

**Network for orofacial Clefts Research, Prevention and Treatment
(EUROCleftNet) 09-RNP-023**



Report of the 2nd EUROCleftNet Steering Group meeting

Date: 14th September 2011, Salzburg

www.esf.org/eurocleftnet

Present: Elisabeth Mangold (Germany), Anette Lohmander (Sweden), Bill Shaw (UK), Gareth Davies (ECO, Netherlands), Borut Peterlin (Slovak Republic) and Peter Mossey (UK, Chair).

Apologies for absence: Mario Merialdi (WHO, Switzerland) reported that he was unable to attend the meeting and Rolv Terje Lie (Norway) has been nominated by Norway as their representative, but was unable to attend. Dr Kirstin Steinhausen, (ESF Scientific Officer) and Ms Blanche Facchini, (ESF Administrator).

1. The tabled DRAFT agenda was formally adopted.

2. **Minutes of the previous meeting** held in Strasbourg on 9th June 2011 were tabled, proposed and accepted as an accurate record.

3. Matters arising from previous minutes.

It was noted that the formal minute of the meeting included an appendix that widely publicised our network in UK national and also international media following a press release from the University of Dundee EUROCleftNet. All other matters were included in the agenda.

4. Revision of the guidelines for running ESF programmes.

The Steering Group acknowledged the receipt of these revised guidelines and the regulations pertaining to procedures for all ESF programmes, the role of the RNP Co-ordinator and Steering Group, management of the budget and guidelines on information dissemination and communication.

5. Strasbourg meeting / workshop budget.

The revised budget as discussed at the Strasbourg was tabled and the procedure for application to ESF for the budget surrounding the Steering Group and workshop meeting in Salzburg including the prior approval of the budget and confirmation of this to the ESF RNP guidelines was outlined. The agreement at Strasbourg for a matching fund (from Transforming Faces

Worldwide (TFW)) arrangement to bring delegates from Eastern Europe to the workshop was outlined.

- **Questions in relation to budget expenditure related to the annual collection from the various contributing bodies particularly those that had agreed to channel their donations through ECO.**
- In future years ECO would require to have received donations from the various bodies prior to reimbursing the ESF centrally.
- It was expected that other aspects of the budget expenditure in relation to future conferences, workshops and invitation of speakers would be discussed on a conference by conference basis.
- There was also a need to discuss exchange visits among the Steering Group members.
- It was noted that the amount available for conferences and workshops in the last 2 years was less than for the first 3 by virtue of the German contribution in years 4 and 5 not having yet been confirmed or pledged.
- It may however be possible to submit a future application to obtain this continuation of funding.
- Mario Meriardi reported in prior correspondence with the Chair that the €4000 per year from WHO would be forthcoming, and the first instalment would be paid later this year, possibly through the University of Dundee as a WHO CC.

6. Procedures for meeting approval and payment of expenses.

Having approved the second Steering Group and first EUROCLeftNet workshop meeting, the meeting budget is to be transferred from the ESF to the University of Dundee. All invoices should be sent from Steering Group members and those who receive prior approval to come to the Salzburg meeting should complete the ESF travel claim form and return this within one month following the meeting to Peter Mossey, Dundee University Dental School, Park Place, Dundee, DD1 4HR. It was also noted in the guidelines that 80% of this budget is paid in advance with the further 20% being paid on receipt of the meeting report (Steering Group and a report of the EUROCLeftNet workshop).

7. Appointment of EUROCLeftNet Administrator.

It was reported that, further to negotiations with Kirsten Steinhausen and Blanche Facchini, a departmental secretary, Kelly Leslie based at the University of Dundee Dental School was appointed to assist with the EUROCLeftNet administration commencing 1st September 2011. Kelly was involved in the preparation of the Steering Group agenda, EUROCLeftNet meeting and workshop programme etc. She will deal with the financial aspects of the network, keep the accounts, deal with the invoices and receipts etc. The time spent and the associated expenditure will be in line with the regulations outlined by the ESF RNP programmes.

8. Review of programme objectives and planned activities.

It was agreed that the aims and objectives of the Workshop following on from the Steering Group meeting would be to consolidate priorities with regard to research in both treatment and aetiology / prevention and there was also a presentation relating to grant funding opportunities – mainly related to EU

Framework Programme 7 as funding would be essential to deliver our objectives. The subsequent workshops would identify future programme objectives and planned activities as the Network evolves.

9. Information dissemination and EUROCLeftNet logo.

The draft logo for EUROCLeftNet as designed by Michele Rubini (Italy) was discussed and subject to a slight modification will be adopted. It was agreed at the Strasbourg Steering Group meeting that we should seek EUROCLeftNet logo, that a brochure would be produced and also that the EUROCRAN website could be revamped and reinvigorated as the EUROCLeftNet website.

- Peter Mossey will (a) proceed to finalise & disseminate the logo (b) liaise with Blanche Facchini and Kirsten Steinhausen regarding the brochure which was mentioned at the Strasbourg Steering Group meeting and (c) seek a date for a website meeting, probably in Manchester hosted by Bill Shaw. Gareth Davies, Anette Lohmänder and Michele Rubini expressed an interest in being party to these Website discussions.

10. EUROCLeftNet workshop (following this meeting)

A number of comments were received from Steering Committee members regarding the afternoon workshops and the following were the main issues and action points:

- We might want to appoint working groups at the EUROCLeftNet meeting to expand particular themes and develop courses of action. This may mean different groups leading research applications.
- We should bear in mind the East-West agenda in Europe. Significant inequalities exist in access to and quality of care between the Western European countries and some of the Eastern European countries such as Bulgaria, Romania, Hungary and Ukraine. Such issues need to be incorporated in our research agendas and organising a conference in one of the Eastern European countries might highlight the importance of their involvement in CLP research.
- Communication/dissemination. An effective strategy for this should be devised in collaboration with stakeholders such as ECO, WHO, ICBD, EUROCAT and other users and the EUROCRAN website should be re-launched with representation from these stakeholders to input to discussions.

11. Draft EUROCLeftNet strategy

The following was tabled as the statement espousing the EUROCLeftNet strategy

Primary objective – to significantly increase the European capability for cutting edge research and to improve the treatment of cleft lip and palate and ultimately its prevention.

Steps towards this objective:

1. Development of a strategy for engaging European cleft teams in laboratories in a new European collaborative research initiative.
2. Development of a priority list of questions for patient research on treatment and on the causes of cleft lip and palate.

3. To develop with affected families a priority list of research questions.
4. To develop with affected families care outcomes.
5. To initiate a portfolio of externally funded clinical and genetics research.
6. To continue promoting the concept of clinicians and geneticists in research which underpinned the success of Eurocran.
7. To engage with a wide range of stakeholders (including beyond Europe) to ensure that this ESF is able to address OFC holistically and globally.

12. Future meetings: Steering Group, workshops and conferences

- Meetings: (6 in total, with 2 in first year).
- Workshops: (4 in total).
- Conferences: (2 in total, years 1 and 3).
- Exchange visits across a range of sites.
- Website production, linking, translation and maintenance

It was agreed that we should aim to have all of our activities aligned to arranged events to optimise the use of ESF funds, and we should explore the possibilities that (a) the next Workshop in 2012 could be aligned to an event in Scotland – the 10 year anniversary of the Scottish Association for Cleft Lip and Palate (SCALP) is scheduled for September 2012 and (b) we should aim to hold a conference in Eastern Europe. Also the 2015 European Craniofacial Conference (as yet undecided) could possibly be the venue for our last Workshop.

Action Points:

- Make further enquiries about the planning of our next major EUROcleftNet workshop alongside the 2012 SCALP conference in Scotland 14 – 16th September 2012.
- Make further enquiries about a conference or Workshop in Eastern Europe in 2013 which Country, what venue, what facilities are available, research programme, budget available etc? – and perhaps most importantly does it serve our overall research aspirations and strategy ?.
- Gareth has suggested that Plovdiv is one possibility, and we should look at that and perhaps also at other possible venues such as Lubljana, Bled, Budapest or Bucharest. Would any of these Eastern European Countries happen to have a conference that we could align to in 2013 ?

There was no other competent business.



Agenda for First EUROcleftNet workshop and Steering Group meeting in Salzburg

Date: 14th September 2011, Salzburg
www.esf.org/eurocleftnet

09.30 – 10.00: Registration for workshop and tea/coffee available.

10.00 – 11.00: EUROcleftNet Steering Group meeting

11.00 – 12.30: Plenary Presentations 1 and 2:

1. “Research priorities in treatment/quality of care” **Shaw / Lohmander** (25 minutes).
2. “Research priorities in genetics/prevention” **Rubini / Peterlin** (25 minutes).

(Each of these presentations would be followed by a 20 minute structured discussion on each topic).

12.30 – 13.30: Lunch break.

13.30 – 14.10: Plenary Presentation 3 – “Funding opportunities for EUROcleftNet” (20 minutes) followed by a 20 minute structured discussion.

14.10 – 14.40: 4 or 5 workshops (x 30 minutes) on topics that will be relevant to the functioning of EUROcleftNet such as:

1. Optimising the use of short exchange visits in the support of EUROcleftNet
Chairs: Elizabeth Mangold / Kirsten Molsted
2. Research methods – strengthening collaboration between clinicians and laboratory researchers in EUROcleftNet research. **Chairs: Bill Shaw / Concha Martinez**
3. Involvement of commerce/industry in EUROcleftNet research. **Chairs: Ashraf Ayoub / Michele Rubini**
4. Communication and politics - bringing users and clinicians together at a European level to address inequalities in cleft care". **Chairs: Gareth Davies / Ann Marie Kuijpers Jagtman**
5. European/Latin American research collaboration. **Chairs: Peter Mossey / Inge Trindade**

14.40 – 15.00: Coffee break.

15.00 – 15.50: Workshop feedback. 10 minutes each.

15.50 – 16.30: Plenary Discussion, with identification of possible gaps in EUROcleftNet in terms of countries, expertise and involvement of or collaboration with overseas units.

16.30: Workshop ENDS



Report of the 1st EUROCleftNet Workshop

Plenary presentations

Following a brief introduction on the background of EUROCleftNet, mapping its evolution from a biomed funded EUROcleft project which spawned the ScandCleft project and in combination with a previous ESF grant two groups working on clefts in Europe combined their expertise to apply for Framework 5 funding and this resulted in EUROCRAN.

The previous ESF funded network (1998-2001) was entitled “Gene-environment interaction in early human development: a demonstration project in orofacial clefts”. The success of EUROCRAN led to the continuation of the model of scientists working alongside clinicians to deliver its objectives and the overall EUROcleftNet project is described as “Post-GWAS genetic research”.

The recent GWAS “phase” of research in the field has spawned a comprehensive list of putative genetic loci, (a) to fine map the cleft loci and identify the functional gene variants (b) embark on epigenetic and functional genomics (c) gene-environment interaction, (d) unravel the epistatic interactions that are part of the aetiology (e) translate genetic findings into clinical practice and prevention strategies.

EUROcleftNet Aims:

Collaborative aims:

- to adopt a multi disciplinary approach
- to be fully inclusive across the EU, including the Eastern European States

in collaboration with

- the World Health Organisation (WHO)
- the European Cleft Organisation (ECO)

Two plenary presentations followed on the priorities in EUROcleftNet for (a) genetic research and (b) research into quality of care.

**Plenary presentation 1: “Research priorities in treatment/quality of care”
Professor Bill Shaw and Professor Anette Lohmander**

Bill Shaw and Anette Lohmander together presented the priorities in orofacial cleft treatment research based on the three broad areas of

1. Evidence based care.
2. Quality assurance.
3. Addressing inequalities in access to and quality of care.

Previous European studies such as EUROcleft enabled collection of information that changed the provision of cleft care in the UK with a reduction from 57 centres for cleft treatment to 11 regional services.

The EUROCRAN research programme integrated clinicians and laboratory scientists working together and the current situation is as follows:

- Several protocols can achieve good results but can't tell what's “best”
- But we *can* make sensible choices based on the burden of care
- Choose a protocol with a good record and the lightest burden
- If you think your method is better but involves an increased burden, get a grant and test it properly
- And above all, don't export complex unproven protocols to developing countries! Export safe, low burden, reliable procedures that can be easily learned

WHO research priorities:

In a series of consensus meetings between 2000 and 2004 the WHO developed, by consensus a priority list and our research remit in Europe is to assist with the delivery of these:

- trials of surgical methods for the repair of different orofacial cleft subtypes, not just unilateral clefts;
- trials of surgical methods for the correction of velopharyngeal insufficiency;
- trials of the use of prophylactic ventilation tubes (grommets) for middle-ear disease in patients with cleft palate;
- trials of procedures in cleft care that place an increased burden on the patient, family or medical services, such as presurgical orthopaedics, primary dentition orthodontics and maxillary protraction;
- trials of methods for management of perioperative pain, swelling and infection; and nursing;
- trials of methods to optimize feeding before and after surgery;
- trials addressing the special circumstances of care
- in the developing world in respect of surgical, anaesthetic and nursing care;
- trials of different modalities of speech therapy, orthodontic treatment and counselling.

These meetings also identified areas of need in the world and the need for improving evidence based care using the EUROcleft model and this has been successfully transported to other sites resulting in clinical audits in America, India, Japan and

Brazil. EUROcleftNet should continue to lead the way in Europe and use the WHO priority list to identify clinical problems that require further research.

Speech research:

Not all babies born with CLP will have speech difficulties. What causes the variation?

- within centre: cleft type, surgeon, additional, hearing impairment
- between centres: also surgical procedure

Rather good knowledge regarding differences related to cleft type.

Increase knowledge on impact of surgical procedure, need to use standardised procedures according recommendations in Eurocleft and Eurocran.

For data collection: decided ages, audio/video recording, decided speech material

For data analysis: randomised blinded recordings, multiple judges, external judge/s, and reliability measures

Prevent speech and communication disorders related to CLP by finding the optimal surgical treatment procedure for the palatal cleft (requiring standardised evaluation of outcome) and the development of strategies for early identification and intervention of additional and hearing impairment.

Expand data collection and outcome variables from Structure and Function to Activity (intelligibility), Participation (communication in society), and Contextual factors such as Personal and Environmental.

Structured discussion: the following issues were raised and discussed:

- What are the clinical research priorities now?
- How can we stimulate/support countries and centres who are still working in isolation?
- How do we get clinicians and geneticists to work together in research
- Blood samples for optimum DNA?
- Questionnaire information incl phenotype?
- How do we involve patients in research planning?
- Do we need to update the register/website /minimum standards from diagnosis and cultural variations etc?
- Educational initiatives to support research?
- Surgical issues influencing speech / communication?
- Neonatal cleft care – standardisation?
- Politics and funding among stakeholders?

Plenary presentation 2: “Research priorities in genetics/prevention”
Professor Michele Rubini / Dr Borut Peterlin

The main highlights in this research were the detailed examination of both genetic and environmental contributors to orofacial clefts, the heterogeneous aetiology, the search for cleft lip and palate genes, recent findings in genome-wide association studies and particularly the finding that the susceptibility genes for cleft lip and palate differ in different populations and only part of heritability of oral clefts can be explained by common susceptibility variance. This emphasises the need for a large number of families and Europe is a useful landscape for this as homogeneous ethnic origin is a major advantage.

Gene environment interaction:

It is important to emphasise risk associated with maternal and paternal genotype, gene environment interaction and this requires detailed information on exposure to environmental factors during early pregnancy. Also in the search for maternal effects the maternal grandparents would provide useful information.

Folic acid and orofacial clefts:

The evidence for protective effective folic acid in orofacial cleft aetiology remains controversial and further research is needed into not only folic acid but other multivitamins also. And this applies more to cleft lip and palate than isolated cleft palate. EUROClleftNet can address this major research problem through basic science research on the processes involved in murine palatogenesis and also by the attenuating effect of folic acid and dietary multivitamins in the mouse model. In addition elements of the folic acid pathway can be investigated in human case control and case triad studies. The animal model is useful to assess the efficacy of natural folates and prevention of occurrence of specific types of cleft. The new EUROClleftNet aims to increase the European capacity for cutting edge research and the benefits from European collaboration include the diversity of populations when looking for consistency of association increasing sample size, a broad range of expertise, engagement with colleagues in Eastern Europe, addressing health inequalities and in the process of all of the above, the training for a new generation of new young researchers in the field.

Conclusions:

Dr Rubini concluded that the top research priority would be to create a fully informative large European data set of non-syndromic orofacial cleft cases, their parents and in at least some studies the maternal grandparents and pedigree with familial cleft lip and palate. In collaboration with clinical colleagues it was also important to collect good phenotypic information and details of pregnancy and exposure to environmental factors. This would form the raw material for the following:

- Identify ns-OFC associated gene variants (**GWAS, NGS**)
- Test gene-environment interactions (**Animal model**)
- Identify functional gene variants (**functional studies**)

- Measure tissue specific **epigenetic profiles** in tissue removed after closure of the cleft by surgery
- Develop a **panel of gene variants** that could be screened for ns-OFC risk assessment purposes in the clinical setting
- Develop **integrated models** to assess the risk of occurrence and recurrence of cleft

Proposed activities

- **WP1** Population based Genomics and Epigenetics studies
 - **Project 1:** Genome wide association studies; Functional studies
 - **Project 2:** Population based Epigenetics (DNA methylation in candidate genes)
- **WP2** Sub-phenotyping in CP and CL/P and computational biology
 - **Project 3** Sub-phenotyping in CP and CL/P; parental craniofacial morphology and residual soft tissue deformities in probands at 10y age
- **WP3:** Animal models: Functional genes in OFC
 - **Project 4.** Folic acid and cleft palate in wild type and *Tgf-β3* null mice
 - **Project 5:** Generation of a 4D gene expression atlas of developing lip and palate in mouse and chick
- **WP4:** Clinical research to optimise protocols and equalise standards in Europe
 - **Project 6:** Assessment of access to treatment, quality of care and genetic research for OFC in the 9 former *soviet bloc* EU member states

Structured discussion:

The main issue arising in the structured discussion was the collection of DNA and whether blood, buccal swabs or saliva samples produce an ideal resource for DNA to be used in future studies in cleft lip and palate. It was resolved that this would be the topic of one of the afternoon workshops.

Plenary presentation 3: “Funding opportunities for EUROcleftNet”

Professor Peter Mossey

Research funding opportunities in Europe:

The aims and objectives of EUROcleftNet can only be realised if we are able to obtain further funding and among the funding opportunities are

1. The European Research Council
2. FP7 Innovation Programme
3. Marie Curie FP7 funding opportunities

1. The European Research Council (ERC): this is a newly formed pan-European funding organisation with a budget of approximately 7.5 billion Euros and is investigator initiated frontier research across all fields on the basis of scientific excellence. The grant opportunities outlined were as follows:

1. ERC starting grant designed for young researchers (deadline 9th November 2011).
2. ERC advanced grant for established researchers (deadline 16th February 2012).
3. ERC synergy grant to “bring together complimentary skills, knowledge and resources in new ways in order to jointly address research problems”. This enables a group of between 2 and 4 excellent principal investigators to pursue a large scale frontier research project (deadline 25th January 2012).

2. FP7 opportunities. Those outlined were in the following areas:

1. large scale data gathering
2. clinical utility of –omics for better diagnosis for rare diseases
3. databases, biobanks and clinical bio-information hub for rare diseases
4. applying systems biology approaches for understanding multi-factorial human diseases and their co-morbidities.

One of the pre-conditions for four above is the active participation of industry and patient organisations.

3. Marie Curie actions:

The advantage of the Marie Curie system is that it is a bottom up approach and therefore it is possible for us to devise and submit an application. The Marie Curie grants also encourage involvement of industrial partners as the overall objective is to train a new workforce to be involved in the commercial development of academic research. The different types of Marie Curie grants are;

1. An initial training network (ITN)
2. Industry academia partnership (IAPP)
3. International research staff exchange scheme (IRSES)

Brief details of these appear below:

An ITN supports researchers:

- With up to 5 years experience (inc. doctoral study)
- From all over the world
- For periods of 3 - 36 months (ESRs)
- For periods of up to 24 months (EXRs)
- Researchers can be seconded to other partners for up to 30% of recruitment

Researchers can be of any nationality but must comply with the mobility rule.

Marie Curie Industry Academia Pathways & Partnership (IAPP)

- It is a two-way partnership with at least one commercial enterprise and one academic organisation in two different Member or Associated Countries
- An IAPP aims to increase industry-academia co-operation by:
- Supporting the creation, development, reinforcement and execution of strategic I-A partnerships

International Research Staff Exchange Scheme (IRSES)

- Aimed at strengthening partnerships through staff exchanges and networking
- Support research organisations through co-ordinated exchange programme
- Exchange good practice

Who can participate in IRSES?

- Researchers, technical, management staff
- EU member states and NAS (further slide)
- EU “neighbourhood” states: Armenia, Algeria, Azerbaijan, Belarus, Egypt, Georgia, Jordan, Lebanon, Libya, Morocco, Palestine, Syria, Tunisia, Ukraine
- Countries with S&T agreement with EU: Argentina, Australia, Brazil, Canada, China, Chile, Egypt, India, Japan, Korea, Mexico, NZ, Russia, South Africa, Tunisia, Ukraine & USA.

Publication dates and deadline:

When the timetable of dates and deadlines was examined it would appear that the Marie Curie ITN is the best possible opportunity provided we are able to identify suitable industrial partners and the deadline for submission of the application is 12th January 2012.

Funding beyond the EU:

It was also noted that the EUROleftNet policy includes a global approach to OFC research and the funding opportunities include:

1. The Gates Foundation – “New grand challenges exploration topics”. This was described as an initiative to encourage innovative and unconventional global health and development solutions among which are exploration of new solutions in global health priority areas. Because of the WHO resolution at the World Health Assembly in May 2010, cleft lip and palate can claim to be a global health priority.
2. One FP7 call in Health is entitled “Multi-lateral co-operation between Europe, Africa and Latin America on public health and health services research”. This includes “strategies in order to provide evidence on best practice” and also “health inequalities affecting children, adolescents and mothers (families)”.
3. A special feature in this triangular co-operation between Europe, Africa and Latin America was that Brazilian authorities were expected to issue a complimentary call to finance Brazilian co-ordinating action in this field and this would be subject to EU Brazil co-operation.

Research priorities:

Comments from Mike Dixon:

- With Wellcome changing their modus operandi, we are having to rethink the best way to submit an application but it will be around integrating high

throughput sequencing technologies with developmental genetics and using the data to inform developmental biology (using model organisms, mainly mouse) and human studies e.g. GWAS.

- The NIH funded “Facebase” initiative is progressing well. The topics include a range of animal studies, mainly mouse but also zebrafish, human studies and technology projects. In total there are 11 projects co-ordinated by a hub and the details can be found at: <https://www.facebase.org/project>
- Finally, in terms of on-going discussions, I think that EU Framework programmes will be crucial and, in this context, influencing calls to include craniofacial malformations is centrally important.
- Although I cannot be at this meeting (and many thanks for agreeing to out me on the next programme), perhaps some thought could be given to global initiatives and interfacing with Facebase (could somebody from the US attend the next meeting, expenses paid).

Structured discussion:

- Is there need for funding to achieve EUROcleftNet objectives?
- What do we need funding for?
- Do units / individuals already have local funding?
- Are researchers in funded collaborations in EU or beyond?
- How do we improve our competitiveness?
- Can we identify opportunities?
- Is OFC alone a sufficient EU priority?
- Are clefts / CFA eligible under “rare diseases”?
- Opportunities in FP7 – many deadlines soon but are any achievable?
- Marie Curie Actions e.g. ITN programme funding?
- Commercial / industrial avenues to pursue joint funding possibilities?
- Link into ongoing initiatives?
- International collaborations beyond EU?
- Address in European Parliament?
- Opportunities to influence FP8?

Report of 5 EUROcleftNet Workshops

**Workshop 1: Optimising the use of DNA in EUROcleftNet research. Chairs:
Elizabeth Mangold / Kirsten Molsted**

In this group three persons had been participating in the Eurocran project.

“The lessons to be learned” from the Eurocran project were discussed.

The amount of blood samples in the Eurocran study was disappointing; the clinical centres seemed to have a lot of problems to manage to take the samples.

The original EUROCRAN questionnaire was too extensive.

We therefore discussed if it was possible to use swaps instead of blood samples.

Advantages using swaps: Easy to collect.

Disadvantages using swaps: Quality of DNA.

Conclusion:

- We decided to examine if it is possible to use swabs or saliva.
- We decided to find out how many blood samples (from cleft patients) that already have been stored in different centres in Europe.

Workshop 2: Research methods – strengthening collaboration between clinicians and laboratory researchers in EUROcleftNet research. Chairs: Bill Shaw / Concha Martinez

The components of Workshop 2 were clinicians in their majority, with only a few being laboratory researchers. Participants analysed possible strategies to establish combined research between professionals working on different aspects related with orofacial clefts (OFC). These were the relevant aspects commented:

a) General Aspects

1. The first thing to start any collaboration between clinicians and laboratory researchers is to have both a question that needs to be answered and the willingness to solve it.
2. Clinicians working on any aspect of OFC should identify the specialties they could collaborate with to investigate the questions raised in their professional activities.
3. Researchers in universities should also identify aspects in their own research susceptible for collaboration with clinicians. First attempts for mutual collaboration should be small non highly ambitious projects.
4. Parents of children presenting OFC could be motivated about the possibilities for investigation in OFC. They would then press their clinicians for further investigation in the field, although too much involvement of parents was considered to be negative.
5. Previous clinical research under the auspices of the EU funded Eurocleft and Eurocran programmes succeeded in progressing some collaboration. This included a Europe-wide registry of clinical teams, their clinical protocols and research interests, agreement on record taking policies, and initiation of multicentre surgical trials. However, there was limited engagement in this by several of Europe's larger countries, where clinical research continues to take place in an isolated and uncoordinated manner.
6. Younger colleagues in attendance confirmed that the new generation of professionals in the field might be keener than the older to participate in new research opportunities.

b) Actions to be taken:

1. To revise the Eurocleft registry of teams, clinical practices and research interests as a starting point for the EUROcleftNet programme.
2. To provide workshops for teams with an interest in collaborative research.
3. To send information to the identified centres about what is going on in the frame of EUROcleftNet and offering them possibilities for participation in grant applications.
4. To send a representative of EUROcleftNet to meetings of local associations of professionals working on OFC to inform about the possibilities for research collaborations.

Workshop 3: Involvement of commerce/industry in EUROcleftNet research.
Chairs: Ashraf Ayoub / Michele Rubini

A. Channels of Industrial collaborations:

1. Diagnostic:
 - a. 3D imaging of facial morphology in cleft cases to quantify facial dysmorphology before and after surgery
 - b. Genetic assessments
 - c. Tissue sampling
2. Preventive:
 - a. The use of multi-vitamins for reduction or prevention of cleft deformities
 - b. Folic acid/ Felonic/ Hydro-foliate
 - c. Prevention and minimising scarring following surgical repair of cleft lip
3. Corrective:
 - a. Prevention of keloid formation
 - b. The sue of bone substitute to replace lost alveolar ridge
 - c. The use of distraction devices for correction of skeletal deformities
 - d. Rehabilitation of the oral cavity using dental implants

B. Methods of industrial contribution to the Eurocleft network

1. Provide the necessary equipments at a reduced cost (3D imaging, Tissue sampling, Genetic kit, dental implants, distractors, etc)
2. Provide training fellowships
3. Funding research fellows
4. Provide the necessary materials for research
5. Financial support toward the overall cost of research projects

C. Identifying potential research partners

1. Local contacts and personal experience of the members of the Eurocleft network with companies
2. Direct contact with leading international manufacturers

D. Action points:

- a. Establish a synergistic relationship between industry and Eurocleft network
- b. Invite potential industrial partners to the next meeting
- c. Establish a list with contact details of key companies

Workshop 4; Communication and politics - bringing users and clinicians together at a European level to address inequalities in cleft care". Chairs: Gareth Davies / Ann Marie Kuijpers Jagtman

It was noted that within Europe the number of individuals walking around with clefts was equivalent to 6 times the population of Salzburg. It is not a marginal issue. We needed a common all-Europe approach to best treatment proactive and ultimately prevention.

- **What is the best way to reach our goal to improve care for individuals with orofacial clefts in Europe?**
 - Willingness to share best practice
 - Partnerships - exchanges of cleft team members and researchers
 - European training symposia - comparing results/outcomes and getting clinicians involved in research
 - Making resources available - political dimension. EU
 - Setting a European Standard for early care (inequality arises as much from lack of protocols as lack of resources)

- **How do we engage with user groups to help achieve these goals?**
 - Empowering parents to ask questions and make informed choices about care.
 - Websites crucial tools in educating targeted groups
 - Mobilising parents/patients to help effect change through lobbying. Patient groups can be instrumental in forging partnerships between users, health professionals and industry
 - Working with other patient health groups at EU level e.g. European Patient Forum
 - Involvement in research

- **Which of the above can be facilitated by the current ESF EUROcleftnet funding?**
 - Exchanges of personnel to share protocols and research expertise
 - Use high profile of ESF network to attain platform at European Parliament to educate the politicians
 - International conference, bringing clinicians, users and industry together
 - Building accessible website which will be a resource for health professionals and users alike
 - Include in our network other patient/research organisations so lessons can be learned from strategies employed for tackling other health conditions e.g. www.egan.eu and the Pfl initiative.

Workshop 5: European/Latin American research collaboration. Chairs: Peter Mossey / Inge Trindade

Do opportunities for EU – Latin America present?

Collaboration with Brazil is part of the EU research portfolio and various calls include either EU-Latin America or EU-Brazil collaboration.

Some calls refer to “multilateral co-operation between Europe, Africa and Latin America on public health and health services research” (Health.2011.3.4-3).

This however also quotes a special feature (it is expected that the Brazilian authorities will issue a complimentary call to finance a Brazilian co-ordinating action in this field and that the EU funded action will co-operate closely with those and other related actions.

What possibilities exist for potential EU/Brazil collaboration in craniofacial/cleft research?

The fact is that Brazil can offer some unique research opportunities by virtue of their Centre of Excellence in Bauru and Brazil also has a research funding agency (FAPESP) which specialises in promoting scientific research – including health services research.

Specific research topics

The scientific advantages of collaboration with Brazil would be in terms of their treatment and clinical expertise, the large numbers of clefts and craniofacial anomalies including syndromes that present at the Centrinho clinics and their increasing profile and expertise in research across a number of disciplines. They have an established track record in participating in randomised surgical trials e.g. the NIH funded timing of palatal surgery (TOPS) trial, their expertise in speech and language therapy, orthodontics, nutrition, psychology, social work and nursing. They are also one of the few centres in the world who offer cochlear implants for conductive hearing impairment.

Research opportunities in Bauru

- (a) The Florida project - opportunities to work together on growth outcomes and speech outcomes. Jennifer keen to explore if there is a higher presence of glottal stops among the Brazilian cleft population and if so the reason why.
- (b) Sub-phenotyping of non-syndromic clefts i.e. cleft palate subsets and CLP subsets, Simonarts bands etc. (Terumi)
- (c) Microforms research. Follow up with Camilla Alvarez and I am also aware that Gisele and Lucimara are keen on looking at hypodontia and the possible association with various clefting genes such as MSX1, PAX9 etc.
- (d) Alveolar bone grafting and volumetric research. Pre and post op CBCT are routinely recorded. Alveolar bone grafting in CLP remains an unsatisfactory operation in that success rate is relatively low and much more research is required to improve the success rate and consistency of this operation including research on donor sites, cortical versus cancellous bone, volume of bone required for the graft, BMP as a substitute etc. (Ivy Trindade)
- (e) Acoustic rhinomanometry as part of the measurement of outcome in cleft and ABG patients.

Other unique opportunities may be in the efficacy of prenatal diagnosis, measurements and biomarkers of human nutrition, randomised trials on other clinical interventions, a randomised trial on multivitamins in addition to folic acid (possible collaboration in this with Italy).

Genotype / phenotype correlation research with an expanded phenotype including speech, hearing, psychology, biochemical markers of nutrition and exposure. Brazil offers some unique collaborative opportunities in this respect.

The Human variome project: this has already been initiated by Vera Lopes, and Isabella Monlleo in Brazil and collaborating with Maria Rita Passos-Bueno. This aims to identify variation in both genotype and environment and identification of the range of human genetic variation on a disease by disease basis. Orofacial clefting, by virtue of good ascertainment at birth lends itself well to the possibility that we can characterise causative mutations in different populations.

Educational programmes: there are well developed educational programmes both at Masters and Doctorate level at the University of Sao Paulo in Brazil and this could be another source of collaborative research. Ongoing Masters/PhD projects in Bauru include.

- A new orthodontic expansion appliance for achieving more inter-canine expansion.
- Alveolar bone grafting - use of BMP versus iliac crest bone.
- Psychology and coping strategies among mothers who have children born with CLP - including an attempt to measure stress.
- Growth outcomes in a centre outside of Bauru.
- Indices, comparison of the Goslon versus the modified Huddart Bodenham (MHB) and the inter-rater reliability of Goslon - particularly for non expert examiners.

Summary & Action points:

1. It would be desirable for EUROcleftNet to look beyond Europe for research opportunities.
2. It appears that research collaborative opportunities between the EU and colleagues in Brazil and perhaps in other parts of the world e.g. Africa and India through EU grant funding schemes will present.
3. Closer scrutiny of schemes in the Marie Curie (with industrial partners), ERC (particularly for individual and synergy grants), FP7 Health and grants initiated by bodies outside of Europe e.g. NIH and Gates Foundation should be explored.
4. Appropriate representatives from these possible collaborating countries will be kept informed of our EUROcleftNet activities.
5. Further information on specific calls (above) and whether FAPESP in Brazil would be interested in partnership projects is required.
6. A meeting with University of Dundee EU FP7 administrator to discuss the above will be sought asap.



Attendance at EUROCleftNet Workshops

List of participants who attended the EUROCleftNet meeting in Salzburg on 14th September 2011

1. Professor Anette Lohmander, Sweden
2. Professor Anne Marie Kujipers-Jagtman, Netherlands
3. Professor Bill Shaw
4. Dr Ann Molloy, Ireland
5. Professor Ashraf Ayoub, UK
6. Professor Bill Shaw, UK
7. Professor Biruta Barkane, Latvia
8. Dr Borut Peterlin, Slovenia
9. Professor Concha Martinez, Spain
10. Dr Elisabeth Mangold, Germany
11. Professor Jan Vojtassak, Slovak Republik
12. Ms Emma Southby, UK
13. Mr Gareth Davies, France
14. Dr Heiko Peters, UK
15. Dr Irena Klimova, Bratislavia
16. Dr Jitka Vrtiskova Klinika, Czech Republic
17. Professor John Scott, Ireland
18. Associate Professor Kirsten Molsted, Denmark
19. Professor Michele Rubini, Italy
20. Professor Peter Mossey, UK
21. Dr Vesna Kozelj, Slovenia
22. Dr Youri Anastassov, Bulgaria
23. Professor Alexander Hemprich, Germany
24. Hassan Monssa, Egypt
25. Heleia Nestal Zibo, Brazil
26. Maria Hortis-Ozierzbicka
27. Abou Chebel, Lebanon
28. Ahmed Mohamed Modra, Egypt
29. Mahamoud H. A. Monsa, Egypt
30. Servet Odean, Turkey
31. Olif Erbay, Turkey
32. Asli Yzel, Turkey
33. Deniz Gumru Gelikel, Turkey
34. Didem Aktan, Turkey
35. Ege Duean, Turkey
36. Coudia Maiteure-Alsarez, Spain
37. Christian Rippel, Salzburg
38. Professor Inge Elly Kiemle Trindade (Brazil)

39. Gisels da Silva Daeben (Brazil)
40. Corstiaan Breugem (Netherlands)
41. Heuriette Swareuburg dr Veye (Netherlands)
42. Susanne Wriedt (Germany)
43. Bilal Al-Nawas (Germany)
44. Maria Anna Hortis-Dzierbicha (Poland)
45. Rados Velikova
46. Sevdjihan Eobova
47. Nicolinu Bratu
48. Radu Spataru
49. Judith Hohlfeld

