Cleft Research Workshop
Bristol Marriott Royal Hotel
26th – 27th of February 2009
The workshop was organized under the aegis of the Craniofacial Society and the NIHR programme “Evidence based health care for major congenital and acquired problems of the head and neck”. Clinicians, researchers and user representatives participated in the workshop with a focus upon the objectives of the NIHR grant. These broadly are to host workshops and develop a formal research strategy; to conduct systematic reviews and to evaluate the current care of children with cleft lip and palate. We hope that the NIHR grant will contribute to increased collaboration and research between the centres over the next five years. The dynamic participation in the workshop generated valuable discussion that will inform our future research and ultimately improve cleft care at all levels.

You will find in the proceedings; the attendees list, the program and the presentations and notes in the order they appeared in the program.

We would like to thank all those who attended for their contributions that made this workshop so successful.

Yours sincerely,

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Head of Department of Oral & Dental Science.

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Professor of Epidemiology/
Co-Director the Avon Longitudinal Study of Parents and Children
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Clinical Director  
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Frenchay Hospital

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Director of Dental Research  
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The University of Queensland

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Department of Social Medicine  
University of Bristol

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Press Officer  
Public Relations Office  
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Outreach Specialist / Counsellor  
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Great Ormond Street Hospital for Children NHS Trust  
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Queen Alexandra Hospital  
Portsmouth

Dr Andrea Waylen  
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Department of Oral & Dental Science  
University of Bristol

Dr Margo Whiteford  
Clinical Geneticist  
NHS Greater Glasgow and Clyde
# Thursday 26th February

## Session 1  Progress to date (Chair Jonathan Sandy)

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<thead>
<tr>
<th>Lecturer</th>
<th>Topic</th>
<th>Time</th>
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<tbody>
<tr>
<td>Jonathan Sandy</td>
<td>Welcome and introduction</td>
<td>10.30-10.50</td>
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<tr>
<td>Sirisha Ponduri</td>
<td>Systematic review of grommets</td>
<td>10.50-11.20</td>
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<tr>
<td>Lucy Stead</td>
<td>Cleft gene bank pilot studies</td>
<td>11.20-11.40</td>
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<tr>
<td>Sarah Smithson</td>
<td>Report of cleft genetics group</td>
<td>11.40-12.10</td>
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<tr>
<td>Andy Ness</td>
<td>NIHR programme in cleft and head &amp; neck cancer</td>
<td>12.10-12.30</td>
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<tr>
<td>Brendan Eley</td>
<td>The Healing Foundation call</td>
<td>12.30-12.50</td>
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<td>Discussion</td>
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### LUNCH

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## Session 2  Views on the future (Chair Rosanna Preston)

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<td>Introduction</td>
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<td>Rosanna Preston</td>
<td>User perspectives on cleft research</td>
<td>2.10-2.30</td>
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<tr>
<td>Nicky Rumsey</td>
<td>Patient centred research</td>
<td>2.30-2.50</td>
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<tr>
<td>Terry Gregg</td>
<td>View of the craniofacial society</td>
<td>2.50-3.10</td>
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<td>Discussion</td>
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### TEA/COFFEE

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## Session 3  Informing the future (Chair George Davey Smith)

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<tr>
<td>Jane Blazeby</td>
<td>Multi-disciplinary working and centralisation</td>
<td>4.00-4.20</td>
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<tr>
<td>Bill Shaw</td>
<td>Trials in cleft lip and palate</td>
<td>4.20-4.40</td>
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<tr>
<td>Mike Dixon</td>
<td>Genetics of cleft</td>
<td>4.40-5.00</td>
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<tr>
<td>Dave Evans</td>
<td>Genome wide association studies</td>
<td>5.00-5.20</td>
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### DINNER

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**Friday 27th February**

Andy Ness
3rd December 2008
Jonathan Sandy

The Craniofacial Society of Great Britain and Ireland
A Society for the study of Cleft Lip and Palate
and other Craniofacial Anomalies
A United Research Effort

Craniofacial Society
Great Britain and
Ireland

Swansea - April 2005

Leeds CFSGB&I conference-2002

Conference dinner

“Out of body experience”

“Girl in the little black dress who can make
an old man happy - Professor Sandy is in room 209”

“Jonathan, I have a job for you......”

Dai Roberts-Harry
The Trial - Bath 2003

Craniofacial Society Research

• Remit - national multi-centre research

• Collaboration with international studies
Craniofacial Society Research

- CRANE - The Way Forward
- Three manageable groups
- Database, Audit and Research

Problems

- CRANE - Funding & re-location
- Database needed for Research
- Database, Audit & Research co-located
Research Solutions

- Identify clear projects
- Establish a “Trials Unit”
- Establish funding

Trials Unit

- Research Assistant, Statistician, Secretary, Research Nurses etc
- Minimise intrusion on Teams
- Deal with “Ethics, protocols etc”
Funding

• Partnership Funding
• Five years core funding
• MRC, Healing Foundation, CLAPA

Projects

• Relevant - identified by SIG Research Leads
• Avoid large Surgical Trials
• Surgical and Non-Surgical issues
Trials Unit

• A model for other anomalies?

• Social Medicine will run an RCT course

• ? SIG Research Leads to attend and formulate questions

Workshop 18-19 March 2005

• Funded by CFSGBI

• Mix of CD's, specialties, geography

• Run by Social Medicine, U. Bristol
Aims and Objectives

• Understand trials and surrounding research issues

• Identify research questions

• Plan for funding applications

Research Questions

• Parental and patient involvement
• Ventilating ears - are we doing harm?
• Early speech therapy intervention?
• Need for peri-operative antibiotics?
• Types of sutures for closure + “glue”
• Surgical trial of cleft palate repair
Translational Research

- Growth factors stimulate bone cell proliferation
- Autologous serum has all growth factors
- ?Enhanced bone graft - needs RCT
Research Questions

- Potential to develop a unique gene bank
- Parents, grandparents, siblings
- Ethics previously explored (Eurocran)

Funding

- Healing Foundation looking for new strategy
- A response has been made by CFSGBI Healing Foundation + CLAPA attended workshop
- Need a 5 year programme grant
- Once established “Trials Unit” and “Gene Bank” could be self funding - MRC, Wellcome grants.
Funding

- Next move......
- ...tackle the Healing Foundation
- in Swansea, they tackle.......
Progress

- Systematic reviews in research areas - ongoing
- Healing Foundation engaged
- HF strategy founded on research questions
  .......................................................... cont

Progress

- Application to Wellcome to archive CSAG records
- Potential role with Renovo Trial
- Development of linkage of database with gene bank
Renovo in second bite at biotech flotation

‘...likely to value the Manchester-based business of Mark Ferguson at more than £120 million.’

‘Professor Ferguson and Dr Sharon O’Kane, his partner, are expected to crystalise a paper fortune of at least £10 million.’

‘Professor Ferguson said that talks with top pharmaceuticals companies were under way and that he expected to sign a licensing deal within the next 12 months.’

‘One analyst suggested that the drug could generate peak sales of more than $20 billion worldwide.’

---

Workshop 9 March 2007

- Funded by CFSGBI
- Mix of CDs, Clinical and Molecular Geneticists
- Representation from users (CLAPA)
Rationale for proposed gene bank

- Existing collections potentially underpowered
- Large collections to study common variants
- Collections to look at parent of origin effects
- Use of Mendelian randomisation approach

Pilot Studies

- Qualitative studies
- Sample collection
- Sample processing
- Protocol development
- Logistics
- Ethics
Pilot Studies

- Qualitative work
- Laboratory pilot work (smaller blood samples and other tissue handling)
- Process of recruitment (how many centres for pilot?)

Ethics

- Qualitative work
- Nature of consent
- Family involvement
Timetable

- Year 1 pilot work and final protocols
- Years 2-5 gene bank recruitment
- Year 3 preliminary bid for genotyping
- Year 5 further bid for genotyping

Exciting Times

Genes & pathways now implicated
Environmental epidemiology convincing
Genome-wide approaches
Superb animal models
Integrated approach essential

**What can the UK contribute:**
Near-full ascertainment & great phenotyping!!
Human genome project - “30,000 - 40,000”

**Candidate Genes**

Environment more important than previously thought.
Funding

- Need a 5 year programme grant
- Once established “Trials Unit” and “Gene Bank” could be self funding - MRC, Wellcome grants
- Example for other low incidence anomalies

Proposed Research Workshop 2009

- Funded by CFSGBI
- Mix of CFSGBI members
- Education in research methodology
**Funding**

- Bill Shaw $6 million NIH
- Andy Ness £3 million NIHR
- Healing Foundation £2 million
- MCRN support costs - Sally Davies
Sirisha Ponduri

The Craniofacial Society of Great Britain and Ireland
A Society for the study of Cleft Lip and Palate
and other Craniofacial Anomalies
Management of otitis media with early routine insertion of grommets in children with cleft palate
- A systematic review

Sirisha Ponduri
Rebecca Bradley

Otitis media with effusion (OME)

- Fluid accumulation in the middle ear.

- 10-30% in non-cleft children (1 to 3 years olds). Fiellau, 1977, 1983

- 97% of children with cleft palate (CP). Grant et al., 1988
Management of OME

- Watchful waiting
- Decongestants, steroids, antibiotics
- Hearing aids

Surgical: Myringotomy +/- grommet insertion

Management in children with CP

- Early placement of grommets at time of palate repair
  (Paradise & Brandwein, 1974; Moore et al., 1988; Gordan et al., 1988; Merrick et al., 2001, 2007)
- Speech and language development.
Complications

- Otorrhoea
- Tympanic scarring
- Infection
- Tympanic membrane perforation

Previous Research

- Cochrane review by Lous et al. (2005) on non-cleft children
  - Short term benefit only
  - Side-effects common
  - Overall evidence limited and of poor quality
  - Further well-conducted RCTs necessary
  - Conservative management of OME recommended
No systematic reviews on grommet placement in children with CP

Research Question

Does routine early placement of grommets in children with cleft palate result in improved hearing and speech and language development compared to a more conservative approach?

Study Design

Systematic review
**Inclusion criteria**

- Randomised controlled trials, controlled clinical trials, observational studies (cohort and case-control), cross sectional studies, case series
- Children with UCLP, BCLP, CPO, SMCP

**Inclusion criteria...**

- Studies investigating effects of grommets on hearing and speech and language development
- English and non-English language journals

**Exclusion criteria**

- Adults
- Cleft lip only
Outcome measures

- Hearing loss
  - Side effects
  - General development
  - Speech and language development
  - Quality of life

Identification of studies

- CDSR
- Cochrane Controlled Clinical Trials Register
- EMBASE
- Medline
- CENTRAL
- CINAHL
Results

- Citations: n=368
- Potentially relevant: n=34
- Fulfilled inclusion criteria: n=16

Study type

- RCTs
- Prospective cohort
- Historical cohort
- Case series

Number

0 1 2 3 4 5 6 7 8

Analysis of studies by type: RCTs (0), Prospective cohort (1), Historical cohort (6), Case series (8).
Geographical distribution

Study type

1 RCT
- Zheng et al. 2003 (China)
1 RCT - Zheng *et al.* 2003

- **Treatment group**
  - (n=24)
  - palatoplasty & grommets

- **Control group**
  - (n=38)
  - palatoplasty only

- **Outcome measures**
  - presence of OME
  - hearing levels

- **Conclusion**
  Hearing better following early grommet insertion

**Critique:**

- No details of method of randomisation
- Small sample size
- No power calculations
- Different follow-up times for each group
- Results difficult to interpret
Study type

3 Prospective cohort studies
- Moller, 1982 (Norway)
- Hormann et al., 1991 (Germany)
- Broen et al., 1995 (USA)

6 Historical cohort studies
- Potsic et al., 1979 (USA)
- Freeland et al., 1981 (UK)
- Hubbard et al., 1985 (USA)
- Gordan et al., 1988 (New Zealand)
- Robson et al., 1992 (UK)
- Shaw et al., 2003 (UK)
Study type

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<td>Smith et al., 1994 (USA)</td>
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<td>Grieg et al., 1999 (UK)</td>
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<td>Sheahan et al., 2002 (Ireland)</td>
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<td>Liu et al., 2004 (China)</td>
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Overall results

- Quality of studies generally poor
- Small sample sizes
- No formal sample size calculations
- Heterogeneous
- Little agreement
Conclusion

- Little evidence to support early routine grommet placement in children with cleft palate.

- Need to develop evidence based protocols

Recommendations

- **UK National Institute for Health and Clinical Excellence, 2008**
  - Management by local otological and audiological services
  - Grommet insertion at same time as palatoplasty only after careful examination.
The management of otitis media with early routine insertion of grommets in children with cleft palate - a systematic review

Cleft Palate Craniofacial Journal 2009 Jan; 46 (1):30-8

Acknowledgements

- Rebecca Bradley
- Professor J Sandy
- Professor A Ness
- Mrs P Ellis
Lucy Stead

The Craniofacial Society of Great Britain and Ireland
A Society for the study of Cleft Lip and Palate
and other Craniofacial Anomalies
Cleft Lip and Palate Gene Bank
Pilot Studies

Lucy Stead BDS MFDS RCS (Eng)
Specialist Registrar in Paediatric Dentistry

26th February 2009

Introduction

• From success of meetings in March 2005 and March 2007
• Report:
  • Identified priorities in planning and support of gene bank
  • Need for pilot studies
• Funded by Craniofacial Society of Great Britain and Ireland
Pilots required

- Qualitative studies
- Sample collection
- Sample processing
- Protocol development
- Logistics
- Ethics
Final report

http://www.craniofacialsociety.org.uk/downloads/index.html#1

Qualitative Studies: Aims

- To identify:
  A. How and when to approach families for consent
  B. What ethical issues exist
  C. Acceptability of providing samples
Qualitative Research

- In-depth exploration
- Evaluation, explanation, consultation
- In-depth interview or focus group
- Rich data

Materials and Methods

- Ethical approval from Southmead Hospital LREC
- 100 parents of cleft children invited
- Recruitment by letter via cleft centre
- Focus groups commenced 4th March 2008
- Five undertaken (16 parents)
Focus Groups: Setting

- Written informed consent
- University of the West of England (4/5)
- One at participants' home

Focus Groups: Conduct

- Warm-up: describe time cleft diagnosed
- Processes of gene bank explained
- Questions from topic guide
- Open questions
- Digital audio recording
**creating a gene bank**

child is diagnosed with a cleft
↓
parents approached by cleft team
↓
information given to parents about gene bank
↓
parents agree to take part
↓
samples taken for research and storage
↓
questionnaire completed by parents
↓
research on samples and answers to questions
↓
research is published

---

**Data Analysis**

- Recordings transcribed verbatim
- Transferred to NVivo8
- Analysis by reading / understanding transcripts
- Themes derived inductively
- Grounded Theory principles
- Verification of analysis
Results

A. How and when to approach families for consent
B. What ethical issues exist
C. Acceptability of providing samples

A) How and when to approach families

- Background factors
- How, when and who?
Background Factors

Antenatal diagnosis
"BUT"
Time pressures
Feeding pressures
Whether or not to proceed
Parallel with Down’s
Too much information?
"The first thing you are offered is a termination"
Associated syndromes: "Horrendous"

Postnatal Diagnosis
Pressure to perform
"BUT"
Feeding pressures
Time pressures
Amniocentesis

Antenatal diagnosis
20 weeks to prepare
"Lucky"
Scanning provides a benefit
Accept the cleft
Gathering and processing info

Background Factors
Shock
Overwhelmed
Surgery
"All surgery is major surgery"
Climbing a ladder or a treadmill?
"The first thing you are offered is a termination"
Postnatal diagnosis

• “Our second child has, was born with a cleft lip and palate, quite a wide one, [date of birth], he was born at home so we didn't know he had a cleft so it was all quite a traumatic time, I had a rapid labour and the midwife didn't make it and so then suddenly it's quite distressing, And we thought he was dead, you know we got this disfigured pale little child, so but then he had his lip done at 3 months and his palate done at 6 months which was very traumatic and traumatic for our daughter as well”

(J3, Mother of a boy with UCLP diagnosed at birth)

Antenatal diagnosis

“I think it was the 20 week scan or thereabouts, um, and I think the first thing that is talked about is you are offered a termination”

(C11, Father to two boys; R1 with UCLP, and R2 with CP)

“you can do a lot in 20- weeks whereas if you don’t know, that’s got to be a hell of a shock, you know, to just find out in 5 minutes, it’s a completely different story”

(A1, Mother to a boy born with BCLP)
Feeding difficulties

“really hard, in his early days we had to feed him with a syringe, you know, um, and, yeah, and life was crazy because it was just this constant cycle of trying to feed him and sterilising all the equipment and we had our daughter as well who needed our support and I think for me if I had been approached at that point it would have all been a bit too much, I would have said ‘could you wait a few months’”

(A3, Father to a boy born with UCLP diagnosed at birth)
When to approach

- Avoid difficult times: diagnosis, surgery, weaning
- Ranges from a few days to up to a year

“I'm just thinking that the timing is going to be different for different families”

(CL1)
How to approach (1)

• Sensitivity:

“I mean you know as long as somebody approached it very sort of like carefully, you know I mean when J was born the cleft team were like very good because they sort of approached things and if we said no they backed off and left it a while and then sort of come forward and then try, you know you’ve got to have time to, some people take longer to accept it than others you know”

(A1)

• Awareness of cultural differences

How to approach (2)

• Importance of information provision - amount:

“when my second child was born with far more severe issues they tried while we were in special care they tried to give us information on what his condition was, I just told them what to do with it (laughs)”

(S2, Mother to a girl born with CP)
Who to approach

- No consensus but cleft nurse mentioned more often:

  “yeah, well I think so, I think so because by their very nature I think those people that are, individuals that are, or right on the coal face of helping you with the baby, and if they are a sympathetic, the ones I have come into contact with are lovely and do a fantastic job and you feel so comfortable with them”

(N4, mother to a boy born with UCLP)

- Trust, experience, knowledge

B) What ethical issues exist

- Information provision
- Questionnaire
- Data protection
- Positive about gene bank
- Benefits globally
- Feedback of results
Information provision

- Contradiction in amounts of info provided

“I think for me that’s why I would want to be asked at a separate time from the diagnosis because you get so much information then to then be processing another set of information”

(J3, mother of a boy born with UCLP)

- Leaflet then personal contact
- Commitment

Questionnaire

- Skeletons \(\rightarrow\) separate questionnaires to complete
- Guilt / blame \(\rightarrow\) signposting towards help

“I ended up going flying to Australia when I was in my early pregnancy with E and if you asked a question you know just straight out, ‘did you fly in early pregnancy?’ you know I’ve already gone over that, over and over and over and over again, and certainly now it would be ok answering it, but at the time I’d have found that horrible, I wouldn’t have wanted to tick anything, you know, I wouldn’t have wanted to say yes or no to that, I would have wanted to blank it really”

(S3, Mother of a girl born with UCLP)
Data protection

“I expect it’s the dark paranoid thought but there is that sort of fear of handing over information to, a sort of faceless bureaucracy if you like, and just sort of reassurance about you know what might happen with that information in the future I suppose”

(CL1)

Positive about gene bank

“By doing this hopefully when it happens to other people they will be able to have the answers, cos I know when you find out that’s the first thing you want to know is why, why me” (A1)

“I think it’s more to do with the impact that this research could have, personally I don’t mind contributing to anything that’s going to give answers, because we haven’t had any answers before, but, I would like answers not just for E but for C as well and if, I'm quite happy to contribute to anything that's going to give me answers” (S2)
Benefits globally

“I think it’s useful as well in different countries as well because we obviously have the medicines and things here to cope with it but I know in other countries if your child is born with a cleft then they are pretty much outcasts and it’s sad, you know some of the information could be passed on there as well”

(J5, mother to a girl born with a unilateral cleft lip)

Feedback of research

“If I was in the study perhaps it might be quite nice to write to everyone and say ‘we are going to have this meeting here’ and then everyone comes along and hears a speaker or something and says it that way, that way you can be sure that everyone’s questions are answered and you know, and might be quite sort of unity from everyone then that took part in the study”

(J5)
C) Acceptability of providing samples

- Security of samples
- Blood
  - Cell lines
- Saliva
- Tissue, e.g. gum or lip
- Sperm

Security of samples

- Very important for participants

“yeah, and maybe just some kind of explanation as to where it is actually stored, just you know that you don't think, that no one has got in their head that it’s going to be used by somebody else or for some other purpose than just this one, security” (N4)
Blood and saliva

- Benefits outweigh 'risks':
  “I mean to be honest everything that they go through, a simple little blood test is, I mean I would just sit there and go like that” [holds arm out straight with antecubital fossa upwards] (A1)

- Cell lines:
  “I suppose I'm starting to think // you know sort of, you know, what other things could be done with the blood, untoward, that sounds really bizarre and sort of science fictiony” (N4)

Tissue

- Not acceptable
- More tangible:

  “It’s something just a bit more kind of tangible of your child that’s being taken away and it’s almost a bit, sort of, you can’t pinpoint why you feel a bit strange about it, it seems a bit illogical” (N4)
Sperm

• Not explored in great detail
• All or nothing for samples

Further work

• Process of analysis utilises grounded theory principles
• Constant comparison
• Theories require testing
• Comparison with other groups
Conclusions

A. How and when to approach families for consent
B. What ethical issues exist
C. Acceptability of providing samples

Acknowledgements

• Mrs Liz Albery
• All of the participants
• Craniofacial Society of Great Britain and Ireland
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• Professor Andy Ness
• Professor Nicky Rumsey
• Dr Susan Ring
• Dr Wendy McArdle
• Mr Nigel Mercer
• Professor Jonathan Sandy
• Dr Andrea Waylen
• Mrs Rosemarie Winter
http://www.craniofacialsociety.org.uk/downloads/index.html#1
Sarah Smithson

The Craniofacial Society of Great Britain and Ireland
A Society for the study of Cleft Lip and Palate and other Craniofacial Anomalies
Role of clinical geneticist

- formation of UK cleft genetics group 2006 – Dr Helen Firth
- provide genetic information for families/cleft team
  - isolated CLP
  - familial cleft
  - clefts associated with congenital malformations
- delineation of syndromes with clefts
  - diagnosis and genetic counselling
  - recognition of new entities
- advance knowledge/understanding of genetic mechanisms of cleft: research interface
Genetic approaches to cleft

- Genetics of NS CLP  Dr Melissa Lees
- Pierre Robin sequence  Professor David Fitzpatrick
- Syndromes with cleft  Professor Jill Clayton-Smith

Non-syndromic cleft lip +/- palate

- Environmental factors
- Folic acid
- Smoking
- Diabetes
- Anti-convulsants
- Alcohol
- Non-syndromic CLP
- Syndromes clefts/facial involvement

Single genes associated with syndromes are increasingly implicated in CLP

Stanier and Moore Hum Mol Genet 2004 13:R73-81
Evidence for involvement of genes in NSCLP from family studies

- The rate of concordance is higher in monozygotic (25–40%) than dizygotic (3–6%) twins.
- There is an increased relative risk to siblings (ls $\approx 30–40$) compared to the general population.
- Variation in $2–14$ genes is estimated to contribute to NSCLP.

Key gene families in craniofacial morphogenesis

<table>
<thead>
<tr>
<th>Polarizing signals</th>
<th>Shh, Bmp2, Bmp4, Smad2, Smad3, Smad4, Wnt5a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth factors and receptors</td>
<td>Egr1, Egfr, Tgfβ1, Tgfβ2, Tgfβ3, Fgf1, Fgf2, Fgf11, Fgf2</td>
</tr>
<tr>
<td>Transcription factors</td>
<td>Dlx1, Dlx2, Dlx3, Dlx4, Dlx5, Dlx6, Gli2, Gli3, Hoxa2, Tbx1, Tbx22, Irx6, Pax9, MSX1</td>
</tr>
<tr>
<td>Cell adhesion molecules</td>
<td>Pvl1, Connexin43, E-cadherin</td>
</tr>
<tr>
<td>Extracellular matrix</td>
<td>Col2A1, Col11A1, Col11A2, Mmp2, Mmp3, Mmp9, Mmp13, Fibronectin</td>
</tr>
</tbody>
</table>

Stanier and Moore
Hum Mol Genet 2004
Overall genetic risks for clefts in families

<table>
<thead>
<tr>
<th>Relationship to index case</th>
<th>Cleft lip + palate</th>
<th>Isolated cleft palate</th>
</tr>
</thead>
<tbody>
<tr>
<td>sibs - overall risk</td>
<td>4.0</td>
<td>1.8</td>
</tr>
<tr>
<td>sib - no one else in family</td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td>sib - 2 affected sibs</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>sib and parent</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>children of affected</td>
<td>4.3</td>
<td>3</td>
</tr>
<tr>
<td>second* relative</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>third* relative</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>general population</td>
<td>0.1</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Classification

- CPO vs CL+/-P

  - Nonsyndromic
    (isolated) vs Syndromic
    - (21-38% of cases, Milerad, 1997)
Gene identification of isolated clefts

- Linkage studies
- Association studies
- Sequencing of candidate genes

Genetic analysis to date

- At least 16 candidate loci to date
- Rare point mutations or significant association has been found between human non-syndromic CL/P and missense mutations or polymorphic variants in several genes
- Only the IRF6 variant finding has been consistently replicated, and recent evidence ascribes its affect to a point mutation in a TFAP2A binding site
- Approximately 12–25% of the genetic variation causing NSCLP is estimated to have been identified
- Non-syndromic CPO is less well studied
Gene identification of isolated clefts

But

- Inconsistent results
- Different populations
- Different study designs
- Genes of minor effect/susceptibility genes
- Pooling of clinical sub-types
- Need to specify model

Environmental factors

Nature or nurture?
Simple single gene disorders
Complex multigene disorders

- Altered splicing
- Contiguous genes
- Metabolic pathway genes
- Post translational processing
- Chaperones
- Protein trafficking

Simple single gene disorders
Complex multigene disorders

Future

- Careful sample collection
- Molecular analytic methods
- Statistical evaluations
- Mendelian clefting disorders
pierre robin sequence

Associated syndromes:
- PRS with skeletal dysplasia
  - stickler/OSMED (15-34%)
  - SOX9 cis-regulatory mutations
- PRS with arachnodactyly
  - VCFS / TBX1 (2.5-11%)
  - SATB2
- PRS with prominent brain stem dysfunction
  - carey-fineman-zitter
  - 5q23 deletions
  - disruptions
- PRS with major facial dysostosis (5-8%)
  - treacher-collins
  - acrofacial syndrome

David FitzPatrick
Manchester Meeting 2008
Why Study Cleft Syndromes?

- Relatively common amongst individuals with clefts

- Diagnosis of a syndrome or underlying chromosome abnormality impacts on patient management

- Provide information about normal human development and clues to the underlying causes of clefting

- Important implications for genetic counselling and the extended family

- Need to distinguish between syndromic and non-syndromic clefts in clinical trials

How Common Are Cleft Syndromes?

- 40-50% of infants born with a cleft have associated problems

- 280 CL and 568 CP syndromes on London Medical Database

- Relatively high frequency of chromosomal abnormalities amongst syndromic and “non-syndromic” cleft patients (Osoegawa K et al. J Med Genet 2008)

- These conditions are individually rare but collectively important
Impact on Management

- Diagnosis
- Surgical Approach
- Screening for complications
- Health surveillance
- Developmental surveillance
- Genetic counselling

Clues to Normal/Impaired Development

- Teratology
- Animal models of genetic syndromes
- Single gene disorders in “non-syndromic” clefting

Ingraham et al. Nat Genet 2006

Genetic Variants in JRF6 and the Risk of Facial Clefts: Single-Marker and Haplotype-Based Analyses in a Population-Based Case-Control Study of Facial Clefts in Norway

Adina A. Ingraham,1,2,3 Yolanda Kudina,1,2,3 Isabel T. Lin,1,2,3 Allen J. Wilson,1,2,4 Eileen K. Grayson,1,2 Roy M. Nilsen,1,4,5 Thao Trung Nguyen,1,4,5 and Jeffrey C. Murray1

1Section for Epidemiology and Medical Statistics, Department of Public Health and Primary Health Care, University of Bergen, Bergen, Norway
2Department of Pediatrics, University of Poona, Pune, India
3National Institute of Environmental Health Sciences, Research Triangle Park, Durham, North Carolina
4National Institute of Public Health, Oslo, Norway
5Norwegian Institute of Public Health, Oslo, Norway
Implications For Extended Family

- Single incisor
- Died 4h "Brain Condition"
- Cleft lip and palate

- Holoprosencephaly with Sonic Hedgehog Mutation
- Single incisor
- Died 4h "Brain Condition"
- Cleft lip and palate
Non-Syndromic v Syndromic Clefts: Telling the Difference

- Good medical history
- 3 generation family tree
- Clinical examination for congenital anomalies and dysmorphic features
- Other tests as appropriate eg echocardiogram, genetic tests
- Do the features constitute a syndrome?

Syndrome Diagnosis

- Clinician’s experience
- Literature and databases
- Colleagues' experience
- Review at dysmorphology meetings/workshops
Dyscerne: A Network of Centres of Expertise in Dysmorphology

- 78 participating European centres led by Manchester
- Submit cases online to secure system
- Reviewed by expert panel (28 experts)
- Report issued to submitter
- Educational component
- www.dyscerne.org
Andy Ness

The Craniofacial Society of Great Britain and Ireland
A Society for the study of Cleft Lip and Palate and other Craniofacial Anomalies
NIHR programme in cleft and head & neck cancer

Andy Ness

Structure of talk

- The Lifecourse Epidemiology and Population Oral Health Group
- The NIHR programme
- Proposed research on head and neck cancer
- Proposed work on cleft lip and palate
The Lifecourse Epidemiology and Population Oral Heath Research Group

Andy Ness - previous experience

- Medicine at Nottingham 1981-86
- Wellcome Training Fellow at Cambridge 1993-97
- PhD - Vitamin C and Cardiovascular disease
"Well, so much for antioxidants."

Andy Ness - previous experience continued

• Consultant Senior Lecturer in Bristol 1997-2006
• Co-Director of ALSPAC 2003-
• Professor of Epidemiology 2007-
“And it was so typically brilliant of you to have invited an epidemiologist.”

Research programmes

- Facial deformity
- Lifecourse determinants
- Nutrition and cancer
Research leads

Jonathan Sandy
Facial Deformity

Andy Ness
Lifecourse Determinants

Steve Thomas
Nutrition and Cancer

The Research Team

Sam Leary
Statistics

Charlotte Atkinson
Nutrition

Andrea Waylen
Psychology

Alex Griffiths
Statistics

Martin Persson
Project manager

More posts with NIHR programme…
The NIHR programme

Evidence based health care for major congenital and acquired problems of the head and neck

Ness AR  Birchall M
Burton M  Fisher S
Nutting C  Peters T
Rogers S  Rumsey N
Sandy J  Thomas S
Thompson C  Worthington H
Link between cleft lip and palate and head and neck cancer

- Facial disfigurement
- Functional defects
- Require surgery (usually)
- Resource intensive
- Multi-disciplinary
- Centralised or centralising

Aims of the programme

- Identify KEY RESEARCH QUESTIONS in partnership with users and clinicians and incorporate these into FORMAL RESEARCH STRATEGIES

- SYSTEMATICALY REVIEW & SYNTHESISE quantitative and qualitative evidence and translate this into EVIDENCE-BASED PRACTICE GUIDELINES

- EVALUATE & DISSEMINATE THE OUTCOME of centralisation in CLP and H&N
Proposed research on head and neck cancer

Head and neck cancer

- 7,000 cases per year in UK
- 2 year mortality 35%
- Limited evidence base – few trials and 4 Cochrane reviews
- 2.4% of H&N patients in trials (versus 28.6% for breast cancer)
Survival in people with laryngeal carcinoma in the UK


Laryngeal cancer survival by deprivation

## Head and neck cancer survival in SW England

<table>
<thead>
<tr>
<th>Year of diagnosis</th>
<th>2 year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996-1997</td>
<td>64.1</td>
</tr>
<tr>
<td>1999-2000</td>
<td>65.1</td>
</tr>
<tr>
<td>2002</td>
<td>69.0</td>
</tr>
<tr>
<td>2003</td>
<td>71.4</td>
</tr>
</tbody>
</table>

Preliminary confidential data

## NIHR programme grant

- Workshops and strategy
- Systematic reviews
- Clinical cohort head and neck cancer
Clinical cohort head and neck cancer

- 5,000 cases of head and neck cancer
- Centre questionnaire
- Individual characteristics
- Care provided
- Blood sample (DNA and biomarkers) and consent
- Outcome – quality of life, morbidity and mortality
- Plans for MRC translational research bid

Proposed research on cleft lip and palate
Cleft lip and palate

- ~1 in 700 births
- ~1,000 cases per year in UK
- Limited evidence base – few trials and 2 Cochrane reviews
- Outcome in UCLP at age 5 in 1998
  - 40% poor dental arch relations
  - 40% untreated caries
  - 19% impossible to understand or just intelligible

NIHR programme

- Workshops and strategy
- Systematic reviews
- Care and outcomes for cleft children
- IN PARTNERSHIP
Cleft survey

- First thoughts!
- 250 5yr old children UCLP
- Cleft centre questionnaire
- Child characteristics
- Care received
- Outcome – speech, appearance, dental arch

Call for a UK cleft centre 2009
“And it was so typically brilliant of you to have invited an epidemiologist.”
Brendan Eley

The Craniofacial Society of Great Britain and Ireland
A Society for the study of Cleft Lip and Palate
and other Craniofacial Anomalies
Invitation to submit a proposal to host the Healing Foundation UK Centre for Cleft Research supported by VTCT
CFSGB&I Special Interest Groups

Orthodontic SIG
Surgical SIG
Nursing SIG
Paediatric Dentists SIG
Managers/Clinical Directors SIG
Psychology SIG
Speech & Language Therapists (SLT) SIG
Research SIG
Speech & Language Therapy SIG
Hearing SIG

Stephen Robinson
Christopher Hill
Susan Butcher
Victoria Clark
Richard Willerton
Louise Dalton
Julie Davies
Jonathan Sandy
Julie Davies
Victoria Parfect

Research objectives

The Healing Foundation UK Centre for Cleft Research supported by VTCT, will improve the treatment, long-term care and support for CLP patients and their families by pursuing each of the following key objectives:

• to better understand the genetic factors contributing to cleft occurrence,
• to better understand the environmental factors contributing to cleft occurrence,
• from this developing knowledge, to better inform treatment options and improve treatment outcomes,
• through nationally coordinated research, to test, prove and disseminate evidence on the best clinical treatment options for cleft, and
• to involve patients and their families, as much as possible, in the research and in improving the information, support and long-term care options.
Research objectives

GENE BANK
- Genetic & environmental influences
- Direct impact on delivering best treatments
- Resource to research community
- Short-medium term deliverables
- What samples? Size of bank? Collaboration

Research objectives

CLINICAL RESEARCH PROGRAMME
- Study aetiology, treatment and care
- New treatments
- Multi-centre collaborative network
- Other sources of support
Postulated costs and structure

“The initial funding available is £2,000,000. The total Healing Foundation commitment will be up to £5,000,000 over 10 years”

The Selection Timetable

• 12 January 2009  Application Pack published and distributed.
• 23 April 2009  Closing date for applications.
• 24 April 2009 to 25 June 2009  Peer Review and short-listing.
• July to September 2009  Site Visits and Interviews.
• October 2009  Outcome announced, applicants informed.
• October 2009 to January 2010  Written agreement drawn up
• Spring 2010  Recruitment of key academics and establishment of the Healing Foundation UK Centre for Cleft Research supported by VTCT.
Key questions – Gene Bank

• Demonstrable ability/capacity
• National coordination for sample collection
• What ‘samples’ collected and from whom
• Patient and family epidemiology details
• How to develop into research resource
• Competing short-term academic demands

Key questions – Clinical Research

• Multi-centre collaboration
• Understanding of clinical research questions
• Coordinating role of hosting centre
• Role of UKMCRN and others
Key questions

• Commitment to patient benefit
• Multi-disciplinary focus
• Multi-centre focus
• Understanding of clinical cleft landscape
• Access to additional support
• Involvement of patients/families/carers
Rosanna Preston

The Craniofacial Society of Great Britain and Ireland
A Society for the study of Cleft Lip and Palate
and other Craniofacial Anomalies
User perspectives on Cleft Research

Rosanna Preston
Chief Executive, CLAPA

NIHR Conference
26th February 2009

Terminology

• “Users” – people with cleft lip and/or palate, their parents and families
• CLP – Cleft Lip and/or Palate
Why is the user perspective important?

Users...

- Have detailed and specific knowledge about the condition and its impact
- Know the practical problems that need solving
- Have a right to have a say on research that will affect their lives
- Need to feel part of the process and have confidence in the care they are receiving
What does this mean for researchers?

The researcher’s perspective

• The user is a valuable resource
• See the person not the scientific problem
• Research directed towards improving care rather than the latest “hot topic”

• “with and for the benefit of the user”
What do users want?

User Research Priorities

• Understand the condition and its causes
• Be sure that they or their child are getting the best possible treatment
• Know that they are giving the best care to their child
• Know they are doing everything they can to avoid it happening again
• Outcomes that will be of practical benefit
• Confidence that the teams are working together to build on previous research
Users need to be involved at the start but how…?

- Do users know what research is being done?
- How can users:
  - Influence research topics
  - Set priorities
  - Evaluate proposals?
- Need to start a dialogue

CLAPA’s role

- User support organisation for 30 years
- Point of contact and source of reliable and accurate information for users
- Future plans: increased local presence, research policy, local representation
- Branches, parent contacts, volunteers, forums
- “expert users”
- Conference 2009
Topics for Research

• Three broad areas:
  – Causes of cleft lip and palate – what are the chances of having another child with CLP?
  – Relative effectiveness of different treatments
    • Care and management
    • Feeding issues
  – Long term impact of cleft lip and palate

A desire to make sense of it

• Lack of a known cause makes it easy for parents to blame themselves and wonder if they could have prevented it happening

• Parents tend to pick up on specific things that happened in the pregnancy, particularly if someone else had the same experience
Suggested research topics
(source discussion boards)

- Why sometimes lip only, palate only or both
- Genetic link
- Alcohol consumption: quantity and timing
- Nasal sprays
- Lack of Folic acid and Vitamin A
- Link to progesterone and aspirin supplements
- Cough syrup containing guafesenin and terbutaline sulfate
- Factor V Leiden
- Link to previous miscarriages or difficult pregnancies that were medicated
- Link to other problems: Coloboma, Reflux, hypertonia

Care and Management

- Easy to get fixed on cure for CLP but not realistic in near future and will always be incidences so need to focus on practical research into care and management of CLP eg outcomes that are useful to them and will lead to improved care
Care and management

- Variations between teams – how do parents know they are getting the best care for their child when another team would do things differently
- Timing of repair and its impact on feeding, physical and speech development
- Taping and strapping lips prior to surgery
- Lip massage and scar management
- New solutions to speech development difficulties
- Optimal treatment for glue ear in cleft patients: Grommets vs hearing aids
- The importance of psychology services (not all teams have one)

Feeding

- Feeding options and successes
- Effects of poor nutrition as a baby
- Impact of CLP on attitudes to food and willingness to feed
- Ages expect children to have sorted out their feeding difficulties
- Solid food/weaning
- Tube feeding
Long term psychological effects

- Why do some people cope and others not
- What coping strategies do adults and parents use
- What are the long term effects of CLP on: education, job prospects, relationship successes etc
- Long term effects of bullying at school
- What is the effect of discussion forums: promoting increased positive self awareness or re-inforcing negative attitudes?

Long term psychological effects

- Impact of society’s attitudes and culture
- Is there a benefit to having a cleft in terms of personal development, compassion etc
- Is there a difference in the psychological development of people born more recently with clefts (eg 10 years ago compared with 30 years ago)
What happens to the research?

Impact of Research

• What happens to the results of research?
  – are they disseminated between teams
  – Do they lead to changes in practice
  – Does planned research build on existing research
  – International perspective
Research vs Information

Information and Research

- Research/information continuum – is it that no-one knows (research) or that parents don’t know (information)
- Users have a strong desire to know what research has been done so far and what are the outcomes
- topics and causes will continue to be revisited until user’s questions have been answered with evidence
Information

• Propose a regular research update for non-medics
• Find the appropriate format for presenting information
• Cleft nurse specialists are a key source of information to parents – do they know about what research is going on

Views on the future

• Clear research strategy that builds on existing research and leads to improved care for people with clefts and their families
• Collaborative working
• Building trust of parents and people with CLP
• Accessible information
• Confidence in the quality of care
PATIENT-CENTRED RESEARCH
Setting an Agenda…

Nicky Rumsey
VTCT Professor of Appearance Research
Centre for Appearance Research
UWE, Bristol

Overview

– What do we know?
– Where to next?
– Opportunities and challenges…
What do we know?

• Appearances do count….
  – Society and the media
  – First impressions
  – Stereotyping

Society & the media

• Standards of beauty have never been more exacting & unremitting
  – Over-reliance on appearances problematic
  – “If all they’ve got is their book cover and there’s no content, they’re in trouble. No matter how good you make that book cover, you’re not going to make a happy book” (Tashcen, 2006)
  – Worry about looks (self preoccupation/ self focussed attention not a good relationship skill)...social difficulties compounded
Impact of appearance overplayed

• First 15 seconds of an encounter……
• Considerable variation in judgements of appearance
• Other cues very powerful
  – Perceived similarity in values & attitudes
  – Reciprocity
• Social skills (entirely possible to control interaction….
  – Eye contact
  – Smiling
  – Focusing attention on others

DISFIGUREMENT

• Early research
  – Impact on affected person
    • Negative emotions (anxiety; depression)
    • Detrimental effects on self perceptions & self evaluations
  – Responses of others
What are the psychological issues (Children)

- Teasing & bullying (7/8ys)
  - 69% of 10 year olds
- Reactions of others (unwelcome questions, 65%)
- Friendship formation
- Changing social groups (e.g., schools, 10 ys)
- Burden of care (speech therapy; orthodontics; bone grafting)

What are the psychological issues (adolescent)

- Teasing/bullying (58% of 15 year olds)
- Unwelcome questioning from others
- Pressure from society/media to “do looks”
- Negative self perceptions (body image; 73% of 15/20 yr olds felt self confidence affected
- Concerns about friendships; romantic relationships
What are the psychological issues (adolescent)

- Concerns about genetic predisposition to clefting
- Career decisions
- Changing social groups (16ys; 18ys)
- Burden of care (orthodontics; bone grafting; MDTs)

Concerns in adulthood

- Social difficulties (speech; appearance)...particularly meeting new people
- Exposure to ‘beauty myths’
  - Negative self perceptions
  - Concerns about relationships
  - Employment opportunities
- New technologies; reorganisation of care
Difficulties in Social Encounters

“Must wear the difference like a badge…” (Crank 1997)
- Unwanted questioning
- Loss of anonymity
- Avoidance by others
- Social anxiety
- Social avoidance

Research focus on problems and difficulties

But….individual differences considerable

- 30-50% of outpatient attenders (Rumsey et al, 2005)
- Similar proportion of community sample (n=1250) (ARC, 2009)
More recently, focus on positive adjustment…..

- Visible difference need not be a ‘social death’
- Adjustment and social functioning weakly/not related to aetiology or severity
- Happiness more trait than state
- 50% genetic….

Biomedical model of care

- Emphasis on improving appearance & function
  - Clinician centred outcome measures
- “Life will be better if you look better” (fuels the beauty myths)
- Can lead to unrealistic expectations re quality of life/ happiness
- Treatment may become a ‘hook’
Adjustment……

73% 15-20 year olds felt self-confidence had been affected by their cleft (Turner et al 1997)
BUT
Topolski et al (2005) – although adolescents had self identity challenges, they reported higher quality of life than their peers

Adjustment…………

• Large numbers (up to 65% of 10 & 15 yr olds) upset by teasing/bullying re cleft...but 47% of those without cleft similar experiences….and
  – Families perceived as more supportive
  – Families allowed more choices
  – No differences in support from friends
  – 15 yr olds MORE satisfied with the way they look
  – More favourable perceptions of ability & self-worth
Adult population: “Physically attractive people have it all, (wo)men, money…the whole world at their feet”

- Women and men (15% in 1972 to 43% in 1997) increasingly dissatisfied with their bodies
- 10% of women free of concern re weight/shape (Dove, 2006)
- 1:4 men actively dieting (Prynn, 2004)
- 61-82% dissatisfied (Harris & Carr, 2001; Liossi, 2003)

Adjustment……

- 70% sample from CLAPA reported +ve consequences of a cleft lip/palate (Cochrane & Slade 1999)
- Eiserman (2001) 11 parents and 11 affected adults
  - > half would choose not to remove the cleft from their lives if option existed
  - Valued social circle
  - Had developed ‘inner strength’
Key components of resilience
(ARC 2009)

• Self esteem (role of cleft/appearance)
• Appearance schemas (filtering & interpreting info from social encounters and the media;)
• Social comparison
• Family environment/social support
• Social confidence & social skill
• Temperament – optimistic outlook

Individual differences in emphasis placed on appearance

- Self esteem
- Appearance
- Other
Individual differences in emphasis placed on appearance

Self esteem

- Appearance
- Fun to be with
- Good social skills
- Academic
- Sports
- Other

Interventions.....

Systematic reviews (Bessell & Moss, 2008; Payne 2009)

- Methodological issues....more research needed
- Cognitive behavioural interventions
- Social interaction skills
Where to next?

- Is post-CSAG care ‘better’?
- Is the burden of MD care acceptable?…
- Is care more patient centred? (Does this help?)
- Do psychologists add value?

Where to next?

- Identify key process and outcome variables
- How to promote resilience (eg role of family environment)?
- Develop and evaluate interventions
- Overcome limitations of cross sectional research…..Longitudinal/epidemiological designs needed….physical & educational outcomes
Challenges…..

• Variability in cleft types
• Variation in treatment histories
• Adjustment is multi-factorial
• Developmental stages
• Lack of time and resource for data collection and analysis

Opportunities

• Can increase our commitment to patient centred research
• Collaborate and establish collective resources for research (UK, Europe and World wide)
• Maximise sample sizes
• Make longitudinal and epidemiological research happen
• Involve patients and families in research and in the development of information, support (key aim of Healing Foundation)
Thank you!
Terry Gregg

The Craniofacial Society of Great Britain and Ireland
A Society for the study of Cleft Lip and Palate
and other Craniofacial Anomalies
History

- **Founded 1970 40 members**
  - Arnold Huddart, Dennis Glass

- Private Society of interested members

- Research always at the Heart
  - *The need to know more* ......

- Multidisciplinary
  - Surgery – Plastic and Maxillo-facial
  - Speech Therapy
  - Orthodontics

- **Formal Constitution 1985**
The Craniofacial Society is an inter-speciality group set up for the study of cleft lip and palate, and other craniofacial anomalies.

main functions are to:

• organise an annual scientific meeting;
• **sponsor research**
• comment on medico-political issues relating to cleft lip and palate service provision

• **provide an archive of conference material**
• provide a membership directory.

1990 – **Focus** – 75 members

• Cleft Lip and Palate

• CSAG 1994
  – Professors Shaw and Sandy driven,
  – Chaired by Professor John Murray

• Co-incident with ..................

• Evolution of Clinical Effectiveness (Audit)
Research is stimulated by Audit

• Are we doing it the best way?

• Comparison with others
  – Europe
  – Scandinavia

• Even if we are do we get the best results?

Chairman of Research Committee
- Professor J Sandy

Chairman of Audit Committee
- Mr P Revington
CSAG Highlighted the role of Additional Specialties

- Dentistry
- Nursing
- Psychology
- ENT

- Cardiology
- Genetics
- Neonatology
- Epidemiology

- Surgery
- Orthodontics
- Speech Therapy

Present Craniofacial Society

- Surgeons 47
- Speech Therapists 64
- Specialist Nurses 33
- Orthodontists 45
- Paediatric Dentists 22
- Psychologists 9
- Other 12
- Total paid up 232
Research the Current position

• Funding of projects
• Funding of medical students
• Funding of Trainees
• Prize Competition

Arnold Huddart Medal

• The Arnold Huddart Medal was established in 1990 for the encouragement of original and promising research papers at the Annual Scientific Conference.

• The adjudication panel consists of one member from each of the Society’s five main membership categories and is chaired by the Vice President of the Society.
  – Surgery, Nursing, Orthodontics, Speech Therapy, Other

• Papers are judged on content, presentation and handling of the discussion following presentation of the paper.

• The paper should be of general interest and understandable to all disciplines of the Society. The prize is normally be awarded to a presenter under the age of 40 years, at the time of presentation.

• The rules have been amended in recent times and priority is now given to sole authors over multi-authored papers. The decision of the adjudication panel is final.
Arnold Huddart Medal Winners

- 2006 *Intra Operative Blood Loss – Anaesthetic Type and Adrenaline Concentration* Patrick Gillespie, Specialist Registrar in Plastic Surgery, Addenbrookes Hospital, Cambridge

- 2004 *Effects of the Fgfr2 Crouzon-type Mutation on Palatal Shelf Development* Chad Perlyn, Dept of Human Anatomy & Genetics, University of Oxford

- 2003 *Assessment of Early Dental and Facial Deformity in Repaired Unilateral Cleft Lip and Palate* Dr A Garrahy, Glasgow Dental Hospital

- 2002 *Sequalae of Otitis Media with Effusion among Children with Cleft Lip and/or Cleft Palate* Patrick Sheahan MB AFRCSI, Specialist Registrar in Otolaryngology, Dublin, Ireland

- 2001 *Can maxillary growth be predicted from 3-dimensional parameters of neonatal study models in patients with unilateral Cleft Lip and Palate?* Ms Felicity V Mehendale, Cleft Fellow in Plastic Surgery at Great Ormond Street Hospital for Children, London and St Andrew’s Centre for Plastic Surgery, Broomfield Hospital, Essex

- 2000 *The Tendons of the Levator Veli Palatini* Ms Felicity V Mehendale, Cleft Fellow in Plastic Surgery at Great Ormond Street Hospital for Children, London and St Andrew’s Centre for Plastic Surgery, Broomfield Hospital, Essex

- 1999 *The Orthodontist's contribution to the management of Obstructive sleep Apnoea* Mr A Johal, Senior Registrar in Orthodontics at the Royal London Hospital

- 1998 *Reorganisation of Cleft services - implications of non cleft anomalies* Ms Lucinda Huskisson, Senior Registrar in Paediatric Surgery at The Children's Hospital, Birmingham

- 1997 *Craniofacial abnormalities in Nicosia, Cyprus, and the significance of parental consanguinity* Ms Varoukian, Dental undergraduate at King’s College Dental Institute, London

- 1996 *A twenty year follow-up assessment of nasal symmetry in patients with unilateral complete Cleft Lip and Palate* Norma Timoney, Senior House Officer in the Department of Plastic & Reconstructive Surgery, Royal Devon & Exeter Hospital
• 1995 Does the McComb primary cleft nose correction affect nasal growth? A longitudinal study. Mr Brian Coghlan, Senior Registrar in Plastic Surgery in the Yorkshire region.

• 1994 Management of 100 cases of phoneme specific nasality - a two centre audit. Mrs Liz Albery, Speech & Language Therapist at Frenchay Hospital, Bristol. Mrs Kim Harland, Speech & Language Therapist at St. Andrew’s Hospital, Billericay.

• 1993 Growing up with a Cleft. Ms Eileen Bradbury, Clinical Counsellor in Plastic Surgery at Withington Hospital, Manchester and Lecturer at the University of Manchester.

• 1992 The vascular basis of posterior pharyngeal flaps. Mr Nigel SG Mercer, Consultant Plastic Surgeon with Frenchay Healthcare Trust, Bristol.

• 1991 The characteristics of pre-speech vocalisations in Cleft Palate children. Mrs Jane Russell, Principal Speech Therapist at Birmingham Children’s Hospital. Prepared in conjunction with Professor Pamela Grunwell.


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**Healing Foundation**

**Partnership**

Healing Foundation/CFSGBI Student Elective Awards 2009/10

The Craniofacial Society of Great Britain and Ireland, in partnership with the Healing Foundation, support Student Elective Awards in the area of research activities relevant to “disfigurement and visible loss of function”.

The purpose of the award is to give undergraduate students the opportunity to broaden their perception and experience of research in the area of cleft care, craniofacial surgery, medicine and care and to improve treatments for patients. The research must be carried out in the UK or Ireland.

Closing dates:
Friday 27 February 2009
Cleft Palate Journal

- America

- Britain – significant contribution

- Europe

CRANE

- Anomalies database

- Joint between RCS and CFSGBI

- Audit lead – Scott Deacon

- Accurate register of births ........
Annual Scientific Meeting 2009

- Surgeons (47)
- Speech Therapists (64)
- Specialist Nurses (33)
- Orthodontists (45)
- Paediatric Dentists (22)
- Psychologists (9)
- Other (12)

- Total 232
- Registered for conference 180

Belfast 2009

- 45 abstracts
- 7 Arnold Huddart
- 28 Verbal
- 10 Posters
- 8 Guest speakers
  - Neonatology
  - Cardiac
  - Genetics
  - Dentistry
  - Speech Therapy
  - Surgery
  - Psychology
  - Science ......
The future Craniofacial Society

• Improvements in treatment
  – already evident
  – CSAG II

• Improvements in care after birth ... CLAPA

• Genetics research
  – Gene Bank
• Prevention.........??

The future Craniofacial Society

• Audit will continue to stimulate research

• The multidisciplinary meeting will serve to increase joint projects on a national basis

• The clinicians will join with the scientists
  
  Healing Foundation Initiative
Success

Film star

Olympic Rower
Jane Blazeby
Multi-disciplinary Cancer Teams and Centralisation

Jane M Blazeby MSc, MD, FRCS (Gen. Surg.)
Professor of Surgery & Honorary Consultant
Upper Gastrointestinal Surgeon,
Department of Social Medicine
Division of Surgery, Head & Neck

Overview

- How we centralised cancer services
- The role of multi-disciplinary teams
- Optimising clinical decisions in MDTs
- Not consider evidence for centralisation
The NHS Cancer Plan
A plan for investment
A plan for reform

Cancer Reform Strategy
MDT meeting weekly at BRI
2001 Surgeon from Weston Super Mare operates in BRI
All Yeovil patients to Bristol

2001 all NBT resections to UBHT
Bile duct exploration to NBT

2003 Satellite clinic in Taunton & attendance at local MDT

2003 All Taunton resections to UBHT

2005 Fast tract staging pathway at UBHT

2005 All pancreas surgery at UBHT

2007 All Upper GI surgery, RUH surgeon operates at UHB

Benefits of centralisation

- Major resections offered appropriately
- Specialist team, 24 hour cover
- Increase palliative options
- Improve information provision
- Training opportunities
- Opportunities to innovate
- Research opportunities

Effective MDT critical
Multi-disciplinary cancer teams

Evidence for the benefits of MDTs lacking

Do not know how to evaluate teams

Fleissig et al. Lancet Oncology 2006:11;935-43
Coory et al. Lung Cancer 2008:60;14-21

Pilot work: MDT decision-making

- How to evaluate MDT decision-making

- What influences MDT decisions
  - In upper and lower GI cancer
  - In gynaecological cancers

- Other roles of MDTs in randomised trials, & in NHS cancer targets
Analysis of clinical decision-making in multi-disciplinary cancer teams


Department of Social Medicine, University of Bristol, UK; "Clinical Sciences at South Bristol, University of Bristol, Bristol, UK

Received 12 September 2005; revised 7 November 2005; accepted 9 November 2005

Management decisions for patients with cancer are frequently taken within the context of a multi-disciplinary team (MDT). There is little known, however, about decision-making at team meetings and whether MDT decisions are all implemented. This study evaluated team decision-making in upper gastrointestinal cancer. Consecutive MDT treatment decisions were recorded for patients with oesophageal, gastric, pancreatic and peri-ampullary tumours. Implementation of MDT decisions was investigated by examining hospital records. Where decisions were implemented it was recorded as concordant or discordant if the decision changed.

Hypothesis:

If all relevant information and personnel are present at the MDT meeting, then the MDT treatment recommendation is optimal and will be implemented
Methods

Analysed records MDT records

Compared MDT decision, with the final treatment received (implemented)

Anticipated 10% not implemented

Inclusion criteria

Included:
Primary treatment decisions
Oesophagus, stomach, pancreas

Excluded:
Recurrences, rare tumours, liver disease,
Decisions for investigations
**UPPER G.I. MULTI-DISCIPLINARY TEAM MEETING**

**Friday 1st April 2005**

<table>
<thead>
<tr>
<th>Patient Details</th>
<th>Diagnosis/Clinical Information</th>
<th>Radiology</th>
<th>Histology</th>
<th>Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>R. C.</td>
<td>7 Adenocarcinoma GOJ</td>
<td>Review</td>
<td>Histology/Cytology from EUS</td>
<td>Neoadjuvant chemo &amp; surgery To see oncologist</td>
</tr>
<tr>
<td>DOB: 09.08.44 Aged 60</td>
<td>CT: 04.08.05 - probable neoplasm of the distal oesophagus just above the GOJ - T2 No</td>
<td>EUS: 1.09.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRI/RUH</td>
<td>MDT: 12.08.05</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R.</td>
<td>Ca Oesophagus Adenocarcinoma distal oesophagus</td>
<td>Review CT 22.03.05</td>
<td>Histology 01.03.05</td>
<td>EUS requested. CT no liver or lung mets. Chase EUS.</td>
</tr>
<tr>
<td>DOB: 26.05.39 Aged 65</td>
<td>OGD 01.03.05</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRI/RUH</td>
<td>Review histology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K.</td>
<td>Ca Oesophagus Adenocarcinoma</td>
<td>Review CT 03.05.05</td>
<td>Histology 12.04.05</td>
<td>Fit for OEO5. Staging lap first.</td>
</tr>
<tr>
<td>DOB: 23.12.47 Aged 57</td>
<td>OGD 12.04.05 - review histology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRI/RUH</td>
<td>Review CT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R.</td>
<td>Ca Oesophagus Adenocarcinoma</td>
<td>Radiology prev. reviewed</td>
<td>Review Histology</td>
<td>Laparoscopy OEO5 if lap OK EUS=T3 N1</td>
</tr>
<tr>
<td>DOB: 02.03.43 Aged 62</td>
<td>OGD: 14.07.05 - histology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRI/RUH</td>
<td>MDT: 01.08.05</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Further staging - EUS 'surgery EUS: 16.08.05 For Discussion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M.</td>
<td>Adenocarcinoma oesophagus</td>
<td>Review histology/ cytology</td>
<td></td>
<td>EUS - tumour extending from 36. Pedunculated tumour. Probably T2 Needs lap. For neoadjuvant chemo and surgery</td>
</tr>
<tr>
<td>DOB: 11.10.30 Aged 75</td>
<td>OGD+Histology: 19.10.05</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRI/RUH</td>
<td>CT: 6.11.05</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>EUS: 17.11.05 - For review only</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Results**

300 MDT decisions

27 excluded

2 missing

271 decisions
### Results n=271

<table>
<thead>
<tr>
<th>Mean age years (range)</th>
<th>68.7 (26 - 98)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, male (%)</td>
<td>172 (63.5)</td>
</tr>
<tr>
<td>Diagnosis (%)</td>
<td></td>
</tr>
<tr>
<td>Oesophageal</td>
<td>153 (56.5)</td>
</tr>
<tr>
<td>Gastric</td>
<td>64 (23.6)</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>54 (19.9)</td>
</tr>
<tr>
<td>Treatment intent</td>
<td></td>
</tr>
<tr>
<td>Curative</td>
<td>121 (45%)</td>
</tr>
<tr>
<td>Palliative</td>
<td>150 (55%)</td>
</tr>
</tbody>
</table>

#### MDT treatment decisions n=271

- 230 implemented
- 41 (15%) changed, 95% CI 11.1% -20%
### How did the decisions change

<table>
<thead>
<tr>
<th>Change in decision</th>
<th>n = 41</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curative to palliative</td>
<td>14</td>
</tr>
<tr>
<td>Palliative to best care</td>
<td>25</td>
</tr>
<tr>
<td>Palliative to curative</td>
<td>2</td>
</tr>
</tbody>
</table>

### Discordant decisions

<table>
<thead>
<tr>
<th>Reasons for change</th>
<th>n = 41</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>18 patient choice (44%)</td>
</tr>
<tr>
<td></td>
<td>12 co-morbidity/death (29%)</td>
</tr>
<tr>
<td></td>
<td>8 op. findings (19%)</td>
</tr>
<tr>
<td></td>
<td>2 doctor choice (5%)</td>
</tr>
</tbody>
</table>
Patient choice

I saw this lady in out-patients again, she is completely adamant that she does not want to have an operation and I think this is a reasonable decision. She seems to be fully informed about the risks involved. She remains in pain and her jaundice seems to be worsening and we will arrange for an urgent ERCP and have another go at stenting her at ERCP and if this fails we will consider percutaneous stenting. I will write to the RRI and make sure that they also know that this lady definitely does not want to be considered for a Whipple's resection.

With best wishes

Yours sincerely

Mr Jonathan Vickers MD FRCS
Consultant Surgeon

<table>
<thead>
<tr>
<th></th>
<th>Concordant N = 230</th>
<th>Discordant N = 41</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>152</td>
<td>20 (11.6%)</td>
</tr>
<tr>
<td>Female</td>
<td>78</td>
<td>21 (21.2%)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>86</td>
<td>8 (8.5%)</td>
</tr>
<tr>
<td>65 - 74 years</td>
<td>66</td>
<td>14 (17.5%)</td>
</tr>
<tr>
<td>75 years +</td>
<td>78</td>
<td>19 (19.6%)</td>
</tr>
<tr>
<td><strong>Treatment intent</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Curative</td>
<td>108</td>
<td>14 (11.5%)</td>
</tr>
<tr>
<td>Palliative</td>
<td>122</td>
<td>27 (18.1%)</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oesophageal (n=153)</td>
<td>140</td>
<td>13 (8.5%)</td>
</tr>
<tr>
<td>Gastric (n=64)</td>
<td>49</td>
<td>15 (23.4%)*</td>
</tr>
<tr>
<td>Pancreas, peri-ampullary (n=54)</td>
<td>41</td>
<td>13 (24.1%)*</td>
</tr>
</tbody>
</table>

*p = 0.001
Referring Hospital vs Concordance

<table>
<thead>
<tr>
<th>NHS Trust</th>
<th>No. of decisions N=271</th>
<th>No. changed N=41</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taunton</td>
<td>31</td>
<td>4 (12.9%)</td>
</tr>
<tr>
<td>BRI</td>
<td>63</td>
<td>6 (9.5%)</td>
</tr>
<tr>
<td>Bath</td>
<td>55</td>
<td>5 (9.0%)</td>
</tr>
<tr>
<td>North Bristol</td>
<td>76</td>
<td>15 (19.7%)</td>
</tr>
<tr>
<td>Yeovil</td>
<td>17</td>
<td>3 (17.7%)</td>
</tr>
<tr>
<td>Weston</td>
<td>30</td>
<td>6 (20.0%)</td>
</tr>
</tbody>
</table>

Pearson’s chi squared p = 0.283

Summary - Upper GI MDT

1. 10 -20% of decisions not implemented
2. If decisions change, treatment becomes less aggressive
3. Change when information regarding choice/co-morbidity not considered at the meeting
An evaluation of treatment decisions at a colorectal cancer multi-disciplinary team

J. J. Wood*, C. Metcalfe†, A. Paet†, P. Sylvester*, P. Durdey*, M. G. Thomas* and J. M. Blazey††

*Department of Surgery, Head & Neck, United Bristol Healthcare Trust, Bristol, UK; †Department of Social Medicine, University of Bristol, Bristol, UK and ‡Clinical Sciences at South Bristol, University of Bristol, Bristol, UK

Received 5 September 2007; accepted 22 October 2007

Abstract

Objective: It is mandatory for treatment decisions for patients with colorectal cancer to be made within the context of a multi-disciplinary team (MDT) meeting. It is currently uncertain, however, how to best evaluate the decision, nine (40%) related to co-morbidity, seven (35%) to patient choice, two changed in light of new clinical information, one doctor changed a decision and for one changed decision, no reason was apparent. When deci-

<table>
<thead>
<tr>
<th>Reason</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 patient choice</td>
<td>35%</td>
</tr>
<tr>
<td>9 co-morbidity</td>
<td>45%</td>
</tr>
<tr>
<td>2 op. findings</td>
<td>10%</td>
</tr>
<tr>
<td>1 doctor choice</td>
<td>5%</td>
</tr>
<tr>
<td>1 unknown reason</td>
<td>5%</td>
</tr>
</tbody>
</table>

Lower GI MDT (n=201)

- 20 changed (10%), 95% CI (6.3% to 15.2)

<table>
<thead>
<tr>
<th>n = 20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reasons change</td>
</tr>
<tr>
<td>7 patient choice (35%)</td>
</tr>
<tr>
<td>9 co-morbidity (45%)</td>
</tr>
<tr>
<td>2 op. findings (10%)</td>
</tr>
<tr>
<td>1 doctor choice (5%)</td>
</tr>
<tr>
<td>1 unknown reason (5%)</td>
</tr>
</tbody>
</table>
Lower GI MDT

1. Between 6-15% of decisions are not implemented
2. Treatments become more conservative
3. Decisions change where patient-centred information not considered at the MDT meeting

MDT decision-making: a complex intervention
Clinical decision-making in a multidisciplinary gynaecological cancer team: a qualitative study

J Kidger, J Murdoch, J Donevan, JM Blazeby

1 Department of Social Medicine, University of Bristol, Bristol, UK, 2 Division of Women and Children’s Health, United Bristol Healthcare Trust, Bristol, UK, 3 Clinical Sciences at South Bristol, University of Bristol, Bristol, UK, 4 Ethics of Surgery, Rad and Neck, United Bristol Healthcare Trust, Bristol, UK.

Correspondence to Dr J Kidger, Department of Social Medicine, University of Bristol, Coney Hill, Whitchurch Road, Clifton, Bristol BS8 2TS, UK. E-mail: judth.kidger@bristol.ac.uk

Accepted 2 November 2006.

Objective: To explore the factors that influence treatment decision-making in a gynaecological cancer team (MDT).

Methods: Qualitative study using interviews and observations.

Sample: Gynaecological cancer MDT and members of that team.

Results: Disease-oriented information was central to decision-making, whereas patient-oriented factors such as patient choice and co-morbidity were more peripheral. This was partly due to variation in team members’ type and level of participation; senior clinicians occupied the more dominant role in discussions and decision-making, whereas junior contributed less but were more likely to focus on patient-related factors. There was a consistent decision-making pathway: a short discussion followed by a clear decision, a prolonged discussion ongoing as a minor treatment plan, and a lengthy discussion with an unclear decision at the end. The type of pathway followed depended on a case’s complexity and the extent of agreement among team members.

Conclusions: Disease-oriented information was central to decision-making, whereas patient-oriented factors such as patient choice and co-morbidity were more peripheral. This was partly due to variation in team members’ type and level of participation; senior clinicians occupied the more dominant role in discussions and decision-making, whereas junior contributed less but were more likely to focus on patient-related factors. There was a consistent decision-making pathway: a short discussion followed by a clear decision, a prolonged discussion ongoing as a minor treatment plan, and a lengthy discussion with an unclear decision at the end. The type of pathway followed depended on a case’s complexity and the extent of agreement among team members.

Keywords: Cancer, multidisciplinary teams, oncology, qualitative methods, treatment decisions.


Methods

- Non-participant observation 10 MDTs
- Semi-structured interviews n=17
- Standard thematic analyses
Three themes emerged

MDT focuses on disease-centred information

Variation in type and degree of participation in the decision process by team members

Three pathways to decision-making
MDT focuses on disease-centred information

All interviewees confirmed importance of disease information, contrast with others

‘If the pathology is not there, you can’t make a decision’ Consultant oncologist

Patient-centred information

- Co-morbidity was included if:
  - Patient in poor health
  - Patient had an unusual condition

- Co-morbidity ill defined:
  - ‘frail’, ‘not that bad’,
  - ‘psychologically wrecked’
‘Although you can quantify co-morbidity fairly objectively, there’s nothing like seeing them for yourself’

Consultant surgeon
Patient choice

- Patient’s views were included:
  - Patient expressed unusually strong opinion
  - Patients’ views contrary to those of the MDT
  - The MDT was uncertain what to do

Patient A with strong opinion

Gynaecologist:

*I don’t think that I should do more surgery in this case, but the patient and her husband are very determined to continue treatment*

Oncologist:

‘Chemo isn’t an option because of bowel obstruction’

Gynaecologist asks radiologists to do further tests

Gynaecologist:

‘So, taking the personalities of the patient & her husband into account, we will pursue, but its totally unrealistic’
Patient choice

- Patient’s views were included:
  - Patient expressed unusually strong opinion
  - Patients’ views contrary to those of the MDT
  - The MDT was uncertain what to do

Summary

- Centralisation of services takes time/talking
- MDTs pivotal in centralised care
- Evaluate team decisions by examining decision implementation
- Decision-making complex in teams
Conclusions/thoughts

- Opportunity for UK to lead
- Develop interventions for decision-making MDTs
Bill Shaw

The Craniofacial Society of Great Britain and Ireland
A Society for the study of Cleft Lip and Palate
and other Craniofacial Anomalies
Growth of Oral Health Group Trials Register

Reports of Trials

Published Trials 2000 - 2007

- U.K.
- U.S.A.
- Turkey
- Brazil
- Germany
- Italy
- Australia
- Japan
- Belgium
- Greece
- Israel
- Netherlands
- Norway
- Austria
- Finland
- N Zealand
- S Korea
- Sweden
- China
- Denmark
- India
- Mexico
- S Arabia
- Venezuela
Good Clinical Practice (GCP)

Developed by regulatory authorities of EU, Japan, USA: Tripartite International Conference on Harmonisation (ICH, 1996)

- Data/results of investigations credible and accurate
- Rights, safety, confidentiality protected
- Since 1997 effective as “best practice”
- Since 2004 EU Directive “legal obligation”

13 Principles of GCP

- Ethical, risks/benefit, well-being of subjects, available info to support trial, sound protocol, IRB/IEC approval, care by qualified physician, all qualified/trained for tasks, informed consent, process allows accurate recording reporting, confidentiality, product appropriately handled, systems assure quality of every aspect
National Institute for Health Research
5 year R&D strategy in England (Cooksey)
New structures, programmes, reallocation
NHS support costs and infrastructure
Where will CLP fit?
- Medicines for Children Research Network
  (Topic specific networks) MCRN
- Comprehensive Clinical Research Networks
  (CCRN)
NIDCR Grant Application Submission Process

Planning grant proposal submitted  Oct 2004
Planning grant awarded  Sep 2005
Definitive proposal submitted  Feb 2007
High score (but not high enough!), revisions suggested July 2007
Resubmitted  Oct 2007
Funded  Aug 2008
Network Coordinators
USP-HRAC Enrollment Coordinator (Co-PI): Trindade
Scandcleft Enrollment Coordinator (Co-PI): Semb

Recruiting Centers
Brazil, Denmark, Finland, Norway, Sweden, UK

Scandcleft Network Coordinator (36)

United Kingdom Site Coordinators
NW England (7.95)
NE England (3.81)
Mid England (7.95)
SW Eng (6.23)
N Ireland (1.75)

Sweden Site Coordinators
Göteborg (3.09)
Stockholm (4.46)
Linköping (1.75)
Malmö (2.64)
Uppsala (2.64)
Umeå (2.20)

Norway Site Coordinators
Bergen (3.11)
Oslo (4.42)

Denmark Site Coordinators
Aarhus (5.31)
Copenhagen (3.35)

Finland Site Coordinators
Helsinki (12.47)
Site coordinator completes paper CRF

Site coordinator enters data onto MACRO database via web interface

Automated data validations generate queries as data is entered

DCC study coordinator generates queries during central monitoring checks

Site coordinator responds to data queries

Site coordinator sends paper forms to DCC within 1 week of study visit/procedure

Data management reports generated for Trial Management Group (TMG)
Mike Dixon

The Craniofacial Society of Great Britain and Ireland
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and other Craniofacial Anomalies
Orofacial clefting

- Incidence 1:500 – 1:1000 live births
- Prevalence depends on ethnic background, geographic origin and socio-economic status
- Cleft lip +/- cleft palate and isolated cleft palate are embryologically and genetically distinct
- 70% of cases are non-syndromic, 30% are syndromic
- Syndromic cases are composed of >300 syndromes

Evidence that orofacial clefting has a genetic component

- Population based studies
- Familial clustering evidenced by raised relative risk to siblings
- Segregation analysis in families
- Concordance rates in monozygotic twins 25–40%
- Concordance rates in dizygotic twins 3-6%
Genetics of non-syndromic clefting

- Inheritance patterns are not well defined
- Most cases are sporadic
- Reduced penetrance
- Heterogeneous disorder, multiple genes
- Evidence for a major susceptibility gene
- Influenced by environmental factors

History of OFC DNA collections

- Individual collections of syndromic cases
  - Wellcome Trust-funded collection
    – 156 case families/220 control families
  - EUROCRAN
    – 1088 complete triads
  - NIDCR-funded
    – Access to large, ethnically-diverse cohorts
- Others – often under-powered, but new data now emerging
- FaceBase
Approaches to dissecting the aetiology of orofacial clefting

- Single gene disorders
- Location (chromosomal)
- Candidate genes (animals/expression)
- Genome-wide studies
- Environment
- Treatment/prevention

Clefting syndromes

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Deletion</th>
<th>Translocation</th>
<th>Gene</th>
<th>Year</th>
<th>Symbol</th>
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</thead>
<tbody>
<tr>
<td>EEC/AEC</td>
<td>-</td>
<td></td>
<td></td>
<td>1999</td>
<td>TP63</td>
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<tr>
<td>Hypodontia-clefting</td>
<td>1970</td>
<td></td>
<td>2000</td>
<td>MSX1</td>
<td></td>
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<tr>
<td>CLPED1</td>
<td>-</td>
<td></td>
<td>2000</td>
<td>PVRL1</td>
<td></td>
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<tr>
<td>X-linked CP</td>
<td>-</td>
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<td>2001</td>
<td>TBX22</td>
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<tr>
<td>Bamforth-Lazarus</td>
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<td></td>
<td>2000</td>
<td>FOXE1</td>
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<tr>
<td>VWS/PPS</td>
<td>1987</td>
<td>1994</td>
<td>2002</td>
<td>IRF6</td>
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<tr>
<td>”Cleft palate”</td>
<td>2001</td>
<td>1999</td>
<td>2003</td>
<td>SATB2</td>
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<tr>
<td>VCSF</td>
<td>1981</td>
<td>1991</td>
<td>2003</td>
<td>TBX1</td>
<td></td>
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<tr>
<td>Kallmann 2</td>
<td>2002</td>
<td>2005</td>
<td>2003</td>
<td>FGFR1</td>
<td></td>
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<tr>
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<td>2004</td>
<td>2004</td>
<td>CHD7</td>
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<tr>
<td>BOF</td>
<td>-</td>
<td>1992</td>
<td>2008</td>
<td>TFAP2A</td>
<td></td>
</tr>
</tbody>
</table>
Van der Woude syndrome

Cleft palate
Cleft lip with/without cleft palate
Hypodontia
Lip pits
Popliteal pterygium syndrome

VWS/PPS mutations

DBD

IAD

1 2 3 4 5 6 7 8

Arg 84
V274I

Nonsense VWS mutations
Missense VWS mutations
Missense PPS mutations
Nonsense PPS mutation
The role of IRF6 in non-syndromic CLP

V274I significantly associated with NSCL/P but not causative variant

140 kb linkage disequilibrium block

18% attributable risk for cleft lip

Approaches to dissecting the aetiology of orofacial clefting

- Single gene disorders
- Location (chromosomal)
- Candidate genes (animals/expression)
- Genome-wide studies
- Environment
- Treatment/prevention
Pierre Robin sequence

- Mapped to “gene desert” on chromosome 17q24
- Three families with translocations involving 17q24
- CGH analysis identified deletions of this region

- Mutations may lie distant to coding sequence
- These may phenocopy intragenic mutations or
- May result from ectopic transcriptional activation

- Disruption of non-coding site and stage-specific enhancers may underlie CLP
Micro-deletions

- Copy number variants - 12% of genome
- Predispose to deletions/duplications
- Detection by Mendelian loss, homozygosity mapping, CGH, micro-array analysis
- Successes include:
  - FGFR2
  - IRF6
  - TFAP2A
  - SOX9

Approaches to dissecting the aetiology of orofacial clefting

- Single gene models
- Location (chromosomal)
- Candidate genes (animals表达)
- Genome-wide studies
- Environment
- Treatment/prevention
Animal models in the study of OFC

- **Mouse**
  - Development mirrors that in human
  - Expression studies easy
  - Genetic manipulation
  - Epistasis
  - Few models of cleft lip
- **Chick**
  - Useful for study of cleft lip
  - Expression studies easy
  - Cleft palate
- **Zebrafish**
  - “Palate”
  - Lineage tracing

Sequence analysis of candidate genes

- Published studies include:
  - *SKI1, MSX2, SPRY2, GLI2, JAG2, TBX10, LHX8* (Vieira *et al.*, 2005)
  - *PVRL1, PVRL2* (Avila *et al.*, 2006; Warrington *et al.*, 2006)
  - FGF family members (Riley *et al.*, 2007)
- Many Negatives and hard to interpret positives
- Candidate gene-based association studies
Approaches to dissecting the aetiology of orofacial clefting

- Single gene models
- Location (chromosomal)
- Candidate genes (animals/expression)
- Genome-wide studies
- Environment
- Treatment/prevention

Genome-wide linkage and fine mapping

- CIDR linkage analysis
- Meta-analysis
- Fine mapping CIDR (~1500 SNPs)
- Loci identified on 6p and 9q
- Genome-wide association studies on-going
- New locus identified (In press)
Approaches to dissecting the aetiology of orofacial clefting

- Single gene models
- Location (chromosomal)
- Candidate genes (animals/expression)
- Genome-wide studies
- Environment
- Treatment/prevention

Environment and CL/P

- Smoking
- Alcohol
- Nutrition
- Teratogens (eg. phenytoin)
- Geography
- Social class
Summary

Multiple genes now implicated
Superb animal models
Environmental epidemiology convincing
Genome-wide approach successful and expanding
Resources for collaboration critical
Integrated approach essential
Phenotypes
Dave Evans

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Genome-wide Association Studies

David Evans

University of Bristol

Methods of gene hunting

Effect Size

rare, monogenic (linkage)

common, complex (association)

Frequency
Historical gene mapping


Reasons for Failure?

Also association studies focused on candidate genes
Genome-wide Association Studies

![Number of teeth 15m](image)

Enabling Genome-wide association studies: HapMap

![HapMap](image)
Empirical patterns of LD

Coverage

Improving association studies: cheap genome-wide coverage

Availability of Large Cohorts / Case Series

Wellcome Trust Case Control Consortium
Dentition

- Tooth eruption: The process by which teeth migrate from their developmental position within the jaws to emerge in the oral cavity

- The only developmental process during which a developing organ must exit the confines of the bony crypt in order to develop

- Highly heritable (Hughes et al. 2007)

- Provides a powerful model for studying epithelial-mesenchymal interactions that control patterning and morphogenesis in other developmental processes
ALSPAC Teeth Variables

- Mother completed questionnaire
- Age at first tooth (6, 15 and 24 months)
- Number of teeth (6, 15 and 24 months)
- Any milk teeth lost? (54, 65, 78 months)
- Number of milk teeth lost (54, 65, 78 months)

ALSPAC GWAS

- Age at first tooth and number of teeth (15 months)
- 1453 ALSPAC children
- 4564 North Finland Birth Cohort
- Illumina 317K SNP chip
Analysis

- Ordinal Regression
- Survival Analysis
- Covariates (Sex, Gestational Age, Age at Completion)
- Meta-analysis
**Significant Associations**

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Date of first tooth eruption</th>
<th>Number of teeth</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NFBC</td>
<td>ALSPAC</td>
</tr>
<tr>
<td>17</td>
<td>$2.5 \times 10^{-14}$</td>
<td>$9.8 \times 10^{-7}$</td>
</tr>
<tr>
<td>17</td>
<td>$1.7 \times 10^{-3}$</td>
<td>$0.01$</td>
</tr>
<tr>
<td>14</td>
<td>$4.4 \times 10^{-4}$</td>
<td>$3.4 \times 10^{-4}$</td>
</tr>
<tr>
<td>12</td>
<td>$5.5 \times 10^{-6}$</td>
<td>$2.5 \times 10^{-6}$</td>
</tr>
<tr>
<td>14</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>17</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>2</td>
<td>n.s.</td>
<td>n.s.</td>
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<tr>
<td>6</td>
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<tr>
<td>17</td>
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<td>n.s.</td>
</tr>
<tr>
<td>17</td>
<td>$3.2 \times 10^{-4}$</td>
<td>0.03</td>
</tr>
</tbody>
</table>
### Suggestive Associations

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Date of first tooth eruption</th>
<th>Number of teeth</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>NFBC</td>
<td>ALSPAC</td>
</tr>
<tr>
<td>17</td>
<td>n.s.</td>
<td>n.s.</td>
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<td>5</td>
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</tr>
<tr>
<td>4</td>
<td>2.5 x 10^-4</td>
<td>0.6</td>
</tr>
</tbody>
</table>

### Genes?

- Tooth development
- Skeletal development
- Growth
Conclusions / Future Directions

• Analyze other dentition phenotypes

• Dentition a marker of other growth processes?

• Genome-wide association approach is a hypothesis free method that can provide information on the biology underlying dentition
Parallel session 1

The Craniofacial Society of Great Britain and Ireland
A Society for the study of Cleft Lip and Palate
and other Craniofacial Anomalies
Cleft Research Workshop, February 2009

Parallel session 1: Design of CSAG II (Chair: Jonathan Sandy)

1) **Workshops**
- Have NIHR funding for annual workshops for 5 years
- Next workshop February 2010, Friday and Saturday (not a satellite meeting)
- Aims of next workshop to be clear, with broader representation (e.g. CDs and SIGs, more junior members of the teams, plus possibly users for part of the meeting), and as much notice of the dates given as possible
- Additionally, 2 day research workshop funded by CFSGB&I will be held later this year, aimed at junior researchers; details will be circulated to chairs of SIGs to ensure people have the opportunity to attend

2) **Systematic reviews**
- Have NIHR funding to appoint systematic reviewer
- Anyone with research questions suitable for systematic review can be supported by the systematic reviewer, and web conferencing facilities can be used so travel to Bristol not essential
- Possible questions suggested:
  - Speech, early intervention and at approximately 5 years (Sue Roulestone)
  - Antibiotic use (Steve Thomas)
  - Primary closure methods (Rona Slater)
  - Suturing methods (Rona Slater)
  - Scarring – benefit of massage/silicone etc (Rona Slater)
  [i.e. all the original questions proposed should be reviewed]

3) **Design of CSAG II**
- Study to be funded by NIHR grant
- Will start as soon as possible, running over 2 years, and must be completed before end of 5 year funding; need to decide which cohorts will be included. These are in some ways restricted because of the grant funding.
- Aim is to assess whether/how the centralisation process has improved cleft care in the UK
- Main issue is whether outcomes measured should be identical to CSAG I, or should include additional measurements e.g. using best possible techniques available. Study should be repeat of CSAG I as far as possible, to give snapshot of current state of UK cleft care/provide benchmarks. However, potential for additional studies to be carried out in future. Alternatively could do core data collection in most centres but some additional data collections in some centres
- Three postgraduate students in Bristol to be involved in data collection
Data will be collected on 5 and 12 year olds, as in CSAG I
- 5 year old data collection to include: study models, oral health, speech, hearing, appearance, psychology (parents)
- 12 year old data collection to provide information on bone grafts.
- Whether or not to include photographs will be discussed further (although 3D images unlikely to be included as not all centres have equipment required)
- Plus centre-based information will be collected e.g. when did centralisation occur, is there a psychology service, how closely integrated are ENT, audiology and paediatric dentistry services?
- Issues requiring careful thought during planning and analysis stages:
  - Inconsistency in timing of centralisation across services
  - Huge variation in how multi-disciplinary teams are run
  - Some tools have changed over time e.g. tool for speech, new index for study models; must compare old and new tools
- CSAG II may not be the most appropriate name for the study, as no longer Clinical Standards Advisory Group; Cleft Care UK 2010 was suggested, but may need to consider CSAG name e.g. as subheading, so users can identify the link between studies
- Jonathan will communicate with CDs, SIG leads, and those involved in CSAG I, to take CSAG II proposal forward, including setting up a chat room for SIG leads.
- Users and carers, especially those who have been involved since before centralisation, should be involved at an early stage

Sam Leary, March 1st 2009
Parallel session 2

The Craniofacial Society of Great Britain and Ireland
A Society for the study of Cleft Lip and Palate
and other Craniofacial Anomalies
Parallel session 2 – Key clinical questions
Chair: Bill Shaw

Key points generated

1. An unique opportunity to put in place a lasting, clinical research infrastructure to optimise the research potential of post- CSAG services and bring about alignment of cleft research under the new Healing Foundation proposal with new NHS research structures in NIHR. However, there are still uncertainties on the precise models that will be submitted for the Healing Foundation proposal. This is mainly due to the fact that applicants may have different visions and their universities may also have a prior view (note – host university have to match funds).

2. One key principal it that the project/proposal must be comprehensive in its inclusion and transparency for all UK cleft centres. This could be possibly achieved via the clinical study group model of MCRN with the national panel appointed by the CFSGBI.

3. Another important key principal is the “pump priming” of research nurse investment at each site in relation to the size of the centre. Each centre should be research oriented; this is a process that needs to be established.

4. It would be useful to provide workshops/training for the research nurses or other staff in order to inform teams of research methods but also start the process of establishing a research oriented environment. It is paramount that all staff involved in the cleft care has an understanding of the importance of researching different aspects in cleft care in order to optimize treatment. This process could for example include “road shows” to the different centres.

5. It is further important to secure involvement of user representation in the National Clinical Studies Group in combination through a collective effort to develop better patient centred methods. It is well established that user groups/patient involvement can provide more relevant focus and direction.
Parallel session 3

The Craniofacial Society of Great Britain and Ireland
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and other Craniofacial Anomalies
Summary of discussion in parallel session 3 – Genetics questions and gene banks

Present: David FitzPatrick, Peter Mossey, Mike Dixon, Usha Kini, Phil Stanier, Sarah Lewis, Jenny Morton, Melissa Lees, Sarah Smithson, Margo Whiteford, Shane McKee, Ian Day, Sue Ring, George Davey Smith, Alex Griffiths, Andrea Waylen

Systematic reviews
- Several possible questions were discussed but in most cases it was felt that there were not enough good quality studies for a systematic review to be carried out.
- Two possible areas for review are:
  - would be to determine the best way to screen for Stickler syndrome
  - what should trigger investigations for the karyotyping of isolated cleft antenatally and postnatally?
- There probably aren’t enough studies for a full systematic review in either area (5-6 cases series), so a recommendation on best practice from an expert panel might be more appropriate. Sarah Smithson to lead on Stickler investigation.

Other research questions
- How much of the heritability of cleft lip / palate within families is due to rare genetic variants and how much to common variants? There is some evidence that parents of children with a cleft have unusual craniofacial features.
- What is the best way to diagnose and manage Pierre Robin sequence? (Dave Fitzpatrick is currently trying to get funding for a European network of researchers to answer this question.)
- Differences in genetic aetiology between cleft palate and cleft lip +/- palate.

Gene bank
- “Gene bank” probably isn’t the best name for it – possible negative associations in people’s minds with the word “gene” (and now the word “bank” as well…)
- The London Neurogenetics Database / London Dysmorphology Database (http://www.lmdatabases.com/about_lmd.html#lddb) should be used to describe/classify craniofacial features in a standardised way – the section on clefts would have to be expanded first to include laterality scores etc.
- Data would have to be recorded by clinicians who had seen the patient, ideally by direct electronic entry.
- All children with a cleft have photographs taken – ideally the parents should also have photos taken and reviewed for facial abnormalities.
- Should 3D images be taken (of parents as well as children)? This is feasible in some areas (e.g. Glasgow) but funding varies. Useful for detailed phenotyping.
- Dave Fitzpatrick will collate information from clinical geneticists on what triggers a referral to them.
- Some exposure data (e.g. birthweight) are automatically recorded at birth, some are already collected for the CRANE database. Environmental exposures are more problematic, especially if the cleft is not noticed at birth (sub-mucosal) – some exposures can be measured from mother’s hair or toenails.
• Aim would be to collect DNA samples from every child with a cleft in the UK and from their parents, together with phenotypic data and possibly other biological samples. There was discussion of timing re: sample collection eg only once or at several timepoints to facilitate dynamic phenotyping?
• Syndromal cases would be difficult to anonymise properly and a different approach might be needed with regard to data access. Some cases may be diagnosed as non-syndromal to start with but re-assessed as syndromal later so the two sets of data would need to be linkable.
• There was discussion about feeding back information to patients: eg it would be important to be able to inform patients about any increased risks of other conditions and any diagnostic results acquired from the data collected.
Suggestions

The Craniofacial Society of Great Britain and Ireland
A Society for the study of Cleft Lip and Palate and other Craniofacial Anomalies
Suggestions for Systematic Reviews

1. 3-D imaging, especially in relation to panels assessment
2. User involvement
3. Psychosocial measure of adjustment/resilience
4. Wounds
5. Antibiotics
6. Speech and language
7. Management of Stickler syndrome
8. Multidisciplinary team working
9. Update feeding review

Suggestions for key people/representatives to invite

1. Fetal medicine
2. Paediatrics
3. Community paediatrics
4. SIG leads