The INNOVO Trial

Neonatal ventilation with **IN**haled **N**itric **O**xide versus **V**entilatory support with**O**ut inhaled nitric oxide for severe respiratory failure:

a multicentre randomized controlled trial

Funded by the Medical Research Council

Protocol

Health status at around four years of age of children recruited to The INNOVO Trial

Background

The INNOVO Trial is assessing the clinical effectiveness and cost effectiveness of the policies of adding or not adding inhaled nitric oxide to the ventilator gases of neonates with severe respiratory failure. One hundred and sixty eight babies have been recruited to the trial during the period March 1997 to December 2001, from the UK, Republic of Ireland and Finland. The primary outcome for the first part of the study is mortality and severe disability at one year (corrected). Researchers evaluating new interventions, especially in children, have a responsibility to ensure that these interventions are provided in the context of knowledge of their longer-term implications. The outcomes for most other trials of inhaled nitric oxide (INO) have been short-term, usually to hospital discharge. There is no information on the potential effects of neonatal INO therapy beyond 30 months of age, and none of the current trials provide or plan to provide this information. Hence INNOVO is the only study likely to be providing longer term follow-up information for randomised cohorts of both preterm (<34 completed weeks gestation at delivery) and 'mature' (≥ 34 weeks) babies entered into a nitric oxide trial. Assessment at around four years of age will allow a formal evaluation of cognitive and behavioural outcomes, not possible at younger ages, particularly among the preterm group, for whom follow-up to at least 2 years is recommended.

Methods

Surviving children recruited to the trial will be assessed around four years of age (corrected for prematurity for assessments carried out in children aged less than four years). Parents were informed in the trial introductory information (appendix 1) that members of the study team would keep in contact until their baby was about five years. The trial team has maintained annual contact with the families since discharge from hospital by sending birthday cards to the children. Prior to the planned assessment, the child's general practitioner and health visitor will be contacted by the study co-ordinator to ensure that continued involvement in the trial follow-up programme is considered appropriate. With agreement from the child's primary health care professionals, a letter will be sent to the family requesting permission to contact them by telephone to arrange an appointment to undertake a follow-up visit. A paediatrician trained in developmental assessment will visit the children at home to undertake a pre-defined and standardised neurodevelopmental assessment. The investigator will have no prior information about the child's gestational age, disease course or earlier assessment findings. Similarly, the families will be asked not to inform her of the child's primary diagnosis or randomisation arm until the assessment is completed.

Assessment protocol

A detailed and standardised assessment protocol has been pre-defined. The protocol has been developed to maximise the information collected and particularly addressing areas identified to be at high risk for long-term morbidity. This has been balanced by endeavours to ensure that the total time undertaking the assessments (estimated to be 90-120 minutes), remains reasonable so that the child's co-operation and parental goodwill is maintained.

Data will be collected about cognitive function, neuromotor and neurosensory function, growth and general health. In addition, information about the child's behaviour and socio-demographic variables together with a record of the use of health and educational resources will be collected by questionnaire completed by the parent or with assistance from the paediatrician if required.

The standardised assessment tools to be used are detailed:

Cognitive

- British Ability Scales (BAS II).[1]
  - Core scales verbal comprehension, picture similarities, naming vocabulary, pattern construction, early number concepts, copying.
  - Cluster scores verbal ability, pictorial reasoning, spatial ability.
  - General conceptual ability score (GCAS).
- Attendance and hours per week in pre-school education.
- Professional support for developmental difficulties.

Neuromotor

- Neurological examination and assessment of neuromotor function.[2]
- Record of the use of aids and the need for additional support for mobilisation or to perform tasks of daily living.

General Health

- Standardised questions to parents at interview detailing seizures, respiratory symptoms and treatment.
- Questionnaire to parents detailing visits to general practitioner, out-patient attendance and hospital readmissions. Details of hospital visits requested with parental consent.
- Examination of respiratory system and measurement of peak expiratory flow rate

Growth

- Measurement of growth) plotted against 'Child
  - Height: Leicester stadiometer.[3]) Growth Foundation'
  - Weight: Seca scales.) (CGF) standards.[4]
  - Head circumference: CGF tape.
  - mid arm circumference.[5]

Behaviour

- 'Strengths and difficulties questionnaire'[6] of childhood behaviour completed by parent.
  - Subscale scores: prosocial skills, hyperactivity, emotional difficulties, conduct and peer problems.
  - Overall 'deviance' behaviour score.
- Record of the impact of behaviour or concentration difficulties on the child's daily lifestyle including home life, friendships, learning or leisure activities.
- Record of referral to specialist services because of behaviour problems.

Vision

- Standardised questions to parents and examination describing visual or eye problems.

Hearing

- Standardised questions to parents describing hearing and communication problems.

Economic evaluation

- Contact with general practitioner and other primary community resources.
- Out patient attendance and hospital admission.
- Long term medication

Socio-demographic data

- Employment status and occupation of parents / carers.
- Structure of family unit
- Maternal years in full-time education (or equivalent) since age16.
- First language used at home.
- Number of smokers at home.

Data Handling

Follow-up data will be collected onto a standardised record sheet and entered onto the database by the Study Co-ordinator at the data Co-ordinating Centre in London.
At their request, a neurodevelopmental report will be sent to the parents, the child's general practitioner and to any paediatricians or other health care professionals actively involved in the child's care. Developmental difficulties that had not been identified previously will be notified to the general practitioner for further assessment and management locally.

Advisory group

The project will be managed by a Neurodevelopmental Advisory Group of the INNOVO Trial comprising the principal investigators; Dr Charlotte Bennett (John Radcliffe Hospital Oxford), Professor David Field, (Clinical Co-ordinating Centre, University of Leicester), Professor Neil Marlow (University of Nottingham), and Professor Diana Elbourne, Professor Charles Normand, and Mrs Ann Truesdale (Data Co-ordinating Centre, London School of Hygiene and Tropical Medicine). Dr Lis Cordingley, consumer member on the INNOVO Steering Committee has agreed to join the Group.

Project management group (PMG)

The PMG comprises the Advisory Group and project staff. Dr Charlotte Huddy has been appointed as Developmental Paediatrician and is based at the Clinical Co-ordinating Centre Leicester. Korotimi Diallo (Administrator), Keith Tomlin (Senior Database Manager) and Pollyanna Hardy (statistician) are based at the Data Co-ordinating Centre London. The group will be in contact regularly by telephone and occasional meetings.

References:

1. British Ability Scales: Second Edition (BAS II). NFER-Nielson Publishing Company, Windsor, Berks, UK
2. Amiel-Tison C. and Stewart A. Follow up studies during the first five years of life: a pervasive assessment of neurological function.
3. Voss L, Bailey B. Equipping the community to measure children's height: the reliability of portable instruments. Arch Dis Child 1994;**70**:469-471
4. Cole T. 'Do growth charts need a facelift?' BMJ 1994;**308**:641-2
5. Voorhoeve H.W.A., A New reference for Mid-upper arm Circumference? Journal of Tropical 6. Pediatrics 1990;**36**:256-262.
6. Goodman R. Using the Strengths and Difficulties Questionnaire (SDQ) to screen for child psychiatric disorders in a community sample. Br J of Psychiatry 2000; **177 (6)**:534-9