Collaborating to accelerate the development of safe and effective therapies for neonates

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Few drugs have been tested in infants. This leads to considerable uncertainty about the medicines given; some may not be beneficial and the best dose is not known for many.

In the past, it was considered unethical to perform research on infants, yet now many believe that it is unethical to use medicines that have not been tested properly. This has led to a rapid increase in the amount of research about medicines and, encouragingly, industry is doing much more to develop medicines for neonates.

Many challenges arise when research involves newborn infants. No single organisation can tackle all of these challenges. To meet this need, stakeholders from Europe, the US, Canada and Japan joined forces on 19 May 2015 in London, to launch the International Neonatal Consortium (INC). Regulators from the US Food and Drug Administration (FDA), Health Canada, the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) and the European Medicines Agency (EMA), together with an international group of practising neonatologists, academics, industry scientists, neonatal nurses, patient advocacy organisations, and the non-profit Critical Path Institute (C-Path), jointly prioritised the projects that the consortium will take on (**FIGURE 1**).

INC will concentrate on the conditions most commonly encountered in neonatal medical care. Therapeutic areas include neonatal brain, lung and gastrointestinal injury; neonatal sepsis; retinopathy of prematurity; and neonatal abstinence syndrome (**FIGURE 2**). Sharing data, expertise, and resources, INC members will reach consensus on standardised research methods, standards of care, blood tests or scans that predict outcomes (biomarkers), clinical endpoints (such as the definition of bronchopulmonary dysplasia), master protocols (for comparing several medicines used for the same condition) and more. While INC will not conduct clinical trials, it will facilitate all neonatal trials (both publically funded and industry-sponsored) by providing the standards that underpin all rigorous studies.

By reaching across borders, INC will draw on the vast collective experience in studying medicines in neonates. Neonatal nurses will contribute to this work because nurses have a unique perspective on the needs of babies during trials and how trials fit into neonatal care. INC aims to optimise the way that clinical trials are conducted and maximise the data generated from routine care. An audacious goal would be to enrol each patient entering a neonatal intensive care unit (NICU) in a protocol designed to establish an optimal standard of care, or to study a promising therapy. Only then will the neonatal community be able to overcome the limitations of the 'experiments' conducted daily in NICUs around the world, as neonatology teams make educated guesses about what treatment to use for which neonate and how to best evaluate the outcome.

INC operates through C-Path (www.c-path.org), a pioneering non-profit organisation dedicated to accelerating the pace and reducing the costs of medical product development. C-Path has established nine global, public-private partnerships that currently include over 1,000 scientists from government and regulatory agencies, academia, patient advocacy organisations, and major pharmaceutical companies. C-Path is headquartered in Tucson, Arizona and has an office in London. *Infant* readers will no doubt be familiar with one of INC's co-directors: Mark Turner, Consultant Neonatologist and Senior Lecturer in Neonatology at the University of Liverpool.

The presentations from the recent INC launch held in London can be found on the EMA website: www.ema.europa.eu

FIGURE 1 Structure of the International Neonatal Consortium. Key: INC = International Neonatal Consortium, FDA = US Food and Drug Administration, EMA = European Medicines Agency, NIH = US National Institutes of Health.

INC AND THE NICU

The International Neonatal Consortium will concentrate its efforts on those conditions most commonly encountered in NICUs, and on the prevention of pre-term birth.

INC
CRITICAL PATH INSTITUTE

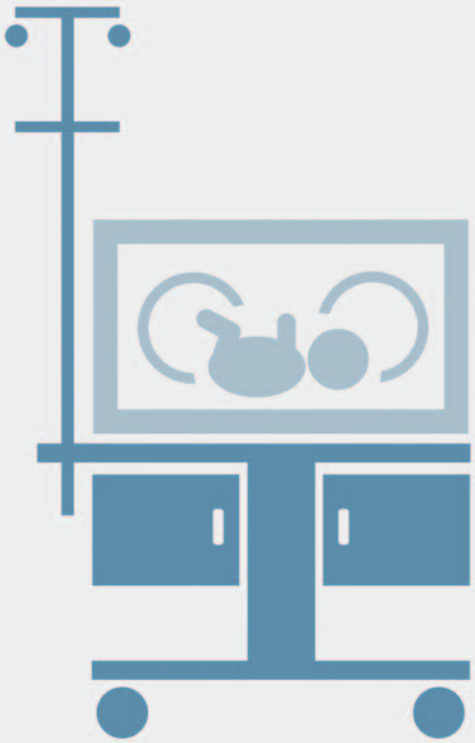
International Neonatal Consortium

NEONATAL ABSTINENCE SYNDROME (NAS)

There has been a dramatic increase in the incidence of NAS resulting from *in utero* exposure to opiates, with rates tripling in the last 10 years. There is significant uncertainty on whom to treat, when to treat, and how to treat affected infants. In-depth studies with better assessment techniques and short- and long-term outcome measures are urgently needed.

NEONATAL LUNG INJURY AND CIRCULATORY FAILURE

Bronchopulmonary Dysplasia (BPD) is the most common sequela of neonatal intensive care, most often occurring in preterm infants. Infants with BPD can develop repeated pulmonary infections, pulmonary hypertension and asthma. Novel approaches to the prevention and treatment of BPD and the resulting chronic respiratory morbidity are urgently needed. Term infants can develop Persistent Pulmonary Hypertension of the Newborn (PPHN) when the normal transition of the fetal circulation does not occur at birth and during severe respiratory failure. These infants continue to be extremely ill despite the use of high-frequency ventilation, exogenous surfactant, and inhaled nitric oxide (iNO) and would clearly benefit from new treatment modalities. Defining optimal treatment options will require better definitions and validation of endpoints for assessment of pharmacologic interventions.



PERINATAL/NEONATAL INFECTIONS

A significant number of preterm and term infants will develop serious bacterial and viral infections resulting in death or NDI. Over 25% of preterm infants will develop early-onset or nosocomial sepsis, with an increasing number of infections resistant to traditional antibiotic and antiviral agents.

RETINOPATHY OF PREMATURITY (ROP)

Many preterm infants develop ROP, with more severe forms requiring treatment with laser ablation or anti-angiogenic agents (off label use). The risk of visual impairment or blindness in this high-risk population remains unacceptably high. New approaches to the prevention and treatment are urgently needed.

NEONATAL GASTROINTESTINAL INJURY

Between 5 and 10% of all extremely preterm infants will develop Necrotizing Enterocolitis (NEC), a devastating illness associated with death, short gut syndrome, and neurodevelopmental impairment. Despite significant research on breast milk, probiotics, and other novel agents (e.g., lactoferrin, prebiotics) the incidence of NEC has not substantially changed in the last 20 years and represents a leading cause of late mortality for preterm infants.

DRUGS TO PREVENT PRETERM LABOR

More than one in ten babies worldwide are born prematurely. Considerable research into possible genetic and/or environmental factors has failed to establish a definitive pathogenesis and few treatments have made a significant impact (the incidence remains at >10%). Prevention strategies involving cerclage and progesterone have not been as successful as previously hoped. New therapeutic approaches to significantly reduce preterm birth would be expected to result in dramatic improvements in infant mortality and outcome.

NEONATAL BRAIN INJURY

Term infants continue to develop encephalopathy, stroke and seizures around the time of birth. Despite the use of newer anti-seizure drugs and brain cooling, morbidity and mortality remains unacceptably high. In preterm infants, the prevention and treatment of severe intraventricular haemorrhage (IVH) and white matter injury (WMI) is crucial. These conditions are leading factors in the development of significant neurodevelopmental impairment (NDI).

FIGURE 2 The International Neonatal Consortium will concentrate on the conditions most commonly encountered in neonatal medical care.