EURO-WABB: An EU Rare Diseases Registry for Wolfram syndrome, Alström syndrome and Bardet-Biedl syndrome

INTERIM TECHNICAL IMPLEMENTATION REPORT
Documenting activity between 01 January 2011 and 01 January 2012

This report arises from the Euro-WABB project which has received funding from the European Union, in the framework of the Health Programme.
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Abbreviations
AP  Associate Partner
BBS  Bardet-Biedl syndrome
CP  Collaborating Partner
EAHC  Executive Agency for Health and Consumers
LOVD  Leiden Open Variation Database
MS  Member State
PMC  Project Management Committee
RDS  Rare Diabetes Syndromes
SAC  Scientific Advisory Committee
TRMA  Thiamine-Responsive Megaloblastic Anaemia
VRIE  Virtual Registry and Information Environment
WABB  Wolfram, Alström and Bardet-Biedl syndromes
WR  Wolcott-Rallison syndrome

Associate Partner Abbreviations
ASUK  Alström Syndrome UK
CNRS  Centre National de la Recherche Scientifique
IDIBELL  Fundació Institut Investigació Biomèdica de Bellvitge
INSMER  National Institute of Health and Medical Research
MUL  Medical University of Lodz
NeSC  National e-Science Centre, University of Glasgow
TU  Tartu University
UB  University of Birmingham
UNIPD  Università degli Studi di Padova
## Project Summary Sheet

<table>
<thead>
<tr>
<th><strong>TITLE</strong></th>
<th>An EU Rare Diseases Registry for Wolfram syndrome, Alström syndrome and Bardet-Biedl syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACRONYM</strong></td>
<td>EURO-WABB</td>
</tr>
<tr>
<td><strong>START DATE</strong></td>
<td>01 January 2011</td>
</tr>
<tr>
<td><strong>REPORTING PERIOD</strong></td>
<td>Year 1 Activity: 01 January 2011 to 01 January 2012</td>
</tr>
<tr>
<td><strong>TOTAL COST OF ACTION</strong></td>
<td>€ 1,500,000</td>
</tr>
<tr>
<td><strong>PRE-FINANCING PAYMENT</strong></td>
<td>Received</td>
</tr>
<tr>
<td><strong>1st INTERIM PAYMENT</strong></td>
<td>Requested</td>
</tr>
<tr>
<td><strong>2nd INTERIM PAYMENT</strong></td>
<td>Not Due</td>
</tr>
</tbody>
</table>

| **MAIN PARTNER** | University of Birmingham (UB), UNITED KINGDOM |
| **8 ASSOCIATED PARTNERS** | University of Tartu (TU), ESTONIA |
| | Alström Syndrome UK (ASUK), UNITED KINGDOM |
| | Medical University of Lodz (MUL), POLAND |
| | Fundacio Institut Investigacio Biomedica de Bellvitge (IDIBELL), SPAIN |
| | National Institute of Health and Medical Research (INSERM), FRANCE |
| | Universita degli Studi di Padova (UNIPD), ITALY |
| | University of Glasgow (NeSC), UNITED KINGDOM |
| | Centre National de la Recherche Scientifique (CNRS), FRANCE |
Executive Summary

EURO-WABB is a 3 year project, initiated on 1st January 2011 and co-funded by the EU within the Health Programme Framework.

The general objective of the project is to support efficient diagnosis, treatment, and research for Wolfram, Alström and Bardet-Biedl (WABB) syndromes and other rarer diabetes syndromes in Europe. A key element of the project is the development of an EU registry for WABB syndromes.

The registry will enable:
- The establishment of the natural history of these diseases (their characteristics, management and outcomes)
- The assessment of clinical effectiveness of management and quality of care
- The development of a register of patients for recruitment to intervention studies
- The establishment of genotype-phenotype correlations

This report summarises the activity undertaken as part of the project during year 1. In the first 12 months of the action, across all work packages, and with support from Associate partners, collaborators and stakeholders, significant progress has been made towards achieving the overarching objectives of the project.

Highlights to date include:
- The development of an agreed common core dataset of clinical, investigation and molecular diagnostic data to distinguish between the WABB and rarer syndromes, and to provide a searchable database for researchers.
- Alignment of dataset to WHO ICD codes to allow unambiguous repeatability across EU states and language barriers.
- The registry was formally launched at the end of December 2011.
- Five EU Member States currently open to recruitment, with 75 participants recruited to date.
- As part of WP5, and in line with the objective to support equal access to genetic testing, nine accredited molecular diagnostic laboratories, able to offer genetic testing for WABB and the rarer syndromes have been identified to support the delivery of testing for registry participants without a genetic diagnosis.
- The launch of the multi-language project website in month 6 initially facilitated awareness raising and the development of collaborative links outside the existing network. The website continues to support the dissemination of information as the project develops. To this we have added a Facebook page for the EURO-WABB project, a Twitter link, and a blog.
The creation of an open access mutation database listing all published mutations for Wolfram, Alström, Thiamine responsive diabetes, and Wolcott-Rallison syndrome (Bardet-Biedl work in progress).
Introduction

This project addresses the needs of children and adults with overlapping disease presentations, who are often misdiagnosed or diagnosed late; may receive inappropriate investigations or treatment, have the wrong genetic counselling, and suffer social isolation and stigmatisation. The overarching aim of the project is to improve diagnosis, treatment, and research for the overlapping diseases Wolfram, Alström and Bardet-Biedl (WABB) syndromes and other rarer diabetes syndromes in Europe.

EURO-WABB is a 3 year project, initiated on 1st January 2011 and co-funded by the EU within the Health Programme Framework.

Wolfram, Alström, Bardet-Biedl (WABB) and other rare diabetes syndromes each affect less than 1:300,000 people, are poorly recognized, and often diagnosed late. The EURO-WABB project hopes to provide faster diagnosis, more research, and support better medical care for patients with Wolfram, Alström and Bardet Biedl syndromes across Europe. The funded project partners (Associate Partners) include clinicians, scientists and patient groups with representation from 6 EU countries. The project is further supported by Collaborating Partners and also benefits from input from a diverse group of stakeholders.

The project involves the establishment of a European registry of patients with WABB syndromes. A registry of this scale will provide invaluable insights into the diseases and their causes, enabling the development of international guidelines on management of the diseases and ultimately leading to improvements in quality of care.

Furthermore, the registry will be an important resource for researchers, including pharmaceutical companies developing orphan drugs, endocrinologists caring for the patients, specialist health care providers and also for the rare diseases community. We hope that the registry data will also lead to an increase in the volume and quality of clinical research in WABB syndromes, other rare diabetes syndromes and also common diabetes and obesity.

The following report provides more detail about progress to date and current plans related to the project goals and in relation to objectives set.
Specification of the Project

The project is divided into 6 work packages including 3 horizontal WPs concerned with project management, evaluation and dissemination; and 3 project specific core WPs concerned with the IT infrastructure (Virtual Research and Information Environment), the datasets and pathways and the genetic basis of these rare diseases.

General Objective of the Project

Our vision is to make the EU health service a more supportive environment for RDS patients, to reduce morbidity and premature mortality, and to improve quality of life. Our strategic objective is to support efficient diagnosis, treatment, and research for RDS diseases in Europe. This will be achieved through the implementation of an EU registry for WABB and other RDS, containing clinical, genetic diagnostic and outcome data. This is a collaborative effort to establish open and accessible data collection and maintenance.

The purpose of the registry is:

- The establishment of the natural history of these diseases (their characteristics, management and outcomes)
  - Establishment of the natural history of the WABB diseases including assessment of variance between population groups and changes over time
Use of natural history data of these diseases groups of children and adults with different outcomes to identify stages during their disease when they may be amenable to intervention

- **The assessment of clinical effectiveness of management and quality of care**
  - Assessment of the learning needs of healthcare professionals
  - Assessment of the information needs of WABB patients/carers
  - Assessment of the barriers to clinician data entry
  - Evaluation of service components required in disease management and the corresponding indicative costs

- **The development of a register of patients for recruitment to intervention studies**
  - To provide an evidence base for treatment and to facilitate research

- **The establishment of genotype-phenotype correlations**
  - To investigate whether observed data provide insights into common conditions including type 2 diabetes and obesity
  - To evaluate the genotypic differences between WABB patients with an identified mutation and those presenting with a partial form phenotype

High usage of the registry is achieved through linking it to rapid genetic testing; and over the coming months to up to date, accurate information, FAQs, and teaching resources via the website. This will support equal access to genetic testing in the EU; educate health professionals; and empower patients.
## Specific Objectives of the Project

<table>
<thead>
<tr>
<th>Specific Objective</th>
<th>Summary</th>
<th>Process Indicators</th>
<th>Output Indicators</th>
<th>Outcomes Indicators</th>
</tr>
</thead>
<tbody>
<tr>
<td>SO1 (WP1,6)</td>
<td>To review the technical, language and working practice barriers to physicians submitting data to an EU Registry, in 20 representative centres across the EU; and scope their support requirements for submitting data to the Registry, by Month 6</td>
<td>The number of validated, quantitative questionnaires (translated into 8 EU languages and back translated to ensure consistency) returned from centres in 8 EU states (WP6)</td>
<td>This should be at least 20 by 6 months</td>
<td>A review of barriers report, and a scoping report</td>
</tr>
<tr>
<td>SO2 (WP4)</td>
<td>To determine the data elements that will constitute the core and member state specific extended datasets for RDS diseases, that will conform to professional standards and to international nomenclature, and be coded in standard formats; by 6 months</td>
<td>The number of teleconferences to review the proposed datasets and discuss modifications (WP4)</td>
<td>Minimum 6 in 6 months</td>
<td>Publication of a consensus core dataset for each rare disease on the project website and in an international peer reviewed scientific journal</td>
</tr>
<tr>
<td>SO3 (WP6)</td>
<td>To develop prototypes for the Euro-WABB registry, making them available to the partners for evaluation and refinement of procedures, and road-testing with client groups of health professionals; by 9 months</td>
<td>Distribution of registry prototype to project partners for review, evaluation and refinement (WP6)</td>
<td>One registry prototype distributed by Month 9</td>
<td>Agreement on a shared prototype that ensures quality and consistency of data collection for pilot testing among the project partners</td>
</tr>
<tr>
<td>SO4 (WP5)</td>
<td>To identify and catalogue all the mutations (published and unpublished) in the RDS genes</td>
<td>Responses listing identified mutations according to international nomenclature, from centres offering genetic tests for WABB listed on Orphanet</td>
<td>Expected responses from at least 50% of centres within 6 months.</td>
<td>A comprehensive inventory of all known published / unpublished mutations in the RDS disease genes (principally Wolfram, Alström, Bardet-Biedl) by 6 months.</td>
</tr>
<tr>
<td>SO5 (WP2,4)</td>
<td>To assess the information needs of 60 patients/carers (20 for each disease) to inform the development of FAQs, and the learning needs of 20 health professionals to develop educational material for RDS diseases; by 12 months</td>
<td>The number of validated quantitative questionnaires (translated and back translated to ensure consistency) from patients/carers and health professionals</td>
<td>We expect at least 20 questionnaires from participating EU member states</td>
<td>A summary report of the information and learning needs by 12 months</td>
</tr>
<tr>
<td>SO6 (WP4)</td>
<td>To develop educational material for health professionals and information for client groups, with multilevel forum functionalities for patients, experts, and interactions between the two; by 24 months.</td>
<td>The number of teleconferences to peer review, edit and ensure consistency of education and information material (WP2,4,6)</td>
<td>We expect at least 12 teleconferences in 24 months</td>
<td>Publication of WABB education material and information on the project website and the Orphanet website by 24 months.</td>
</tr>
</tbody>
</table>
### Overview of Activities – Year 1

<table>
<thead>
<tr>
<th>Work Package</th>
<th>Associated Specific Objectives, Milestones &amp; Deliverables</th>
<th>Month Due</th>
<th>Month Achieved</th>
<th>Date Achieved</th>
<th>Level</th>
<th>Justification / Problems Encountered</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WP 1 Coordination</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>Set up management structures</td>
<td>3</td>
<td>4</td>
<td>08/04/2011</td>
<td>100</td>
<td>PMC and SAC terms of reference and membership agreed. Progress reporting and risk register systems implemented.</td>
</tr>
<tr>
<td>M</td>
<td>Kick-off meeting</td>
<td>3</td>
<td>4</td>
<td>08/04/2011</td>
<td>100</td>
<td>Held in Paris on 08/04/2011</td>
</tr>
<tr>
<td>M</td>
<td>Scientific Advisory meeting</td>
<td>12</td>
<td>15</td>
<td>02/03/2011</td>
<td>100</td>
<td>To take place via conference call on 2nd March 2012</td>
</tr>
<tr>
<td>D1</td>
<td>Interim reports, final report, layman’s version and promotional leaflet</td>
<td>33</td>
<td></td>
<td>Not Due</td>
<td>30</td>
<td>Multi-language leaflet for awareness-raising produced in English, Spanish, French and Italian.</td>
</tr>
<tr>
<td>D6</td>
<td>Input of datasets on at least 300 patients with WABB syndromes</td>
<td>33</td>
<td></td>
<td>Not Due</td>
<td>20</td>
<td>Ethical approvals in place in 5 EU MS with 60 participants recruited by M13.</td>
</tr>
<tr>
<td><strong>WP 2 Dissemination</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>Stakeholder analysis</td>
<td>6</td>
<td>6</td>
<td>09/06/2011</td>
<td>100*</td>
<td>Identified stakeholders summarised in Dissemination Plan Report (Appendix 1).</td>
</tr>
<tr>
<td>M</td>
<td>Dissemination plan</td>
<td>9</td>
<td>9</td>
<td>31/01/2012</td>
<td>100</td>
<td>Report provided (Appendix 1)</td>
</tr>
<tr>
<td>SO5</td>
<td>Assessment of information and learning needs of patients &amp; health professionals (WP2,4)</td>
<td>12</td>
<td></td>
<td>Ongoing</td>
<td>40</td>
<td>Difficulty in getting communication between WP2 lead and WP4 lead due to pressure of work of WP4 lead. In retrospect, our month target was overambitious. We would like to amend this target to month 24. The delay on this objective and deliverable has been added to the risk register.</td>
</tr>
<tr>
<td>D8</td>
<td>A report on the learning needs of Health Professionals</td>
<td>12</td>
<td></td>
<td>Delayed</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>D10</td>
<td>Delivery of an EU workshop to disseminate the findings at the end of the project</td>
<td>33</td>
<td></td>
<td>Not Due</td>
<td>10</td>
<td>End of project symposium to take place in 2013. Symposium agendas submitted to 3 European Conference Committees.</td>
</tr>
<tr>
<td><strong>WP 3 Evaluation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>Internal evaluation plan</td>
<td>3</td>
<td>14</td>
<td>29/02/2012</td>
<td>100</td>
<td>Report provided (Appendix 2a)</td>
</tr>
<tr>
<td>M</td>
<td>Commence internal evaluation</td>
<td>6</td>
<td>6</td>
<td>08/04/2011</td>
<td>100</td>
<td>Plans for internal evaluation outlined by Ségolène Aymé during Kick-Off meeting.</td>
</tr>
<tr>
<td>M</td>
<td>External evaluation plan</td>
<td>12</td>
<td>14</td>
<td>29/02/2012</td>
<td>100</td>
<td>Report provided (Appendix 2b)</td>
</tr>
<tr>
<td>D2</td>
<td>External evaluation report of the project</td>
<td>33</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>WP 4 Core Datasets &amp; Pathways</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>Development of core dataset</td>
<td>6</td>
<td>6</td>
<td>21/06/2011</td>
<td>100</td>
<td>Dataset agreed 21/06/2011.</td>
</tr>
<tr>
<td>SO6</td>
<td>Development of Educational material for health</td>
<td>24</td>
<td></td>
<td>Not Due</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
* A small element of work linked to these activities will continue beyond the defined end-point. This includes ongoing testing of the registry and the identification of project stakeholders.

<table>
<thead>
<tr>
<th>WP5 Genetics</th>
<th>SO4</th>
<th>Identification and cataloguing of all published and unpublished WABB, WR and TRMA mutations</th>
<th>6</th>
<th>90*</th>
<th>Cataloguing completed for ALMS1, WFS1, EIF2AK3, SLC19A2 published 18/09/2011. BBS due to complete M14</th>
</tr>
</thead>
<tbody>
<tr>
<td>D7</td>
<td></td>
<td>Identification of suitable laboratories for genetic testing. Testing undertaken for 50 samples</td>
<td>30</td>
<td>Not Due</td>
<td>Scoping Exercise undertaken and submitted to EAHC. First samples processed by MUL at the end of 2011. CONTRACT AMENDMENT PENDING</td>
</tr>
<tr>
<td>M</td>
<td></td>
<td>Widen the availability of genetic testing</td>
<td>18</td>
<td>Not Due</td>
<td>50</td>
</tr>
<tr>
<td>M</td>
<td></td>
<td>Genotype phenotype correlations</td>
<td>30</td>
<td>Not Due</td>
<td>5</td>
</tr>
<tr>
<td>WP6 Virtual Registry &amp; Information Environment</td>
<td>SO1</td>
<td>Barriers to Data Entry</td>
<td>6</td>
<td>14</td>
<td>28/02/2012</td>
</tr>
<tr>
<td>D3</td>
<td></td>
<td>Scoping Exercise and Reports</td>
<td>3</td>
<td>14</td>
<td>28/02/2012</td>
</tr>
<tr>
<td>SO3</td>
<td></td>
<td>To develop prototype for registry</td>
<td>9</td>
<td>11</td>
<td>17/09/2011</td>
</tr>
<tr>
<td>M</td>
<td></td>
<td>Design, develop and test the registry</td>
<td>9</td>
<td>12</td>
<td>31/12/2011</td>
</tr>
<tr>
<td>D4</td>
<td></td>
<td>Development of a web-based registry</td>
<td>9</td>
<td>80*</td>
<td>02/02/2012</td>
</tr>
<tr>
<td>M</td>
<td></td>
<td>Security and Risk Evaluation</td>
<td>11</td>
<td>13</td>
<td>02/02/2012</td>
</tr>
<tr>
<td>M</td>
<td></td>
<td>Evaluation by partner sites</td>
<td>20</td>
<td>Not Due</td>
<td></td>
</tr>
</tbody>
</table>
Work Package 1: Coordination

This WP is led by Prof. Tim Barrett, Project Coordinator, with support from the project funded Study Coordinator, Amy Farmer. The key activities for this WP in the past year are associated with establishing collaborative and communication links between Associate Partners and the development of robust project management structures.

Partnerships & Communication

Beginning with a successful and well-attended Kick-off meeting in April 2011, a series of 9 Associate Partner meetings have taken place via conference call to foster communication and cooperation amongst Associate partners (Appendix 4). This regular communication, coupled with the establishment of formal project management structures, including risk and progress registers, has facilitated the efficient coordination of the project.

- Monthly conference calls open to all Associate Partners
- Regular emails from Project Coordinator and/or Project Manager
- Use of restricted access document repository on the project website for sharing of key documentation

Project Management Structures (Milestone 1)

The management structures were established in the early stages of the project and discussed as part of the Kick off meeting agenda (08/04/2011).

The diagram opposite shows the Committees, Groups and Individuals involved with the overall project management of the EURO-WABB project, and the interactions and hierarchy within this management structure.

The Project Management Committee (PMC) is in charge of monitoring all activities towards the objectives of the project in order to deliver as promised, in due time and in budget. Comprising 15 members, including Associate Partners and Collaborating Partners, the PMC includes representatives of researcher, clinician and patient stakeholder groups. The next PMC meeting will take place on 4th May 2012.
The project activities are further supported by the Scientific Advisory Committee (SAC) which comprises 17 members. The SAC will be kept appraised of all project activities and will provide additional steering as needed. The first SAC meeting will take place on 2\textsuperscript{nd} March 2012 following the entry of the first 50 datasets into the registry.

**Recruitment of Registry Participants (Deliverable 6)**
The Euro-WABB project will recruit a minimum of 300 affected individuals into the registry. National ethical and regulatory approvals were discussed in detail during the Kick-Off meeting and the responsibility for attaining these approvals was delegated to the respective national coordinator (AP or Clinical Partner) and standardized using the UK documentation as a template. The first national approvals were in place by M6.

Recruitment began in Month 8 and currently 60 patients (20\% of target sample size) have given written consent for their details to be part of the registry. To boost collaboration, registry consent also facilitates data sharing with national disease-specific registries. As new sites open, we anticipate an increase in the recruitment rate over the next 12 months.

**Next Steps**

- **Second Annual Meeting: Project Management Committee (PMC) meeting**
  Taking place in Paris on May 4\textsuperscript{th}, at the Platform Maladies Rare in Paris, the PMC will provide an opportunity for face to face discussion and planning of forthcoming activities.

- **Scientific Advisory Committee Meeting(s)**
  The first SAC meeting will take place on 2\textsuperscript{nd} March 2012. This will coincide with the completion of data entry for the first 50 datasets into the registry.

- **Work with Orphanet and other Rare Disease Networks to boost recruitment**
  This will include identification of clinical collaborators within Member States not currently recruiting participants.

**Work Package 2: Dissemination**

This WP is led by Kay Parkinson, ASUK, and is in place to ensure that dissemination activities are both undertaken and recorded throughout the course of the project. In the first year, significant progress has been made in the identification of stakeholders and in the development and implementation of a variety of awareness raising media including a dedicated multi-language project website, project logo, promotional flyers, magazine articles and scientific posters.
Stakeholder Analysis (Milestone)
The project has made use of the existing rare disease initiatives and infrastructure in place within Europe, including EURORDIS, EuroGentest and Orphanet, to aid awareness-raising and stakeholder identification. Over 40 stakeholders have currently been identified, spanning 16 countries and representing different stakeholder sub-categories including patient associations, clinicians, researchers, policy makers and the pharmaceutical industry. This is an ongoing activity and the current stakeholder list is summarised in the dissemination report included in the appendices (Appendix 1).

Dissemination Content & Means
Planning the effective dissemination of the project requires the input of all Associate Partners and the sharing the same strategy. Dissemination will be carried out through the partners own organisation, regionally or nationally across the EU and globally.

The dissemination plan report defines the objective of dissemination for EURO-WABB and summarises the activity to date and planned future activities (Appendix 1).

Dissemination Activities
See Appendix 1 : Dissemination Report for details of publications, scientific posters and other awareness raising outputs.

Assessment of Learning Needs of Patients, Carers and Health Professionals (Specific Objective 5)
Working alongside fellow Associate Partner, Prof. Véronique Paquis, ASUK are working with patients, their families and also health care professionals to develop an understanding of their respective learning and information needs. This includes collaboration with the Laurence-Moon Bardet-Biedl Society (LMBBS) and the French Wolfram Association. The results of this activity will be reported separately.

Website Development
The website is the principle communication tool for the project. The EURO-WABB temporary website was replaced by its permanent replacement on 20 June 2011. Viewable in 8 European languages, and with built-in accessibility for people with visual impairments, we hope that it will help in achieving Europe-wide engagement and involvement. Since its launch in June, the site has been visited 2,788 (2,232 within Europe) times and has been accessed from a total of 94 countries.

<table>
<thead>
<tr>
<th>Sub Continent</th>
<th>Visits</th>
<th>Pages per Visit</th>
<th>Avg. Time on Site</th>
<th>% New Visits</th>
</tr>
</thead>
<tbody>
<tr>
<td>N. Europe</td>
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<td>4.33</td>
<td>55.40</td>
</tr>
<tr>
<td>W. Europe</td>
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<td>3.85</td>
<td>2.08</td>
<td>74.89</td>
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<tr>
<td>S. Europe</td>
<td>432</td>
<td>4.31</td>
<td>2.32</td>
<td>80.79</td>
</tr>
<tr>
<td>E. Europe</td>
<td>238</td>
<td>3.29</td>
<td>2.12</td>
<td>82.77</td>
</tr>
</tbody>
</table>

Data Source: Google Analytics - June 25th 2011 to 1st January 2012

Next Steps
➢ End of Project Symposium (Deliverable 10)
Draft symposium agendas have been submitted to the 2013 scientific conferences below. Further planning activities will be undertaken over the next 12 months.

<table>
<thead>
<tr>
<th>Organisation</th>
<th>Event</th>
<th>Date</th>
<th>Venue</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Association for the Study of Diabetes</td>
<td>EASD Annual Meeting 2013 49th Annual Meeting</td>
<td>23rd September 2013</td>
<td>Barcelona, Spain</td>
</tr>
<tr>
<td>European Society for Paediatric Endocrinology</td>
<td>9th Joint ESPE/LWPES Meeting</td>
<td>19th September 2013</td>
<td>Rome, Italy</td>
</tr>
<tr>
<td>European Society for Human Genetics</td>
<td>European Human Genetics Conference 2013</td>
<td>8th June 2013</td>
<td>Paris, France</td>
</tr>
</tbody>
</table>

- **Development of Website Content (Information Provision)**
  Over the coming months, and as the contributing deliverables are completed, the website will be updated and expanded to provide a valuable source of information, both about the project and also Wolfram, Alström and Bardet-Biedl syndromes and their clinical management.

- **Completion of Specific Objective 5**

**Work Package 3: Evaluation**

Led by Prof. Sé golène Aymé (INSERM/Orphanet), the evaluation WP monitors the project progress and quality in line with agreed specific objectives and associated indicators. The initial evaluation plans were discussed during the project Kick-Off meeting (April 2011). Detailed reports summarising Internal and External evaluation plans are included in the appendices.

The internal evaluation is supposed to monitor the project progresses towards its initial objectives on a trimester basis and to identify possible barriers to achievements in order to propose a re-schedule or a modification of the planned actions.

During the first year, we monitored the overall management of the project which very precisely followed the initial plans. No problems were encountered.

Most of the specific objectives were met on time and as expected: The questionnaire to assess the working practice barriers to physicians submitting clinical data to the EU registry was sent to 45 clinicians, of which 25 responded; The report final report is available but not yet the scoping paper; The preparation of the dataset to be included in the web-based registry ended in the adoption of the core dataset and of the optional one which respect the International nomenclatures; The development of the prototype for the Euro-WABB registry and the testing by partners and by future contributors. The collection of data on mutations in genes involved in RDS started as scheduled, with a
review of the literature and a questionnaire sent to 9 laboratories, of which 7 replied. The identification of 40 potential stakeholders was carried out: 8 Researchers, 6 Clinicians, 3 Press, 12 Patients / Patient Organisations , 6 Professional Society / Organisation, 3 Education Providers / Experts, 1 Policy Maker, 1 Pharmaceutical Industry from 17 countries.

The only specific objectives which had to be re-scheduled for M15 were the assessment of the information needs of patient and carers.

In summary, the project is progressing very satisfactorily and according to initial plans. The external evaluation is scheduled for the third year.

The Internal and External Evaluation Report are provided in the appendices (Appendix 2a & 2b)

Work Package 4: Core Datasets and Pathways

This WP is led by Prof. Véronique Paquis who is supported by project funded Study Engineer, Mickaël Vivien. Year 1 activities have centred around the development of the registry datasets, facilitating national approvals and beginning to consider the reassessment of patients.

Development of Core Dataset (Specific Objective 2)

Following a series of planning meetings and correspondence via email, consensus core and extended datasets have been developed and agreed. The core dataset includes 44 data fields of which 5 relate to referring physician and consent data; 18 define the clinical and molecular genetic features and differentiate between syndromes; and 10 relate to age of onset of symptoms, and optional free text. The extended dataset comprises 370 fields of detailed phenotyping information. Where possible, the datasets are standardised using ICD-10 and ESPE Classification coding systems.

Copies of the registry datasets and ICD-10/ESPE coding used are given in the appendices (Appendix 5).
Collaboration with Existing Registries & Projects

Euro-WABB datasets have been developed concurrently with the Spanish Wolfram registry datasets (IDIBELL and collaborating partner CIBERER), allowing for joint working and data sharing at national level. Discussions with Prof. Dr. med Reinhard Holl of the German DPV registry are ongoing and plans are being put in place for a similar collaborative link between the Euro-WABB and German registries during 2012.

Next Steps

- **Reassessment of Patients (Milestone 2)**
  This will be undertaken with support from all clinical Associate Partners and will involve using agreed diagnostic criteria.

- **Development of Health Professional Education Materials & Diagnostic Criteria (Specific Objective 6)**
  This will be done using the evidence from the registry and will include guidelines for referral, care and management pathways.

- **Completion of Specific Objective 5**
  We have experienced difficulty in establishing regular communication between WP2 and WP4 leaders. This is due to the pressure of other work on WP4 leader. We are addressing this directly with her, and adding this to our risk register. In retrospect, our target for completion by month 12 was over-ambitious. We
would like to request a new timescale to achieve this target, of Month 24. This will give us time to address this issue with WP4 leader.

- **Publication of consensus core dataset**
  The registry dataset will be submitted to an international peer reviewed journal in early 2013.

### Work Package 5: Genetics

This WP is led by Prof. Tim Barrett with support from Dr Dewi Astuti, a project funded Research Fellow. As well as undertaking genotype-phenotype correlations, the WP will also ensure that the project meets its aim of supporting equal access to genetic testing. The primary activities within this WP over the past 12 months have been the identification and cataloguing of existing mutations in the WABB and TRMA and WR genes and a scoping exercise to identify EU accredited laboratories who are undertaking W/A/BB diagnostic testing.

#### Identification and Cataloguing of Mutations in WABB Genes (Specific Objective 4)

This task was undertaken by Dr Dewi Astuti, with support from Dr Miguel Lopez de Heredia (CIBERER, Spanish Wolfram Registry). With the exception of the BBS mutations, which will be released in Year 2, this activity is complete.

Following comprehensive searching of published mutations, the Euro-WABB mutation database currently lists 1017 variants, of which 358 are unique variants. The database utilises the Leiden Open Variation Database (LOVD) software. Using LOVD means that the database is publicly available and also includes the facility for clinicians to submit unlisted mutations for inclusion in the database. It is hoped that this resource will be useful to clinicians in their practice. The databases are updated on a monthly basis to include any new mutations published.

<table>
<thead>
<tr>
<th>Disease</th>
<th>OMIM</th>
<th>Mutated Gene(s)</th>
<th>Database</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wolfram syndrome</td>
<td>222300</td>
<td><em>WFS1</em></td>
<td>LOVD-ALMS1</td>
</tr>
<tr>
<td>Alström syndrome</td>
<td>203800</td>
<td><em>ALMS1</em></td>
<td>LOVD-WFS1</td>
</tr>
<tr>
<td>Bardet-Biedl syndrome</td>
<td>209900</td>
<td><em>BBS1</em>, <em>BBS2</em>, <em>ARL6</em>, <em>BBS4</em>, <em>BBS5</em>, <em>MKKS</em>, <em>BBS7</em>, <em>TCC8</em>, <em>BBS9</em>, <em>BBS10</em>, <em>TRIM32</em>, <em>BBS12</em>, <em>MKS1</em>, <em>CEP290</em></td>
<td>PENDING</td>
</tr>
<tr>
<td>Thiamine-responsive megaloblastic anaemia</td>
<td>249270</td>
<td><em>SLC19A2</em></td>
<td>LOVD-SLC19A2</td>
</tr>
<tr>
<td>Wolcott-Rallison syndrome</td>
<td>226980</td>
<td><em>EIF2AK3</em></td>
<td>LOVD-EIF2AK3</td>
</tr>
</tbody>
</table>
Widening the Availability of Genetic Testing (Deliverable 7)

In a change to the planned activities, the project will fund the cost of diagnostic testing using existing accredited EU laboratories rather than to developing a Gene Chip. In line with this, a comprehensive scoping exercise was undertaken to identify existing laboratories and to find out more about the technologies currently used and the associated costs and capacities. Nine labs have been identified across the EU who are able to accept and test project samples. Funding previously allocated to the development of the Gene Chip will be used to fund testing where costs aren’t met by a participant’s national healthcare infrastructure. Following discussion, this revision has been agreed in principle by the EAHC, and will be incorporated into a revised contract in due course.

Next Steps

- **Completion and Maintenance of Mutation Database**
  The mutation database for the 15 Bardet-Biedl genes will be released via the LOVD database during Month 14 and fully completed by Month 17. The database will also be updated as new mutations are identified and/or published.

- **Participant Samples Processed for Genetic Testing**
  MUL has undertaken the first of the sample testing for registry participants. Over the coming months, as more recruiting sites are established the demand for testing will increase and the network of testing centres will be utilised.

Work Package 6: Virtual Registry and Information Environment

The VRIE has been developed and is hosted by the National e-Science Centre (NeSC), University of Glasgow. With the support of a project funded Information Scientist, Susan McCafferty, the primary activities for this work package over the past 12 months have been development of the registry.

Following completion of the design, development and user testing phases, the core dataset area of the registry was launched at the end of December 2011 (M12). The registry website is: [www.registry.euro-wabb.org](http://www.registry.euro-wabb.org).

Design, Develop and Test the Registry (Specific Objective 3)

Working closely with the Project Coordinator, the NeSC team has designed the registry database to the agreed specification. A prototype was launched in September 2011, allowing potential users to provide feedback which was incorporated into the current design. A test registry was set up in early December 2011 to allow for user testing and data input. Testing was undertaken by Associate and Collaborating clinical partners. Design, development and testing of the Euro-WABB system is an iterative process and is therefore ongoing. The current Euro-WABB System comprises a front end portal for access to client interfaces; mid-tier server hosting services that allow secure access to and upload of Euro-WABB core data sets; LOVD Database and portal all hosted on a web server located at NeSC. The back-end database collating contributed Euro-WABB core
data and back-end database for other information/data on Euro-WABB, e.g. user registrations are hosted on separate database servers not accessible from the web. The current system supports secure access via a web portal hosted at NeSC which allows a registered user to: upload Euro-WABB core data sets; and delete/edit data sets (subject to privileges). All access to the Euro-WABB system is monitored, logged and audited.

**Scoping Exercise & Reports - Barriers to Data Entry (Deliverable 3)**

Existing health data will be collected for research purposes via web-based electronic data capture forms. Data entry will be undertaken by a number of different individuals from participating sites across Europe. As such, it is necessary to assess the needs of this group to ensure that the design and interface used are optimal to ensure accurate and complete data.

To assess this, a brief survey was distributed to 45 clinicians (ESPE members and/or previously identified stakeholders) and a link to the survey was also included on the Euro-WABB Project website and circulated in the Autumn edition of the Stakeholder and Collaborator project newsletters. Results of the survey are summarised in the report included in the appendices (Appendix 3) and will inform the development of web-forms used for data collection and the support provided for data inputters.

**Security & Risk Evaluation (Milestone 4)**

Overall responsibility for information security of Euro-WABB rests with the NeSC Director at University of Glasgow, Prof Richard Sinnott, with all NeSC staff adhering to a confidentiality policy. NeSC have undertaken an analysis of data flow within the registry.

The registry stores anonymised data, with each record having a unique identifier. This identifier is linked to the recruiting site, and the site retains a master list of all patients taking part. Identifiable data is not stored in the registry.

Access to the registry is password controlled with the Project Coordinator reviewing all username requests. The Project Coordinator will verify that the individual is requesting the correct level of access for their requirements (patient/clinician/researcher). For clinical partners, this will also include confirmation of ethical approval. For patients/families, this will require secondary verification by their clinician.

The NeSC Confidentiality and the Registry’s System Level Security Policy can be viewed at [www.euro-wabb.org](http://www.euro-wabb.org) and are included in the appendices (Appendix 7a & 7b) for information.

**Next steps**

- Release of Extended Dataset
Design of the database for the extended dataset element of the registry is underway and, following user testing, will be launched in Month 16.

- **Continuous security evaluation and risk assessment**
  This is an ongoing activity. Risks identified will be escalated to the Project Coordinator and/or Project Management Committee as required.

- **Evaluation of VRIE by Partner Sites (Milestone)**
  Feedback from participating data collection sites from across the EU will be sought. This activity will commence during month 17, following the release of the extended dataset, and will be completed by month 20.

### Problems Encountered
Problems are reported via the Risk Register which is updated on a monthly basis. The majority of the risks and problems have been internal to the project and operational in nature. Where appropriate, these problems have been forwarded to the EAHC for information and or guidance. The major problems, along with corresponding mitigation and or contingency plans are summarised below and the risk register is included in the appendices (Appendix 6):

**Delay in delivery of Specific Objective 5 - Assessment of the information and learning needs of patients and health professionals.**
As indicated above, we request an extension for this deliverable, to Month 24. We believe this will give us enough time to help WP4 leader to prioritise this work.

**Named Associate Partner employed via Joint Research Unit meaning contract of employment is not with named Associate Partner Organisation.**
Contract amendment pending, discussions with University of Nice are ongoing.

**Failure to engage other major researchers in WABB diseases in Europe:**
- Need to engage Prof Hélène Dolffus, maybe by inviting her to join the Scientific Advisory committee (she has indicated she is too busy to join the project as a collaborating partner; so her patients are not being recruited to the registry);
- Need to extend ethical approvals to more EU states. There is an issue with support for Prof Lisbeth Tranebjaerg (Denmark) and also Dr Julia Rohayem (Germany).
- Need to engage with more clinicians across Europe; for instance Nordic countries; have been approached but currently are not participating.
- Need to ensure that doctors recruiting patients do actually put the data on the registry
- Need to ensure that doctors recruiting patients adhere to research governance and ethics.
Summary
In summary, we have met the majority of our targets for Month 12 of the project; and our recruitment to the registry is ahead of target. We have plans in place to address our one delayed target. Overall this project is beginning to bring patient groups and researchers together. This year we hope to see the first publications directly resulting from this project, on the mutation database, the research protocol, and preparation of patient information and management guidelines.