



### Science Meeting – Scientific Report

***Proposal Title:*** *Completing the circle: shared opportunities to address the challenge of orofacial clefts, Application Reference N°: 4994*

#### 1) Summary (up to one page)

The primary objective of taking the EUROcleftNet conference to Bulgaria was to fulfil one of the major objectives of the Network – to boost involvement from Eastern EU countries in CLP research activities.

The Gateway project has underpinned recruitment to the conference and has been a real success from Gareth Davies and his team using a limited budget (approximately €8000 spent) which has created a good complimentary resource to previous discussions.

The Gateway project has been a 2 step project firstly circulating questionnaires, then analysing the data and building a website. The website has been live since May and the hope is that a new proposal can be sent to ESF for a Research Library to be set up to continue this work which become a hub for professional networking and a place to share ideas. The budget for this would be similar to the Gateway project which we hope ESF would be keen to fund as it is improving research capacity.

The network will seek to facilitate improvement of the research skills and capacity within EUROcleftNet and set up here to collect the samples and create a database with all of the information with the use of a consortium agreement to combine the resource. Michele has expertise in his lab and knows what needs to be done in the lab to house the DNA for future use. To date, 1100 trios have been collected but not all are complete. The original proposal was to collect blood samples but in the latter stages of the project buccal swabs were used as an alternative option to collect larger numbers of DNA samples to achieve the target numbers in the EUROCRAN project.

Short / exchange programmes must be research related with short programmes being up to 15 days and exchange programmes lasting from 15 days up to 6 months. The genetics programmes have already benefitted from exchanges, and opportunities such as the Gateway project, COST project, CLIPSI speech project and the Task Force could also be possibilities for exchange programmes.

#### 2) Description of the scientific content of and discussions at the event (up to four pages)

##### **Plovdiv Conference – workshop 1 Multidisciplinary treatment**

**Facilitators:** Gunvor Semb and Bill Shaw

This was a large workshop with around 50 participants from all disciplines. The main focus for discussion was improved treatment outcomes gained through collaborative

evidence-based research. Participants endorsed the recommendations that came out of the Task Force meeting in Orlando in May.

- Multinational collaboration only way to achieve evidence based cleft care
- Achieve agreement on global standards for documentation and outcome measures for all disciplines and cleft types

To make research collaboration effective it was essential there was an agreed consensus on

- What you measure
- When you measure (short and long term measures are important)
- How you measure

To guide the workshop participants through this there were presentations from top level clinicians in the respective fields: **Orthodontics** (Gunvor Semb), **Speech and language therapy** (Anette Lohmander), **Nursing** (Lisa Smegaard), **Surgery** (Brian Sommerlad), **Psychology** (Martin Persson) and **Patient perspective** (Gareth Davies).

Each presentation highlighted the challenges faced and there was further discussion around points raised within the Task Force:

- Research methodology has developed
- Statistical methods have changed
- Outcome measures changed: more focus on patient centred outcomes
- Not enough collaboration between clinicians and researcher (they do not know each other and do not have opportunities to find out about common areas of interest)
- Collaboration needs to start at the beginning stages of the design of the experiment
- Input from other disciplines is crucial to good study design and controlling of confounding variables

There was a lot of debate about how you effectively measure ‘well-being’ of the patient and family – it was acknowledged that the ultimate test of successful treatment was whether the patient and family were happy. Assessing this was not always straightforward and it was noted that one third of the areas for research listed as important by users related to psychosocial adjustment (James Lind Alliance, UK)

Some participants wondered how you could begin to embark on collaborative research when other centres/clinicians showed no interest in collaborating. One way of addressing this might be through patient organisations where they existed – patients and families are highly motivated and they can be effective in lobbying for a cleft care agenda on a national scale. This was happening in Bulgaria. It was also stressed that collaboration/outcome studies were still valid even if they began on a very small scale

At the end of the session participants were moving into different groups of specialist to discuss strategies and good practice. Whilst there was not enough time to develop discussions, the groups facilitated the exchange of contact details for future advice and networking.

### **EUROCLEFTNET Conference (Plovdiv) – Workshop 2 Genetics Report**

The context in which EUROCLEFTNET as a research network exists is to enhance and advance knowledge on how to a) improve quality of care and b) elucidate the aetiology and strive towards primary prevention of clefts of the lip and palate.

The issue of non-communicable diseases at the 2010 World Health Assembly included, for the first time, birth defects; and cleft lip and palate was included among the birth defects specified. This has led to the Global Burden of Disease (GBD) initiative and risk factors in the aetiology are specifically mentioned. It is therefore incumbent on scientists around the world to assist in the global effort to identify and attempt to deal with risk factors (genetics and environmental).

Countries represented at the workshop were as follows: Denmark (Dorthe Pedersen), Norway (Anil Jujessur), Germany (Elisabeth Mangold), Slovenia (Ales Maver), UK (Sarah Jones and Peter Mossey), Italy (Michele Rubini), France (Phillippe Pellerin), and USA (George Wehby).

In addition to the countries represented around the table, a number of the partners had interests in, and potentially DNA samples from, other populations; examples being other European countries such as Ireland, Hungary, Bulgaria, Poland; populations in other parts of the world such as India, Sub-Saharan Africa, Australia, Middle Eastern Countries (Saudi Arabia, Egypt etc.). Advantages of a range of countries in addition to increased numbers would be the possibility in due course of stratifying according to ethnic group and perhaps aspects of ancestry.

#### *Current status of CL(P) research*

1. *Candidate Genes:* The top candidate genes/loci as determined by previous research that need to be investigated further from a functional viewpoint e.g. IRF6, FOXE1, 18q24, 10q25 (VAX1) etc.
2. *Environmental Factors:* It was uncertain how consistent the information on environmental factors might be and the commonality might only include smoking, alcohol consumption and folic acid intake, other multi-vitamin supplements?, medications and drugs? A master spread sheet could be created to list all the existing information on genetics and environmental factors.

*Specific Interests:* It would be necessary to draw up a series of interesting projects led by individuals whose interests, knowledge and expertise were in particular aspects – and this may be either on genetic loci or specific risk factors such as smoking, alcohol, nutrition or obesity.

The end result of this would be a EUROCLEFTNET directory of resources and biobank. Such a resource would underpin the idea of a pan-European data set and would also provide guidelines for future collection of DNA and environmental data.

In addition, phenotypic data (including sub-phenotypes), family history (cleft recurrence) and specifics on environmental data.

Trans-Atlantic Consortia: George Wehby had provided some information and ideas in advance of the meeting with a view to initiating discussion on possible types of trans-Atlantic consortia for data sharing which could be described as a study in genetics and environmental factors using an instrumental variables approach. A major limitation of this is the problem that the EUROCRAN data set was based on a case triad design and does not contain control data, and that the German patient sample (for which GWAS data are available) is not population-based.

b. Genome wide association studies (GWAS) consortium incorporating environmental factors.

The value of this would be to have GWAS data for much larger samples than previously. It would be crucially important that all cases in such a study had consistently good quality environmental data, thus allowing multiple genome wide GEI analysis. This condition would impose limitations as there may not be a consistent collection of linked environmental data.

c. Global Meta-Analysis of existing genotypic data.

This has the potential to result in a large combined data set, could be case only samples and could include the most commonly investigated candidate genes. It has the added advantage of not requiring the sharing of DNA samples and no additional funding resource would be required at the outset. It was felt that this would be a reasonable collaborative approach and further investigation of pathways and GGI + GEI starting with IRF6, FOXE1, MSX1 and the FGFR pathways. This would enable more robust estimates for the functional significance or the strength of certain candidates in certain types of OFC.

*Future funding:* An additional advantage of pooling would be to prepare ourselves as a trans-Atlantic group that has credibility for applying for additional grant funding on both sides of the Atlantic. Further funding would still be necessary for functional genomics studies and to investigate beyond common variants which are likely to have a small effect size but are acting across different populations.

*Future Funding:* Horizon 2020. Examination of the 2020 preliminary information may provide opportunities to examine OFC pathways using the 'OMICS' approach and requiring bioinformatics. A possible approach would be to use the steering group expertise to identify and prepare a brief outline of a proposal using combined expertise/resources and consider the fit for such a proposal to obtain funding. The initial draft of the Horizon 2020 work programme for 2014/15 includes the following: PHC4 translating 'OMICS' into stratified approaches.

PHC10: Developing new diagnostic tools – INVIVO medical imaging (for phenotype and outcomes).

PHC13: New therapies for rare diseases

PHC17: Effectiveness of healthcare interventions in the paediatric population

PHC26: Innovative e-health approaches (may include SMS messaging for prevention)

Some other aspects of the work programme may apply to clefts if considering the social and psychological aspects; and in Europe we can also refer to health inequalities in the field of OFC. Opportunities for cleft lip and palate in the area of "rare diseases" would be limited to Syndromic as opposed to non-syndromic clefts and further useful work could be done in a number of craniofacial syndromes such as VDW, 22q11 especially if a pan-European approach is required for collecting samples.

*Message to European Teams:* Teams can be offered assistance if they are willing to become involved in genetic data collection and the rationale for doing so is based on the fact that individual populations are likely to have different genetic susceptibilities. Some teams are keen to become involved in genetics projects and for standardisation and for consistency information can be supplied to the clinical teams regarding the methodology for collecting DNA samples and the EUROCRAN questionnaire for collecting environmental data. Procedures related to consent for collecting the samples should also be consistent, particularly if there is a need to transfer samples for genetic analysis.

*Short visit/Exchange programme in EUROCLEFTNET:* This ESF programme enables the collaborating partners in EUROCLEFTNET to take advantage of an opportunity for exchanging skills/expertise targeted towards improving research capacity or carrying out a specific task based research project. This information can be disseminated to those who have expressed an interest in these funded exchanges. The countries that are contributing to the funding of the ESF network stand to benefit most from the exchanges and Bulgaria are applying to become a contributing partner.

A call will be circulated to everyone requesting an outline application so that the programme of exchanges can be submitted to the ESF by say 30<sup>th</sup> November 2013.

*Dates for future meetings:* It is anticipated that the receipt of application for exchanges will generate the need for another get together to discuss the details and distribution of these and it may be best if this meeting is held at ESF HQ in Strasbourg early in 2014.

In 2015 the next meeting of the European Craniofacial Congress will take place in Gothenburg, Sweden and it is likely that we will participate in that meeting.

**3) Assessment of the results and impact of the event on the future directions of the field (up to two pages)**

The location of this conference in Plovdiv was aimed towards engagement with the cleft teams in Eastern Europe. It is hoped that future inter-centre collaborations will involve teams across Europe. Future short visit and exchange programmes will be designed to underpin this collaborative activity. Below are the themes that offer opportunities for collaborations.

**Theme(s) for the Plovdiv conference and future research**

- a. Inter-centre comparison of outcomes (all disciplines)
- b. Task Forces
- c. Systematic reviews?
- d. Future RCTs and other research?
- e. Parent participation
- f. James Lind in a range of countries
- g. Translational research

Points raised were: identify partners for writing into the strategy, do we need to do more where there is data gaps i.e. consanguinity, passive smoking etc., Task Force to start collecting data to start teaching, tapping into existing resources between countries e.g. Healing Foundation protocols can be published and adapted, focus on treatment e.g. hearing, speech and language problems and psychological aspects using data from preliminary studies as this has not been measured in the past.

The James Lind Alliance is a UK based survey looking at patient perspective, taken on by a charity that was an initiative created by the same person that started the Cochrane Collaborations. As families are rarely involved in studies, this programme which has been running for approximately five years is looking to discover what top ten things of what people want. This list that was created has come from a group of patients and families and a small number of surgeons, and used a Delphi process; and while desirable, it would not be easy to reproduce in other countries.

The Gateway Project has been a 2 step project firstly circulating questionnaires, then analysing the data and building a website. The website has been live since May and the hope is that a new proposal can be sent to ESF for a Research Library to be set up as discussed above. Anette suggested linking the EUROCRAN data. More information can be used for training and running clinical trials if the website was interactive. The Gateway project has a link its website to CLIPSI and the potential next step is that it could be used in new languages. Anette has the organisation for video clips etc. to be set up but not the money to facilitate this. A short exchange programme could be sought here to help set this up.

The Task Force initiative has worldwide participation which met in Orlando this year. The next meeting is to be held in India in 4 years' time. They have been given money to set up a resource / library of resources / materials of assessment so there may be potential for these to work together.

**Annex 4a: Programme of the meeting**

## **EUROcleftNet Research Conference**

*“Completing the circle: shared opportunities to address the challenge of orofacial clefts”*

### **Wednesday, 25 September 2013**

16.00 **Registration Opens**

19.30 -21.30 **Welcome Reception**

### **Thursday, 26 September 2013**

08.00 **Registration Opens**

**Introductory session chair: Prof Peter Schachner, (surgery, Austria)**

08.30 – 08.45 **Welcome** - Prof Youri Anastassov (and Mayor of Plovdiv)

08.45 – 09.00 **EUROcleftNet report** – Prof Peter Mossey

09.00 - 09.15 **Introduction to the European Cleft Gateway** – Gareth Davies

09.15 - 09.45 **Keynote lecture:** Prof Michele Rubini: *Genetics and potential for prevention of orofacial clefts* **Chair:** Dr Elizabeth Mangold (genetics, Germany)

09.45 - 10.15 **Coffee and trade stands**

10.15 - 10.45 **Keynote lecture:** Dr George Wehby: *Environment factors and gene-environment interaction in conferring risk for orofacial clefts* **Chair:** Prof Peter Mossey

10.45 – 12.30 **Free papers: research into prevention** (epidemiology, genetics, environment, gene environment interaction, diet and supplements)

12.30 - 13.00 **Keynote lecture:** Dr Ingeborg Barisic: *The EUROCAT Register* **Chair:** Dr Maver (Genetics, Slovenia)

13.00 - 14.00 **LUNCH**

14.00 - 14.30 **Keynote Lecture:** Prof William Shaw: *The potential of European collaboration in cleft research* **Chair:** Prof Vesna Kozelj (Surgery, Slovenia)

14.30 - 15.30 **Free papers – research into treatment (outcome research, nursing, surgery orthodontics, speech therapy, psychology, audit)**

15.30 - 15.45 **Coffee and trade stands**

15.45- 16.15 **Keynote Lecture:** Mr. Brian Sommerlad: *Evidence based primary cleft surgery: what are the alternatives to Randomised Controlled Trials (RCTs)?* **Chair:** Anette Lohmander (Speech and language therapy, Sweden)

16.15 - 17.25 **Free papers – research into treatment (outcome research, nursing surgery, orthodontics, speech therapy, psychology, audit)**

18.00 **Close**

20.00 – late **Gala Dinner**

### **Friday 27<sup>th</sup> September 2013**

**Plenary Chair:** Prof Philippe Pellerin (Surgery, France)

09.00 - 09.30 **Keynote Lecture:** Prof Gunvor Semb: *European Cleft collaboration a world perspective – feedback form the 2013 Orlando Task force*

09.30 – 09.45 **Guest lecture:** Prof Philippe Pellerin *European collaboration – the case for a European federation of professional associations* **Chair:** Prof Youri Anastassov

09.45 – 10.15 **Keynote lecture:** Mr Haydn Bellardie *Sharing and comparing – the importance of outcome measures and intercentre comparisons in Africa*

10.15 – 10.45 **Coffee and trade stands**

10.45 – 12.15 **Parallel workshops:**

*Development of novel research networks and collaborative approaches to outcome measurement*

**1. Genetics and prevention (Lead: Peter Mossey / Elisabeth Mangold)**

**2. Multidisciplinary treatment (Lead: Bill Shaw / Gunvor Semb)**

**Plenary**

12.15 – 12.45 **Feedback from workshops Chair:** Gareth Davies  
12.45 – 1300 **Guest Lecture:** Dr Maria Hortis-Dzierzbicka: "*Speech outcome of early onestage repair of UCLP - personal experience with over 1500 cases*".  
13.00 - 14.00 **Lunch**  
14.00 - 14.30 **Keynote lecture:** Dr Martin Persson - *How to address the psychosocial challenge of orofacial clefts Chair:* Rosanna Preston (CLAPA patient support group, United Kingdom)  
14.30 - 15.40 **Free papers – general**  
15.40 - 16.00 **Coffee and trade stands**  
16.00 - 16.15 Dr Ingeborg Barisic: *Euromedicat (Safety of Medication Use in Pregnancy) Chair:* Jana Angelova (Parent support, Bulgaria)  
16.15 -17.15 **Free papers – general**  
17.15 – 17.30 **Closing remarks**

#### **Annex 4b: Full list of speakers and participants**

Ingeborg Barisic, CROATIA; Yocheved Ben-Bassat, ISRAEL; Teodora Dimitrova, BULGARIA; Ege Dogan, TURKEY; Servet Dogan, TURKEY; Andrejka Eberlinc, SLOVENIA; Susanne Eifer Moeller, DENMARK; Jozef Fedeles, SLOVAKIA; Kalin Georgiev, BULGARIA; Maria Hortis-Dzierzbicka, POLAND; Ognyan Ivanov, UK; Sarah Jones, UK; Xiangyang Ju, UK; Miha Kocar, SLOVENIA; Olga Koskova, CZECH REPUBLIC; Alexandros Laftsis, BULGARIA; Darina Lukasova, CZECH REPUBLIC; Ieva Maulina, LATVIA; Inese Maulina, LATVIA; Andrew McBride, UK; Zuzana Oravkinova, SLOVAKIA; Dorthe Almind Pedersten, DENMARK; Zoran Pesic, SERBIA; Rosanna Preston, UK; Katarzyna Proczek, UK; Julija Roadjicic, SERBIA; Peter Schachner, AUSTRIA; Rona Slator, UK; Helen Smith, UK; Nataliia Tetrueiva, UKRAINE; Branislav Trifunovic, SERBIA; Liat Tzur-Gadassi, ISRAEL; Karolina Wojcicka, POLAND; Miroslava Yordanova, BULGARIA; Slavka Zacharova, SLOVAKIA; Anne Saarikko, FINLAND; Caroline Francois-Fiquet, FRANCE; Ales Maver, SLOVENIA, Gennadii Korotchenko, UKRAINE; Huiqing (Jo) Zhou, NETHERLANDS; Ivailo Radev, BULGARIA; Julia Neely, UK; Martina Drevensek, SLOVENIA; Milena Makaveeva, BULGARIA; Nesrin Saruhan; TURKEY; Phillipe Pellerin, FRANCE; Piotr Fudalej, SWITZERLAND; Radmila Dimovska, MACEDONIA; Radu - Iulian Spataru, ROMANIA; Albena Tzekova, BULGARIA; Alexandra Freeman, UK; Anrieta Petkova, BULGARIA; Cynthia Heynemann, POLAND; Dmytro Luchynskii, UKRAINE; Kateryna Ivanchyshyna, UKRAINE; Lisa Smedergaard, DENMARK; Maria Kazakova, BULGARIA; Marta Vassileva, BULGARIA; Nataly Borchenko, UKRAINE; Nedialka Slaninkova, BULGARIA; Nina Jordanova, BULGARIA; Penka Hristova, BULGARIA; Radost Velikova, BULGARIA; Regina Khater, BULGARIA; Savina Maneva, BULGARIA; Shaheel Chummun, UK; Simoneta Popova, BULGARIA; Svetlanka Bogdanova, BULGARIA; Brian Sommerlad, UK; George Wehby, USA; Gunvor Semb, UK; Ingeborg Barisic, CROATIA; Martin Persson, UK; Michele Rubini, ITALY; Peter Mossey, UK; William Shaw, UK; Anette Lohmander, Sweden; Elisabeth Mangold, GERMANY; Emma Southby, UK, Gareth Davies, FRANCE; Jana Angelova, BULGARIA; Vesna Kozelj, SLOVENIA; Youri Anastassov, BULGARIA; Astanand Jugessur, NORWAY; Haydn Bellardie, UK; Kortadinka Momneva, BULGARIA