EFCNI POSITION ON THE EU FRAMEWORK PROGRAMME FOR RESEARCH AND TECHNOLOGICAL DEVELOPMENT FP8

As an umbrella organisation and representative of patient associations in the EU member states, EFCNI wishes to contribute to the ongoing discussion on the EU Research Framework Programme FP8.

The following position was developed after thorough consultation with leading EU experts in the neonatal and perinatal field. These experts come together in the Political and Scientific Advisory Boards of EFCNI and have reached a broad consensus on the ways in which the EU and its Member States can and should be addressing the challenge of preterm birth within the its 8th Research Framework Programme..

EFCNI POSITION

ON THE EU FRAMEWORK PROGRAMME
FOR RESEARCH AND TECHNOLOGICAL DEVELOPMENT FP8

IMPROVING THE FUTURE OF PRETERM INFANTS

1. **Determinants of preterm delivery, its prevention and maternal health**

   Prevention of preterm delivery remains the best option in cases of spontaneous preterm delivery. However, the underlying mechanisms remain largely unknown. Preventing ascending infection, e.g. by enhancing the physiologic vaginal bacterial milieu, might be one possible route for prevention. Also, early biomarkers and identification of genetic and environmental risk factors are needed and research on the pathomechanisms could allow defining new targets for preventing preterm delivery.

2. **Address the lack of comparable European data**

   Reliable data on the prevalence and cost of preterm birth is difficult to compare because of different reporting mechanisms and methodologies, lack of data collection both across Europe and even within the individual countries. This reveals the urgency and need to establish a single, centralised European registry for epidemiological and quality outcomes data.

3. **Network of networks**

   In Europe, multiple national networks have been created to study the long term development of preterm infants. Research should be funded that aims to bring together a “network of networks”, designed to maximize follow-up and research experience at the EU level and streamline follow-up guidelines across the EU landscape.

4. **Towards an individualised medicine in preterm and full term new born infants**

   Current experimental and clinical studies do not take into account the individual phenotype of the developing organism. One example is that enzymes responsible for drug metabolisms are developmental regulated and are also dependent on genetic factors. In addition prenatal, peri – and postnatal factors like inflammation might already have impacted fetal metabolism altering the response to treatments and interventions. Future preventive, diagnostic and therapeutic approaches should be based on the individual phenotype to increase e.g. efficacy and safety of drug treatment or postnatal interventions (oxygen supply, nutrition).

5. **Research on gastrointestinal immaturity**

   In extremely low birth weight infants, immaturity of the gastrointestinal tract and associated complications including necrotizing enterocolitis and spontaneous perforation contributes significantly to neonatal mortality and morbidity. Experimental and clinical studies should be fostered to prevent and help provide early diagnosis of gastrointestinal complications.

6. **Lung development, asthma and prevention of chronic pulmonary disease**
All preterm children, not only those with neonatal pulmonary disease, appear to be at increased risk for chronic airway disease/asthma. Experimental and clinical studies should be developed that attempt to elucidate the determinants of long term pulmonary disease among children born preterm.

7. **Disease process, diagnosis and prevention of cerebral palsy and developmental brain injury**
Recent research indicates that after preterm birth, some brain damage mechanisms (e.g. inflammation) appear to exert systemic effects for some time after initial insults. Projects should be developed to study the hypothesis that some of such disease processes among individuals born preterm continue after the new born period. In addition research evaluating diagnostic and therapeutic approaches is required.

8. **Determinants of mental health among preterm infants and development of neuroprotective strategies**
Emotional problems and attention deficit problems are very frequent amongst preterm born children. Yet, both issues are highly relevant for academic achievement and later integration into work. Autism is more common among children born preterm. Previous studies have found associations between antenatal infection and mental disorders such as autism and schizophrenia. Experimental and clinical studies should be designed to explore the spectrum of determinants of mental health among individuals born preterm, including, but also above and beyond antenatal infection. Experimental mechanistic and clinical/epidemiologic research focusing on biomarkers should be given special attention. The study of brain function and neuronal networks is additionally important to understand how prematurity or early insult affects the brain and its function.

9. **Disease mechanisms of retinopathy and post-chiasmal vision deficits**
Both retinopathy of prematurity (ROP) and post-chiasmal central nervous system abnormalities play an important role in long term visual health of preterm children. Research is needed to tease apart the respective roles for ROP and central processing abnormalities in visual abnormalities among preterm individuals.

10. **Impact of environmental factors on pre- and postnatal child development e.g.**
    i) *Nutrition:* Postnatal nutrition plays a key role in the survival and neurodevelopmental outcome of very preterm infants. Early enteral nutrition is, hereby, especially important. One of the important areas of research is, for example, the optimal protein intake of very preterm infants: As there are indications that brain growth and later life cognitive function are directly related to protein intake during the neonatal period in preterm infants, further clinical studies aiming to clarify the remaining open questions are needed. Another promising insight that merits further study is the positive effect of probiotics on the prevention of Necrotizing Enterocolitis, NEC. The optimal timing, doses, and duration of treatment with probiotics as well as the best probiotics for use in preterm infants remain to be defined. Dietary optimisation constitutes an effective

and low-cost opportunity of improving the mental development of small preterm infants. Research therefore "pays" for both the small patient and society at large.

ii) *Allergies:* Over the past several decades, the incidence of atopic diseases such as asthma, atopic dermatitis, and food allergies has increased dramatically. It is recognised that early childhood events, including diet, are likely to be important in the development of both childhood and adult diseases. Although atopic diseases have a clear genetic basis, environmental factors, including early infant nutrition, may have an important influence on their development and, thus, present an opportunity to prevent or delay the onset of the disease. At present, inadequate study design and/or a paucity of data limit the ability to draw firm conclusions about certain aspects of atopy prevention through dietary interventions. More studies (e.g. pregnancy and lactation avoidance diets, timing of introduction of specific complementary foods) would be needed to clarify whether there is a positive or negative effect on atopy outcomes.

iii) *Vaccination:* Preterm infants are at greater risk of increased morbidity from vaccine-preventable diseases. Advances in the care of preterm infants have increased survival rates substantially, thereby adding challenges in the selection and optimisation of appropriate immunisation regimens for infants with immature or impaired cellular and humoral immune systems. More information on the immunogenicity, durability, and safety of routinely recommended childhood vaccines given to preterm infants is recommended.

iv) *Drugs:* Most drugs used in the preterm or even full term new born infants are not properly investigated with respect to their efficacy and safety. Since the physiology of the developmental organism in the preterm and term born infant is not comparable to the physiology in adults, there is an urgent need to evaluate drug efficacy and safety in this most vulnerable group of patients.

v) *Environmental factors interfering with normal organ (lung/ and brain development):* It has been discussed that environmental factors like oxygen supply, mode of care and e.g. pain interfere with normal organ development. Future research is necessary to understand the impact of environmental conditions on development particular of the lung and brain in order to optimise therapy and prevention.

11. **Quality of life research (adults born preterm)**

Most quality of life research focuses on children with certain diseases (e.g.) cerebral palsy. These projects should be designed to elucidate the quality of adult life of individuals born preterm. Studies should not only compare individuals born preterm with individuals born full term. Previous research of preterm children has focused on parent reports of their children's quality of life. Recent reports in small samples indicate that preterm children themselves consider their quality of life higher than reported by their parents. Follow-up into adulthood is necessary to determine the quality of life as reported by the prematurely born young adults themselves compared to reports by parents or significant others.

12. **Research on family – centred care and psychological parental support**

The preterm infant or newborn infant with illnesses is in the centre of the individual family. Current data imply that parental education and competence has a significant impact on the outcome of the patients. Increasing parental competence by family centred care and psychological support starting prenatal (women at risk) is hypothesized to increase parental bonding, reduce the time of primary hospitalisation, reduce the rate of child abuse and divorce and increase the rate of acceptance of secondary prevention programmes (e.g. vaccination). Clinical studies should be developed to test this hypothesis.

ABOUT EFCNI

The European Foundation for the Care of Newborn Infants (EFCNI) is the first pan-European organisation to represent the interests of preterm infants, ill newborns and their families. It gathers together parents and medical professionals from different disciplines with the common goal of improving long-term health of newborn and preterm children by ensuring the best possible prevention, treatment, care and support.
For more information please see *http://www.efcni.org/*

PRETERM BIRTH

Preterm birth - occurs when a baby is born before 37 weeks of gestation - is the single major (and often preventable) cause associated with infant mortality and morbidity in both developed and developing countries.

Severity of preterm birth	Gestational weeks
Extremely preterm	Less than 28 weeks
Very preterm	28-31 weeks
Moderately preterm	32-33 weeks
Late preterm	34-36 weeks

In 2009, EFCNI developed a benchmarking report of policies with an impact on neonatal healthcare and support to families affected by preterm birth across 13 EU member states.
To read the full report, please see *http://www.efcni.org/index.php?id=1321* .

According to data from different national statistics and the 2008 European Perinatal Health Report, the prevalence rate of preterm birth in Europe ranges from 5.9% (Sweden) to 11.4% (Austria), meaning **about half a million babies are born prematurely in Europe** every year.

RISK FACTORS FOR PRETERM BIRTH

In about half of all cases of preterm birth, the exact cause of the early delivery remains unknown. However, a number of risk factors have been identified which are likely to increase the chances of preterm labour.

Lifestyle factors	Medical conditions	Demographic factors
Smoking	Infections (urinary tract, vaginal)	Aged under 17, or over 35
Alcohol consumption	High blood pressure	Low socioeconomic status
Drug use	Diabetes	Ethnicity
High stress level & long work hours	Clotting disorders	
Late/no prenatal care	Underweight	
Lack of social support	Obesity	
	Multiple pregnancy	
	Women having experienced preterm birth before	
	Uterine or cervical abnormalities	

MAIN HEALTH COMPLICATIONS LINKED TO PRETERM BIRTH

Preterm infants are at greater risk of developing short and long term health complications. Many infant deaths, chronic disabilities and health conditions could be prevented through improved neonatal prevention, treatment and care.

- Cerebral palsy
- Sensorial and motor disabilities
- Increased risk for infections
- Increased risk for chronic diseases
- Respiratory illnesses
- Learning and behavioural disorders

PREVENTION OF PRETERM BIRTH

Prevention of preterm delivery remains the best option in cases of spontaneous preterm delivery. Preventing ascending infection might be one possible route for prevention. Early biomarkers are needed and research on the pathomechanisms could allow defining new targets for preventing preterm delivery. Generating public awareness about medical and social factors of preterm birth would place prospective parents in the position to act according to what is best for their child.

To date, no single test or sequence of assessment measures that may accurately predict preterm birth are available, and efforts at the prevention of preterm birth have primarily focused on the treatment of women with symptomatic preterm labour. Therapies and interventions for the prediction and the prevention of preterm birth are still greatly needed.

IMPACT OF PRETERM BIRTH ON SOCIETY

These negative health and developmental effects of preterm birth often extend to later life. The costs of preterm birth are, therefore, considerable. Not only is there a personal impact on the child and its family (psychologically, financially and socially), there are also wider cost implications for public health, the healthcare and social welfare system (including direct and indirect costs), the economy and for society.

Preterm birth and low birth weight have a high impact on the employment behaviour of the parents. Many mothers of preterm infants who intended to return to work after the birth either postpone doing so, reduce their hours or leave the workforce altogether to care for their child. This is usually associated with a reduction in family income by up to 32%.

Parents of infants with neurosensory and cognitive disability often require support from social service departments during the immediate period following the infant's discharge from the neonatal unit. In later life, developmental services–which include day care programmes, case management and counselling, respite care and residential care–may also be required to supplement health and educational services.

At school age, preterm children still have poorer cognitive function and academic performance than normal-birth-weight children. Learning problems at school persist into adolescence and are apparent even in children who have normal intelligence and no neurologic impairment: In a longitudinal study, intelligence, levels of educational achievement and rates of chronic health conditions as well as psychosocial factors of preterm infants were compared with those of normal birth (weight) infants. The children were examined at 8 years and again at 20 years of age. The study showed that at school age, preterm children have poorer cognitive function and academic performance than normal-birth-weight controls. The differences in grade repetition, educational attainment, and current enrolment in educational programs remained significant. Learning problems at school persist into adolescence and are apparent even in children who have normal intelligence and no neurologic impairment. Fewer low-birth-weight participants than normal-birth-weight participants had graduated from high school or obtained a general equivalency diploma by 20 years of age.
Besides, the former preterm infants had significantly higher rates of chronic conditions than the controls.

In view of the increasing number of preterm infants in Europe and taking into consideration the ambitious aims of the Europe 2020 strategy, which has as one heading topic the reduction of the share of early school leavers to less than 10% and the increase of the share of the

In adulthood, preterm children are at greater risk of having less working power. Any medical disability is severely affecting the working capacity: Up to 10% of preterm infants suffer from medical disability that will affect their working capacity by more than 50%.

Counted in hard numbers, preterm children represent a total number of about 20,000 children per year unable to contribute 100% to the workforce, not included infants with cognitive deficits etc.

Some of the intangible costs associated with caring for preterm infants include the emotional and physical energy required to care for the infant and the consequent isolation and restricted social contact that ensues.

In view of the increasing number of preterm infants in Europe and taking into consideration the ambitious aims of the Europe 2020 strategy – three of the five heading topics are the “reduction of the share of early school leavers to less than 10% and the increase of the share of the population aged 30-34 having completed tertiary education to at least 40%”, “raising the employment rate of the population aged 20-64 to at least 75%” and “reducing the poverty and social exclusion by lifting 20 million people out of poverty”- the above findings are an alarming sign showing the immediate need for action.

The impacts and costs as well as the significant number of neonatal deaths attributable to preterm birth — an estimated 28 percent of the 4 million annual neonatal deaths are due to preterm birth —indicate an urgent need for greater international attention. Decision-makers should be aware of the substantial long-term economic impact of preterm birth and should be sensitive to the financial constraints faced by parents on low incomes at a critical time in the parent–child relationship.

By combining national efforts in neonatal and perinatal research activities and thus gaining sustainable knowledge about preterm birth in general, prevention, treatment, care as well as possible impacts, Europe can definitely strengthen the position and quality of life of its future citizens.

A FOCUS ON RESEARCH FOR PREVENTING PRETERM BIRTH AND FOR IMPROVING THE FUTURE OF PRETERM INFANTS

Preterm infants and their families constitute a sizeable – and growing – population group in Europe which is overlooked by national governments in the provision of high quality healthcare and social support. Where data is available, it provides evidence of an increasing number of preterm infants across Europe in the last decade.

The cost of prematurity in Europe is a considerable, yet underestimated burden on families as well as social welfare systems. There is a paucity of comprehensive data in European countries measuring the real health-economic impact of preterm birth and each country has its own unique set of challenges that must be addressed in order to improve birth outcomes. Where available, data tends to be limited to direct costs to the neonatal unit in the immediate period after birth, with no assessment of the longer-term costs to the family, health and social welfare system. The feasibility of such cost assessment is to some extent dependent on the availability of comprehensive data on the morbidity linked to prematurity, such as subsequent disabilities, disorders and chronic diseases, which are absent.

Despite the growing prevalence and increasing costs, neonatal and preterm infant health rank low on the policy agendas of EU member states. Only two countries (Portugal and UK) have developed targeted policies aimed at improving neonatal health.

The increasing importance of prematurity should be anticipated, understood and acted upon urgently in order to tackle the growing burden of prematurity on Europe's health and social systems. If Europe as a continent wants to remain competitive, it urgently needs to determine action. The EU needs to significantly increase its investment in research if it wants to meet the ambitious targets of the new Europe 2020 strategy.

The Framework Programme (FP) is one of the best tools through which the EU can stimulate and support research. FP 8 should be set up to reinforce international, intersectorial and interdisciplinary collaboration to reduce the burden of preterm birth. We believe increased research for a better health of our children provides the necessary impetus for policy change in order to achieve high standards of infant health and to reduce health and social inequalities across the European Union. It is only by making neonatal health a common policy priority that we can begin to provide a better future for our children and for the future generation.

WITH REFERENCE TO

EFCNI Image brochure 2010 - http://www.efcni.org/
EFCNI Benchmarking Report, issued May 2010 - http:// www.efcni.org/
Hack et al. (NEJM 346 (2002) 149-57) - "Outcomes in young adulthood for very low-birth-weight infants"
Moster et al (NEJM 359 (2008) 262-73 – "Long-term medical and social consequences of preterm birth"
Petrou et al (Child: Care, Health and Development volume 27, Nr. 297 - 115) -The long-term costs of preterm birth and low birth weight: results of a systematic review
Greer et al (Pediatrics 121 (1): 183 – 191) - "Effects of Early Nutritional Interventions on the Development of Atopic Disease in Infants and Children"
Saari and and Committee (PEDIATRICS Vol. 112 No. 1 July 2003)- "Immunization of Preterm and Low Birth Weight Infants"
Speech of Commissioner Dalli in Malta, 3 June 2010 - http://ec.europa.eu/commission_2010-2014/dalli/personally_speaking/index_en.htm
COMMISSION OF THE EUROPEAN COMMUNITIES WHITE PAPER "Together for Health: A Strategic Approach for the EU 2008"- 2013http://ec.europa.eu/health/ph_overview/Documents/strategy_wp_en.pdf
March of Dimes, USA, 2009 "White Paper on Preterm Birth" – http://www.marchofdimes.com