

# THE INNOVO TRIAL

Trial of ventilatory support with  
INhaled Nitric Oxide versus  
Ventilatory support withOUT  
inhaled nitric oxide

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Newsletter No 1

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Centres with  
Research Ethics  
Committee  
Approval



## **INTRODUCTION**

This is the first in an series of occasional newsletters to keep you up-to-date with developments in the INNOVO Trial and to address topical issues.

## **UPDATE**

In February 1997, the MRC awarded a grant for a pilot study to develop this trial, and to assess feasibility. Since then, most of the necessary procedures and documentation for the pilot trial and sub-studies has been prepared.

As the map shows, a large number of centres are involved. 21 centres have received local research ethics committee (REC) approval, of whom eight have already entered a baby into the trial.

There have been two major constraints on recruitment so far. The first was the serious explosion at the British Oxygen Company factory which led to restricted supplies in the Spring and Summer. Supplies are now fully available again. The second factor has been the need to go to a large number of different local RECs. From October, all applications for multi-centre research involving 5 or more centres in the UK will have to be submitted to the regional multicentre REC of the lead applicant. So we are submitting an application for the INNOVO trial to the North Thames Region. As soon as a positive outcome is obtained, we will send centres standard documentation to pass on to their local REC. This committee can then reject or approve the application, but not make changes (except to the information sheet). We are hopeful that the new system will speed the process and take some of the weight off local co-ordinators.

*Ann Truesdale, London*

## **TOXICOLOGY**

Nitric oxide (NO) is a naturally occurring molecule which has numerous physiological roles in many organs including vasodilation of the pulmonary vasculature.

Concerns about possible toxicity of NO arise because of its occurrence as an irritant pollutant gas in urban environments as well as in tobacco smoke. NO is a free radical which may react with

oxygen, and thus may result in the formation of reactive nitrogen species (NO<sub>x</sub>). These species may react with amino acid residues in proteins. Of particular importance is the reaction of NO<sub>x</sub> with tyrosine resulting in the formation of nitrotyrosine. Since tyrosine is important in many cell signalling cascades which result in normal cell growth and differentiation, nitrotyrosine residues may interfere with these pathways.

As part of the INNOVO trial we will determine if products of NO including nitrotyrosine are formed in the infants treated with NO and compare them with their formation in untreated babies. Bronchoalveolar lavage fluid will be collected from babies randomized to **both** arms of the trial. In parallel, our studies in the laboratories are determining the significance of the NO products to cell growth and differentiation.

The INNOVO trial provides a unique opportunity to establish the safety and to evaluate the potential toxic effects of inhaled NO in the clinical setting.

*David Shuker, Sailesh Kotecha, Leicester*

## **SLE 2000 ALARMS**

It has come to the attention of the Technical Advisory Group that there are some problems inherent in the use of the SLE 2000 ventilator with inhaled nitric oxide.

The problem occurs when the HIGH PRESSURE alarm activates. Due to the way that the ventilator functions in this alarm mode, the nitric oxide and nitrogen dioxide can build up to a toxic level in less than 30 seconds. To prevent this occurring the alarm must be reset, not just silenced, as soon after the alarm sounds as possible.

*Richard Crook, London*

## **RECRUITMENT OF TERM OR NEAR TERM INFANTS**

The results of the NINOS trial in term or near term infants showed that fewer babies in the NO group progressed to ECMO than in the non-NO group (NEJM 1997; 336: 597-604). This has led some neonatologists to question the wisdom of further NO trials in this population.

### **Why should further trials be conducted?**

- There is a potential for toxicity with NO (see centre pages)
- In the NINOS trial, no outcomes other than requirement for ECMO differed significantly between the two randomized groups.
- Avoiding ECMO may not be a good outcome. The UK Collaborative ECMO trial clearly showed that there were fewer deaths with a policy of ECMO. More recent analysis of the data at one year of age has shown poorer respiratory outcomes in the conventionally managed group. The significance of this for the INNOVO trial is that we risk producing more respiratory morbidity by striving to avoid ECMO.

Although the immediate short term improvements in oxygenation with NO are exciting, the longer term balance of risks and benefits remains uncertain. The INNOVO trial offers the opportunity to build on the NINOS study by considering questions relating not only to the need for ECMO but also to mortality, toxicity and morbidity. If this opportunity is lost, future patients may well regret it.

*Duncan Macrae,*

*London*

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