EURO-WABB was an ambitious and risky project as it addressed three very rare genetic diseases having in common to include diabetes among other phenotypic expressions of the disease but managed by different communities which needed to be brought together. Overall the project ended very successfully despite the short time span of such a project.

The current report is divided in two sections: the first one dedicated to the degree of achievement of the project compared to initial ambition; the second one dedicated to the impact of the project.

1- Evaluation of degree of achievement of Euro-Wabb

Specific objective 1: “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.”

An online survey of physicians was launched in September 2011. The web-based survey included 8 questions grouped under 3 categories and included a mix of question types, including likert scale ratings for key factors affecting ability to enter data and with free text sections incorporated to capture factors not identified. The web-link to the survey was circulated by email to 45 clinicians (ESPE members and/or previously identified stakeholders). A link to the survey was also included on the Euro-WABB Project website and circulated in the Stakeholder and Collaborator project newsletters. The project’s Associate Partners contributed to the dissemination of the survey by sharing details at a national level. With some delay, 25 respondents, spanning 12 EU Member States, completed the survey (20 expected). The responses permitted to identify the major barriers to overcome to ensure the success of the planned registry. The only difficult barrier to address was the language barrier. The barrier report and the scoping report were issued.

Specific objective 2: “To determine the data elements that will constitute the core and member state specific extended datasets for the 3 diseases, that will conform to professional standards and to International nomenclature, and be coded in standard formats.”

This task was the object of a sustained effort to implicate in the discussion as many partners as possible as to reach a consensus. Up to 12 versions of the core dataset were necessary for Alström disease, 11 versions for Wolfram disease, and 9 versions for Bardet-Biedl syndrome. This shows the seriousness of the approach. Standards were applied were ever possible and the number of text free zones kept to minimum. This task can be considered as achieved according to plans and standards.

Specific objective 3: “To develop prototypes for the Euro-Rare Diabetes registry, making them available to partners for evaluation and refinement of procedures, and road-testing with client groups of health professionals.”

The online questionnaires have been developed and made available to contributors at the end of December 2011. With experience, the questionnaires demonstrated some limitations to capture these complex phenotypes, making necessary to modify them slightly. This is a normal process as,
due to the small number of patients and the short time span of the project, it was not possible to test the questionnaires before their release. 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 rules for managing the registry and accessing data are well established and conform to International standards and guidelines. An interesting feature of this registry is that patients can register by themselves, their data being subsequently validated by their physician. This is a requirement in the field of very rare diseases as the patients are more motivated than clinicians to contribute to shared data collection to advance knowledge.

**Specific objective 4:** “To identify and catalogue all the mutations in the RDS genes to inform the development of a next generation genetic testing chip for distribution”.

A survey of the literature was performed to identify all published mutations in the involved genes as well as a collection of data from diagnostic laboratories which were requested to notify their identified mutations (7 out of 9 labs reported their mutations). The Leiden Open Variation Database (LOVD) software was selected to store the data. LOVD is the best tool currently in the world to do so: the database is publicly available and includes the facility for clinicians to submit unlisted mutations for inclusion in the database. The remaining question is “How to maintain such a mutation database after the end of the funding”, knowing that it is essential for clinical practice to have a source of information of which variants are causing the disease, and which are neutral. Ideally the 9 European laboratories should contribute to the storing of the mutations they detect.

The original objective was also to develop a chip. This objective was modified to be in line with the real situation of clinical laboratories offering test for these disease. As testing is not financially covered in most EU countries, and as it is essential to establish the molecular diagnosis, it was decided to 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. Funding previously allocated to the development of the Gene Chip was used to fund testing when needed.

**Specific objective 5:** “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 WABB diseases by 12 months.”

To achieve this objective the partners have identified 40 potential stakeholders: 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. They have been requested to fill in a quantitative questionnaire to assess the type of information which was needed. The patient organizations organized also focus groups.

**Specific objective 6:** “To develop educational material for health professionals and information for client groups, with multilevel forum functionalities for patient, experts, and interactions between the two.”
The partners developed clinical guidelines and brochures for patients of very high quality. The experience gained by a previous EC project, “Dyscerne”, was used as a template for the development of the clinical guidelines. The results are excellent as they reflect on the identified needs expressed by the clinicians but also reflect on the best knowledge gained from the clinical data collected throughout the project. The leaflet developed for the patients are tailored at the newly diagnosed patients but they only introduce the general problem of rare diabetes, not the specificities of each disease. Currently the clinical guidelines are not available on the website and the other documents are presented in a way which is not informative.

2- Evaluation of the impact of Euro-Wabb

2.1 Monitoring of Inclusivity (analysis of Stakeholders)

In order to monitor the impact of Euro-Wabb, some indicators have been defined. The first one is the proportion of stakeholders involved in Euro-Wabb activities compared to potential stakeholders identified as follows:

- Professionals located in Europe at large and having published a review article (case reports were excluded) on one of the RDS.
- Professionals listed in the Orphanet database as Clinicians in the field of rare diabetes, biologists in charge of a diagnostic laboratory for one of these diseases, researchers currently working on one of these diseases.
- Patient organisations listed in the Orphanet database as being in the field of rare diabetes.
- Biotechs and Pharmas developing products for one of these diseases.

The results are presented by disease.

2.1.1 Proportion of stakeholders involved in Euro-Wabb activities for Wolfram syndrome compared to potential stakeholders

During the period, six review articles on Wolfram syndrome were published in peer-reviewed journals. Two of them (PMID: 24890733 and PMID: 23429432) were from partners of Euro-Wabb, two were from a major USA consortium (PMc3651298 and PMID: 23217193), two of them were from Italian centres not involved in EuroWabb: one centre from Sicily (PMID: 24497219) and one centre from Messina (PMID: 22790102). The US group gathered data on 18 patients when the Euro-Wabb database includes 170 patients but none from Italy, which is a pity as there are published series from Italy. These centres could be contacted.

In terms of specialised clinics, only 2 European countries have expert clinics officially dedicated to Wolfram syndrome: UK with the clinic in Manchester from the coordinator and Spain with the clinic in Huercal-Overa. This clinic is not a partner, not listed as a contributing site, although it is likely that the patients diagnosed in Spain are all identified as 25 Spanish patients are registered in the database. The other European countries have expert clinics for rare endocrinological diseases (over 70 such clinics in Orphanet) which can be targeted to identify additional patients.

In terms of clinical laboratories offering testing for Wolfram syndrome, the Orphanet database lists 34 European laboratories, of which 13 are accredited and 21 are not accredited. This is far more than the 8 ones which are listed on the Euro-Wabb website and far more than the ones which were approached to contribute to the collection of mutations.
In terms of patient organisations, there are three of them in Europe, in UK, France and Spain, all involved in the project.

In terms of research projects, the only ongoing research are the on the genetic aspect of the disease. There is no therapy development.

2.1.2 Proportion of stakeholders involved in Euro-Wabb activities for Bardet-Biedl syndrome compared to potential stakeholders

During the period, only one review article on Bardet-Biedl syndrome was published in a peer-reviewed journal (Eur J Hum Genet 2013;21(1):8-13) by a UK group from London which is a clinical collaborating partner of Euro-Wabb.

French official clinical guidelines were published in 2012, in French exclusively. The French groups did not participate to Euro-Wabb, although invited to join several times, mainly due to a reluctance to share their data. The partners cannot be blamed for that, but it is very unfortunate.

A clinical utility card, describing how to establish the molecular diagnosis of Bardet-Biedl, has also been published in 2011 by co-authors from the USA and from London (Insitute of Child health) who is a clinical collaborating partner of Euro-Wabb.

In terms of specialised clinics, none of the European countries has expert clinics purely dedicated to Bardet-Biedl syndrome except the UK which has expert clinics for the syndrome in Birmingham, at Guy’s hospital and at the Institute of Child Health in London. In the other countries, patients attend a variety of other types of expert clinics dedicated to retina disease, or syndromic obesity, or genetic syndromes. Orphanet list over 300 such non-specific expert clinics.

In terms of clinical laboratories, 41 European Clinical laboratories providing testing for Bardet-Biedl are listed in Orphanet. They are from Austria, Belgium, Estonia, Finland, France, Germany, Netherlands, Italy, Portugal, Spain, Switzerland, United-Kingdom. Euro-Wabb had contact points for Bardet-Biedl syndrome only in Estonia, Italy, Lithuania, Poland and United-Kingdom, but only 4 clinical laboratories offering tests for Bardet-Biedl are listed on the Euro-Wabb website. For this disease, the network was really not inclusive enough.

In terms of patient organisations, there are 4 patients organisations specific to Bardet-Biedl syndrome listed by Orphanet. They are based in Austria, France, Italy and UK. Only the UK society is mentioned on the website of Euro-Wabb. The three other patient organisations seem not to have been involved in the activities of Euro-Wabb.

In terms of research projects, there is a FP7 European project named EUCLILIA which is dissecting the physiopathology of the disease but with no clinical part. The only on-going project on the natural history of Bardet-Biedl syndrome takes place in Essen (Germany). This group is not involved in Euro-Wabb.

2.1.3 Proportion of stakeholders involved in Euro-Wabb activities for Alström syndrome compared to potential stakeholders

During the period, many basic research articles were published on Alström syndrome but only 1 on the clinical aspect (Curr Genomics;2011,12(3):225-235) by experts from the USA. There is no publication of clinical guidelines, except in Spain (in Spanish) in 2010. The clinical utility gene card for Alström syndrome was updated in 2013 with partners of Euro-Wabb as co-authors.
In terms of specialised clinics, the only country with an expert clinic fully dedicated to Alström syndrome is the UK in Birmingham, the centre coordinating Euro-Wabb. In all other European countries the patients attend unspecific expert clinics.

In terms of clinical laboratories, 26 laboratories in Europe can test for Alström syndrome, according to Orphanet. They are located in Estonia, Germany, France, Italy, Netherlands, Poland, Portugal, Spain, Switzerland and United-Kingdom. Only 6 laboratories are listed on the Euro-Wabb website.

In terms of patient organisations, there are only two of them specifically dedicated to Alström disease, in UK and in France. Both of them are associated with the project.

In terms of research projects, there is no clinical research on the disease listed in Orphanet except from a group in Cambridge and another in Torquay(UK).

2.2 Monitoring of Impact (based on website and the visits it receives)

It was planned to monitor the impact of the project using accesses to the website as a proxy. This is impossible to do as the current version of the website does not provide access to all the products of the Euro-Wabb project: the clinical guidelines are not published; the registration process is not described and there is a total absence of communication about it. Therefore the frequentation of the website reflects only the potential interest for EuroWabb.

It was envisaged to compare statistics of downloads of clinical guidelines for RDS, available of the EuroWABB website and of Orphanet, with comparable clinical guidelines for other diseases in the same range of prevalence. This is not feasible as the EuroWABB guidelines are not accessible yet. To give an idea of the usual number of downloads for this type of document, the clinical guidelines for Bardet-Biedl syndrome in French, published in 2012, are downloaded over 15,000 times per year and the clinical guidelines for Alström syndrome in Spanish, published in 2010, are downloaded over 1,200 times per year.

In conclusion this project can be considered as successful in most of its aspects but failed in delivering so far real services to the patients and the health care community although they are potentially available. It can be recommended that the communication through the website is improved and that the collaboration with Orphanet as a route to these services is implemented.