Peter Van den Bergh | Violeta Mihaylova | Petr Vondráček | Jaana Lähdetie | Inge Schwersenz | Veronika Karcagi | Filippo Buccella | Harumasa Nakamura | 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 | Lauren Hache | Pierre-Yves Jeannet | Janbernd Kirschner | Nick Catlin

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Thank you!

Patients, families and patient organizations

Sponsors and funding agencies

Jan and his team in Freiburg

All CARE-NMD partners

Sunil for all his great work on CARE-NMD

Agata, Catherine, Michael and Rachel for helping with the presentation

Veronika, Martha, Agnes and their team for hosting us

All of you for listening

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