

WELCOME !

DR Management Trial Participants

Vermont Oxford Network

DR MANAGEMENT TRIAL
WEB CONFERENCE #11

Update on DR Management Trial
Data and Safety Monitoring
The COIN Trial

STEERING COMMITTEE



Mike Dunn



Alan de Klerk



Maureen Reilly



Joe Kaempf



Jeanette Conner



Rose de Klerk



Roger Soll



Karla Ferrelli

CONFERENCE FACULTY

Professor
Colin Morley

Professor and Director of Neonatal
Medicine at the Royal Women's and
Royal Children's Hospitals,
Melbourne, Australia
1998-present

TRIAL PARTICIPANTS

- Akron Children's Hospital
- Barbara Bush Children's at ME Medical
- Baystate Medical Center
- Beth Israel Deaconess Medical Center
- Brigham and Women's Hospital
- Bronson Methodist Hospital
- Central DuPage Hospital
- Central Mississippi Medical Center
- Connecticut Children's Medical Center
- Dartmouth-Hitchcock Medical Center
- DeVos Children's/Spectrum Health
- Frankford Torredale Hospital
- Legacy Emanuel Children's Hospital
- The Medical Center at Columbus Regional
- Mercy Children's Hospital
- Meritcare Children's Hospital
- Mississippi Baptist Health Systems
- Ochsner Clinic Foundation
- Providence St. Vincent Medical Center
- Rockford Memorial Hospital
- St. Charles Medical Center
- St. Joseph Mercy Hospital
- St. Vincent Hospital
- Sunnybrook & Women's College
- Summa Health System
- The Medical Center at Columbus Regional
- UC Irvine Medical Center
- University Medical Center—Las Vegas
- Univ. of TN Medical Center—Knoxville
- West Virginia Univ. School of Medicine
- Woman's Hospital

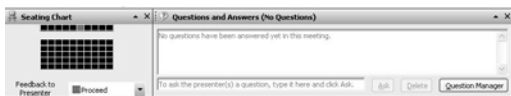
WEB CONFERENCE BASICS

- Follow slides on the Internet
- Listen on your phone or speaker phone
- Your phone will be muted during the presentations

Technical Problem?
Dial *0 (Star Zero)

WEB CONFERENCE BASICS

- To ask a question during the conference use the "Questions and Answers" box located on your screen.
 - Enter your question in the lower box and press ask to submit. Please wait 10 seconds before submitting another question.
- We will try to answer all questions during the session.



WEB CONFERENCE BASICS

- We will conduct a Question & Answer session at the end of the presentations.
- You will be instructed at that time how to queue for questions.

Technical Problem?
Dial *0 (Star Zero)

CME Credits

- CME credits and Nursing Contact Hours are now available for the DRM Web Conferences
- Information and sign up sheets available on our website at <http://www.vtoxford.org/home.aspx?p=research/drm/cmescmematerials.htm>
- Email karla@vtoxford.org with any questions

GOALS OF WEB CONFERENCE

- Update current status of the trial
- Understand the function of the Data and Safety Monitoring Committee
- Review the design and results of the COIN Trial
- Understand the similarities and differences between the COIN Trial and the DR Management Trial
- Exchange thoughts on all of the above

AGENDA

Introduction	Karla Ferrelli
Current Status of the Trial	Roger Soll
Data and Safety Monitoring	Roger Soll
The COIN Trial	Colin Morley
The COIN Trial and the DR Management Trial	Mike Dunn
Q & A Session	DR Trial Faculty
Wrap Up	Karla Ferrelli

REVIEW: STATUS OF THE TRIAL

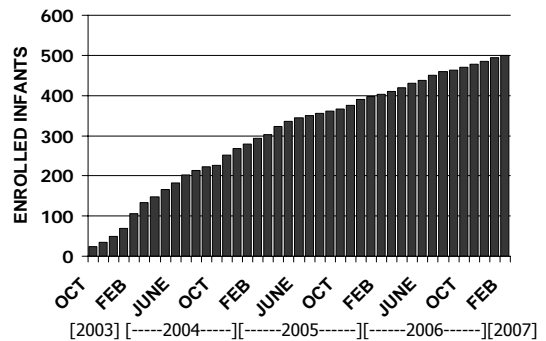


Congratulations

CONGRATULATIONS!

WE ARE FAST APPROACHING
OUR 500th ENROLLED INFANT!

DR MANAGEMENT TRIAL: ENROLLMENT



DR MANAGEMENT TRIAL: PROGRESS

498 Infants enrolled
18 to 24 Month Follow Up underway
Second DSMC Report completed
Next DSMC Report at 500 enrolled infants

DATA AND SAFETY MONITORING



DATA AND SAFETY MONITORING

- PATIENT SAFETY AND DATA COMMITTEE
- DATA MONITORING BOARD
- EXTERNAL SAFETY COMMITTEE
- SAFETY AND EFFICACY MONITORING COMMITTEE

THE ROLE OF THE DATA AND SAFETY MONITORING COMMITTEE

Reviews accumulating data to detect evidence of early dramatic benefit or harm for patients while the clinical trial is in progress

THE ROLE OF THE DATA AND SAFETY MONITORING COMMITTEE

- Reviews efficacy of intervention
- Reviews potential harms of intervention
- Reviews study compliance
- Reviews study recruitment
- Reviews possibility of futility (no chance of treatment success)

THE ROLE OF THE DATA AND SAFETY MONITORING COMMITTEE

The role of the IRB vs. the role of the DSMC

- Both concerned with patient safety
- IRB must review all aspects of local trial conduct
- DSMC must review trial in total
- May be some overlap in roles

THE ROLE OF THE DATA AND SAFETY MONITORING COMMITTEE

Easier to assess "efficacy" than "safety"

Efficacy rules can be established prospectively

"Safety" is a wild card

- sulfonamides and kernicterus
- surfactant and pulmonary hemorrhage
- postnatal steroids and GI perforation

DATA AND SAFETY MONITORING

COMMITTEE MEMBERSHIP

Members should be external to the trial

Members should possess relevant expertise

- Neonatology
- Clinical trials conduct and methodology
- Statistics

Number of members: minimum 3/maximum ?

DELIVERY ROOM MANAGEMENT OF PREMATURE INFANTS

PATIENT SAFETY AND DATA COMMITTEE

Steve Block, MD, Chair
Wake Forest University School of Medicine

Walter Ambrosius, PhD
Wake Forest University School of Medicine

Tom Young, MD
University of North Carolina School of Medicine

DATA AND SAFETY MONITORING

For the main trial, reports for the Data and Patient Safety Monitoring Committee will be prepared ...and have data available on the primary outcome Measure.... The methods of Lan and Demets will be used to adjust the final p value to account for the effect of the interim analyses (Lan 1983).

DATA AND SAFETY MONITORING

DSMC concerns:

Differences beginning to emerge in the primary composite outcome

- need for interim analysis at 500 enrolled infants

Slow recruitment

Clarification of adverse events report

DATA AND SAFETY MONITORING

Issues to consider during the monitoring of interim analyses of trials are:

- the possibility of generating either false-positive or false-negative results by early termination
- the balance of beneficial and adverse effects on different outcomes (and, perhaps, also of early and late effects)
- the certainty of evidence required to influence practice appropriately (given the available evidence from other studies, current opinions and practices, etc.).

DATA AND SAFETY MONITORING

The disadvantages of stopping a trial early:

- lack of credibility
- lack of realism
- imprecision
- bias

Pocock BMJ 1992

THE COIN TRIAL

Professor Colin Morley

Professor and Director of Neonatal Medicine at the Royal Women's and Royal Children's Hospitals, Melbourne, Australia
1998-present

The COIN Trial

Nasal CPAP or intubation at birth for very preterm infants

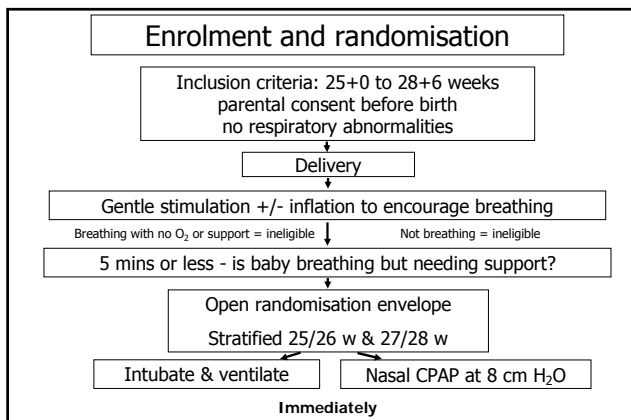
An 18 centre international randomised controlled trial.

April 1999 to March 2006

Funded by the Australian NHMRC Project grant No 148002

Background

- CLD (O₂ at 36 weeks) is associated with ventilation.
- If very premature infants can be cared for without ventilation this might reduce the rate or severity of CLD.
- Observational studies suggest infants can be managed with just nasal CPAP and this may reduce CLD.
- CLD is such a big problem it is important to find out whether this is true.
- Therefore we organised a RCT of CPAP v intubation and ventilation.



Background thoughts

- We did not plan to intubate CPAP babies and give surfactant first because there is good anecdotal evidence that this is not necessary.
- Surfactant trials were before era of CPAP and most did not have A/N steroids. Babies were sicker.
- Did not think infants <25 weeks could be randomised to CPAP so not included.
- Did not think it was ethical to randomise infants >28 weeks to be intubated.
- Started with CPAP of 8 cm H₂O because of evidence it is more effective at aiding FRC.
- Did not want to randomise before birth because it might bias subsequent treatment.

CPAP technique

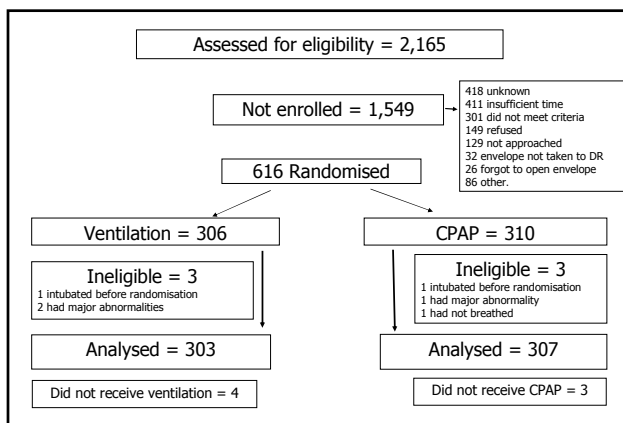
- Recommended the Neopuff.
- Use CPAP 8 cm H₂O.
- Use a cut down ETT in one nostril in DU.
- Use short binasal prongs when in the NICU.
- Adjust pressure as clinically indicated.

Criteria for CPAP failure:

- **Acidosis**
 - PaCO₂ > 60 mmHg and pH <7.25
 - Metabolic acidosis unresponsive to treatment
- **Oxygen**
 - FiO₂ > 0.60
- **Apnoea**
 - unresponsive to stimulation
 - or > 6 in 6 hr receiving stimulation
 - or > 1 episode of bag & mask.

Power calculations

- From the Australian and New Zealand Neonatal Network
 - 43% of infants born at 25 to 28 weeks died or had CLD.
- We assumed this trial would enroll infants whose mothers had been in hospital long enough and were well enough to give consent – more antenatal steroids and less acute illness.
 - So CLD possibly less ~ 30%.
- Need 600 infants to show death or CLD reduced from 30% to 20% with alpha of 0.05 and 80% power.



Demographic data

	Ventilation	CPAP
N	303	307
Birthweight mean (SD)	952 (217)	964 (212)
Gestational age -mean (SD)	26.9 (1.0)	26.9 (1.0)
25 and 26 weeks gestation	35 %	33 %
27 and 28 weeks gestation	65 %	67 %
Antenatal corticosteroids any dose	94 %	94 %
Caesarean section	69 %	66 %
In labour	66 %	66 %
Days ROM (median IQR)	0 (0,1)	0 (0,2)
Male	56 %	49 %
Multiple births	32 %	35 %

Results of the COIN Trial

The Results of the COIN Trial:

- The trial is as yet unpublished
- Results of the trial should not be presented outside the context of this meeting
- Slides 37 to 52 detail the trial results and have been omitted from this handout

Summary

- Infants born at 25 to 28 weeks, who breathe after birth, can be treated with CPAP at birth.
- Their outcomes were similar to, or better than, the ventilated group.
- Increased pneumothoraces in CPAP group
- The two gestational age strata had similar outcomes.
- Recommendation: Start on CPAP if possible

- ✓ Royal Women's Hospital, Melbourne, Australia. Colin Morley
- ✓ Maternite Regionale Universitaire, Nancy, France. Jean Michel Hascoet
- ✓ Alexandra Hospital, Athens, Greece. George Baroutis
- ✓ Royal Brisbane and Women Hospital, Brisbane, Australia. David Cartwright
- ✓ Royal North Shore Hospital, Sydney, Australia, Jennifer Bowen
- ✓ Children's Hosp Montefiore, Weiler-Einstein Hosp Div, New York, USA. Luc Brion
- ✓ King Edward's Memorial Hospital, Perth, Australia. Karen Simmer
- ✓ Klinik fuer Neonatologie, Charité Universitätsmedizin, Berlin, Germany. Charles Christoph Röhr,
- ✓ National Women's Hospital, Auckland, New Zealand. Jane Harding
- ✓ Ghent University Hosp, Ghent, Belgium. Koenraad Smets
- ✓ McMaster University Medical Centre, Hamilton, Canada. Barbara Schmidt
- ✓ Golisano Children's Hospital at Strong, Rochester, USA. Nirupama Laroia
- ✓ Jacobi Medical Centre, New York, USA. Ivan Hand
- ✓ Akershus University Hospital, & Rikshospitalet University. Hosp, Oslo, Norway. Britt Nakstad
- ✓ Center for Pediatrics & Adolescent Medicine, University Hospital Freiburg, Germany. Roland Hentschel
- ✓ Hackensack University Medical Centre, New York, USA. Benjamin Planer

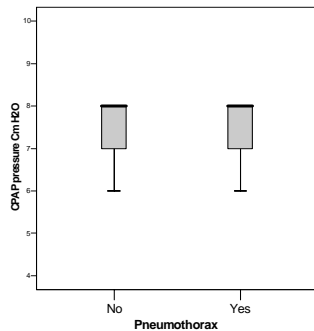
Questions this trial does not answer

- What are the long term outcomes?
- Is intubation, surfactant and immediate extubation better?
- Which babies will fail CPAP?
- What is the correct CPAP pressure and technique?
- What is the optimal ventilation strategy from birth?
- Why does CPAP increase incidence of pneumothoraces?

Pneumothoraces

- Known to be associated with CPAP – Cochrane Ho et al, 2002
- Not from birth: 36% on 1st day, 43% 2nd day.
- We do not know pressure when they occurred.
- We do not know the time they occurred only the day.
- Almost all babies with a pneumothorax were ventilated.
- Many found after babies ventilated so not clear whether present before or after ventilation.
- If due to CPAP pressure why less in ventilated babies?
- Occur evenly across gestations.
- Not clear why some babies develop PTX and others don't.

CPAP pressure on arrival in NICU



Surfactant

- CPAP group did not receive surfactant at birth.
- Half the CPAP group were ventilated on 1st day. Most received surfactant.
- The short term outcome of the CPAP group was better than the ventilated group.
- This does not encourage early intubation and surfactant.
- Surfactant trials – low A/N steroids, all electively ventilated. Babies were sicker. CPAP was not considered.

CPAP pressure

- No good evidence for 5 cm H₂O.
- Gregory used up to 8 to 15 cm H₂O.
- Kamper, Acta Paed 1993 CPAP up to 10 cm H₂O
- Lamb studies show better oxygenation and less lung injury with 8 cm H₂O.
- Increased FRC with increased PEEP.
- Unique situation:
 - Very premature infants
 - No FRC, immature muscles and ribs
 - Lung full of fluid
 - Need to aid lung expansion and lung volume
- No evidence for 8 cm H₂O causing pneumothorax

THE COIN TRIAL AND THE DR MANAGEMENT TRIAL



Eligibility

COIN:

- 25 - 28 6/7 weeks
- Prenatal consent
- No significant congenital abnormality

DR Management:

- 26 – 29 6/7 weeks
- Prenatal consent
- No significant congenital abnormality

Randomization

COIN:

- After delivery
- Spontaneously breathing by 5 minutes of age
- Respiratory difficulty with O₂ requirement

DR Management:

- Prior to delivery
- Delivery imminent

Stratification

COIN:

- By GA (25 – 26 6/7, 27 – 28 6/7 wks)
- By centre

DR Management:

- By GA (26 – 27 6/7, 28 – 29 6/7 wks)
- By center

Interventions

COIN:

1. Nasal CPAP
2. Endotracheal intubation with IPPV
 - All ventilated infants eligible to receive surfactant

DR Management:

1. PS – Intubation, prophylactic surfactant and ventilation
2. ISX – Intubation, prophylactic surfactant with rapid extubation to nCPAP
3. nCPAP – Nasal CPAP with selective surfactant

Primary Outcome and Sample Size

COIN:

- Death or chronic lung disease
- Chronic lung disease defined as need for oxygen at 36 weeks gestation
- Sample size: 300 in each group, total=600 infants

DR Management:

- Death or chronic lung disease
- Chronic lung disease defined as need for oxygen at 36 weeks as demonstrated by an oxygen saturation test
- Sample size: 292 in each group, total=876

Secondary Outcomes

Coin

- Incidence of intubation and ventilation
- # doses surfactant
- Air leak
- IVH
- Days on assisted ventilation
- Days on nCPAP
- Time in hospital
- Time to regain birth weight
- Need for O₂ at 28 days
- FiO₂ at 36 weeks
- Use of methylxanthines
- Use of post natal steroids
- Economic analysis

DR Management

- # infants receiving surfactant
- # doses surfactant
- Use of post natal steroids
- Use of methylxanthines
- Clinical status at 28 days
- Clinical status at 36 weeks
- Days on assisted ventilation
- Days on NCPAP
- Days on oxygen
- Growth (wgt on day 28 and 36 weeks)
- Time in NICU and hospital
- Pneumothorax
- Pulmonary Haemorrhage
- Mortality
- Other complications of prematurity

Secondary Outcomes: Follow Up

COIN:

- One year of age.
- Postal or telephone questionnaire
- Hospital admission for respiratory illness, family doctor attendances for respiratory illness,
- Any antibiotic or other drugs prescribed for respiratory disease
- Weight, height, head circumference, basic elements of development

DR Management:

- Two years of age
- Telephone questionnaire
- Health status (neurodevelopmental and respiratory)

CPAP Methods

COIN:

- In DR: single nasal prong with Neopuff (recommended) or other CPAP device
- In NICU: any short binasal prong CPAP device
- Starting CPAP=8cmH₂O but may go up to 10cmH₂O if necessary

DR Management:

- Bubble CPAP
- Starting CPAP=5cmH₂O but may go up to 7cmH₂O if necessary

Intubation Criteria

COIN:

- >6 apnea spells in 6 hour period requiring stimulation
- >1 apnea spell requiring PPV
- >60% oxygen to keep SaO2 >90%
- pH<7.25
- Need for anesthetic

DR Management:

- >12 apneas spells in 6 hours requiring stimulation
- >1 apnea spell in 24 hour period requiring PPV
- PCO2 >65 mmHg
- FiO2 .40 to .60 to keep SaO2 86-94%

Points for Discussion

- Gestational ages
- Timing of randomization
- 2 arm versus 3 arm (ISX group distinct)
- Surfactant treatment
- ?Target range for blood gases (not specified in COIN)
- ? Extubation criteria (not specified for COIN)
- nCPAP methods
- O2 Saturation test

- ?Meta-analyzable

QUESTION & ANSWER SESSION

INSTRUCTIONS FOR CALLING IN

- Dial "1" to ask a question
- Speaker phone users must pick up the handset first before dialing "1"
- Operator will place you in the queue

Problem? Dial *0

NEXT STEPS



WHAT IS THE FUTURE OF THE DR MANAGEMENT TRIAL?

Patient Recruitment: Will we be able to recruit sufficient subjects for the trial?

Negatives:

- Fewer centers involved than projected
- Difficult process of enrollment

Positives:

- Continued commitment of participating centers
- Importance of trial question

WHAT IS THE FUTURE OF THE DR MANAGEMENT TRIAL?

Secondary goals

Will be able to address certain issues with some precision including:

- Days on mechanical ventilation
- Days in supplemental oxygen
- Usefulness of new saturation test for determining respiratory status

RESPIRATORY CARE OF EXTREMELY LOW BIRTH WEIGHT INFANTS: VON 2005

<u>INTERVENTION</u>	<u>BW 501-750 G</u>	<u>BW 751-1000 G</u>
<u>DELIVERY ROOM:</u>		
INTUBATION	80 (70, 97)	72 (60, 88)
SURFACTANT	50 (15, 75)	44 (9, 70)
EARLY CPAP	13 (0, 17)	25 (3, 33)
VENT S/P EARLY CPAP	82 (67, 100)	58 (33, 100)
ANY CONVENTIONAL VENT	91 (88, 100)	83 (75, 96)
HIFI VENT	57 (28, 76)	30 (10, 43)
ANY SURFACTANT	83 (75, 100)	82 (75, 94)
SURFACTANT > 2 HRS	9 (0, 11)	13 (0, 19)

PEP TALK

How to maintain interest and enthusiasm?

Need to continue to:

- Communicate with VON re: problems and successes
- Communicate with staff
- Maintain interest and enthusiasm for the trial
- Maintain equipoise

NEXT STEPS

After discussing the results of the COIN Trial today, do you feel that the VON DR Management Trial and continued enrollment is more, less, or of unchanged importance?

- More important
- Less important
- Unchanged importance