



**NEO-ACQUA:
NEONATAL ADEQUATE CARE for QUALITY of LIFE**

STUDY PROTOCOL

Version 1.0 of July 26 2005

SYNOPSIS

Study title: NEO-ACQUA – NEONATAL ADEQUATE CARE for QUALITY of LIFE

Supporting Body:

The Italian Neonatology Society (Società Italiana di Neonatologia: SIN), with the cooperation of the SIN STUDY GROUPS Neurology and follow-up; Neonatal Care; Treatment quality in Neonatology; Neonatal Pneumology.

Sponsors:

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- "E. MEDEA" SCIENTIFIC INSTITUTE FOR RESEARCH, HOSPITALIZATION AND HEALTH CARE (SIRHHC) – "LA NOSTRA FAMIGLIA" ASSOCIATION, BOSISIO PARINI (LC);
- THE MACCHI FOUNDATION AND HOSPITAL, VARESE;
- COMMERCIAL UNIVERSITY "L. BOCCONI"-CERGAS, MILANO.

Number of Centers Involved: approximately 30 Neonatal Intensive Care Centers (NICU)

Design: multi-center, longitudinal, observational study

Objective:

To evaluate any existing differences between the quality of life in healthy pre-term infants vs. full-term infants at different stages of development (at 18 and 30 months and at 3, 5, and 7 years).

Population: Consists of Cases: infants born pre-term according to the criteria of the Vermont DataBase and defined as healthy, who comply with the criteria of inclusion in the Protocol, and of Controls: infants born full term and healthy.

Sample size: 200 born pre-term + 200 full term

Length of the study: approximately 7 years and 6 months (6 months enrolment + 7 years of observation)

Number of visits for the cases and the controls: 7 (birth/discharge + 6 follow-up visits)

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1.0 GENERAL AND BASIC INFORMATION

1.1 INTRODUCTION AND STUDY RATIONALE

Even today, pre-term birth constitutes one of the greatest challenges faced by the public health service. In our country, the proportion of pre-term births has increased from 9% to 11% of total births over the last 30 years, which means that approximately 50,000 premature infants are born each year in Italy (Arpino & Curatolo, 2003) and that around 0.8 - 0.9% of total newborns are of very low birth weight (VLBW) (Corchia 2000; Corchia, 2003). Even though the probabilities of survival of pre-term infants with low gestational age (< 32 weeks) or with very low birth weight (< 1500 g.) has increased, due to medical progress, no reduction in the rate of the various developmental disturbances in these infants has been reported (Tin et al., 1997).

Therefore on the one hand, there has been a considerable reduction in the risk of mortality and permanent deficits, thanks to the recent technological and pharmaceutical discoveries in the area of perinatal and neonatal care, on the other hand, numerous studies have documented that these subjects, compared to babies born full term, are more at risk for the onset of languages disorders, learning difficulties, deficits in visual-motor integration and behavioral problems (Ornstein et al., 1991) and problems concerning the quality of life (Theunissen et al., 2001). Often these deficits only emerge at pre-school and school age, thus demonstrating how pre-term birth can even affect children who do not present clear clinical manifestations which can be diagnosed early.

In the light of these observations, it seems appropriate that over the next few years, research will direct more attention to the medium and long-term effects of pre-term birth, not only on a physical and/or cognitive functioning level, but also on an emotional and psychosocial adaptation level. It seems particularly reasonable to state that one of the most significant areas in the field of neonatology, infant neuropsychiatry and developmental psychology will be the optimization of socio-environmental adaptation and the quality of life correlated to the health status of the pre-term infant.

This research proposal involves an approach to treatment and care which considers that the pre-term newborn is already engaged in active interaction with the environment from birth. This implies taking into consideration the overall functioning of the infant (on the motor, autonomic, and attention levels and of regulation of behavioral states) in the exchange with the surrounding environment (physical and social). Moreover, if the infant is considered to be participating in the continual process of co-regulation with the physical and emotional environment, it is therefore necessary to take into account not only his/her functioning, but also the role that the methods, the type of care and the amount of stimulation present in the environment can have in the short, medium and long term development processes.

The Neonatal Intensive Care Unit (NICU) and Pathology Units, which are called upon to provide the abovementioned care, carry out, in our country, a role that is fundamental in pursuing the health objective of the newborn as expressed in the National Health Plan 2003-2005 (Ministry of Health, Health Plan 2003-2005 approved by the Italian Cabinet on April 11, 2003).

The Plan highlights the regional differences that exist in the health conditions in the neonatal and pediatric age group and suggests lines of development in order to promote the qualitative and quantitative equality of the services provided. Amongst the strategic objectives for change, it places the implementation of specific programs for the protection of motherhood and an improvement in care during the neonatal period, at the top of the list. The pursuit of this objective will necessarily pass through future efforts for improving knowledge of the economic and organizational dynamics which firmly direct the behavior of the Pathology and Neonatal Intensive Care Units in the Country, in the same way that verification of the impact that the standards of care and treatment provided by them can have on the medium/long term costs and the assessment that their contribution helps achieve qualitative levels of life that are the same as those of a population which does not need this care. This information would provide support in the formulation of more appropriate policies for financing the abovementioned Units, consistent with the institutional architecture and the overall financing systems of the respective Regions (Cavallo et al. 2004).

This project intends to investigate the connection between the quality of the care commenced during the very first stages of treatment of the infant and the quality of life during the preschool period, duly bearing in mind the role exercised by the emotional relationship with the primary figures. Moreover, the study aims to describe, through suitable indicators, the evolution of the

quality of life and of the direct health costs (e.g. admissions to hospital, drugs, specialist visits, rehabilitative therapy, etc.) and other, non-healthcare costs (paid treatment, loss of productivity by family members, expenses incurred by the family, etc.) (Drummond et al. 1997) associated with pre-term birth, with the aim of identifying the evolution of the correlation between the parameters relating to the quality of life and the consumption of social-healthcare resources in the cohort observed. The medium and long term outcomes relating to cognitive competencies and behavioral attitude will be evaluated as well.

1.1.2 Work hypothesis

It has been documented that risk factors connected to pre-term birth can affect the growth of premature infants, thus delaying or hindering their development (Als et al., 2003; Sansavini et al., 2004). The effects of these early risk factors can show in the short term as well as the long term, with scarce ability to adapt according to the requirements of the environment. This can lead to the development of disorders (behavioral problems, attention deficit, learning difficulties, etc.) which make the quality of life of these children worse.

The elements of risk taken into consideration in this longitudinal study refer to three groups of factors:

- a. **BIOLOGICAL FACTORS:** involve the condition of the infant at birth, such as weight and gestational age;
- b. **ENVIRONMENTAL FACTORS:** include the physical environment (light and sound stimuli) and social environment (touch and contact stimuli) which the infant receives in the first days of his/her life within the NICU, as well as the medical treatment and the care procedures undertaken by the department staff;
- c. **SOCIAL/RELATIONSHIP FACTORS:** refer to the infant's emotional-behavioral and relationship function.

Furthermore, these variables do not affect the infant's subsequent development in an independent way; they interact, thereby creating complex risk conditions. In other words, it is believed that some experiences, both sensorial and social, which are experienced early by the premature infant during his/her stay in the NICU, are linked to his/her subsequent quality of life, as well as to cognitive and behavioral development. However, since the primary emotional environment has an absolutely significant role in the infant's emotional adjustment, being able to favor or limit social/relationship abilities, it appears reasonable to suggest that this link is mediated by the maternal perceptions of the infant and secondarily, by associated variables (such as some social-personal details and the mother's psycho-emotional balance).

In the light of these hypotheses, a longitudinal-type evaluation would enable us to identify the main risk factors associated not only with the characteristics of the infant, but also with the type of environmental stimulation, the quality of the care provided to the newborn in the neonatal intensive care unit and the quality of the relationship established early with the mother.

1.1.3 Operational Impact

On an operational level, the identification of risk factors, and also of protective factors, could encourage the planning of early intervention programs aimed at increasing the pre-term infant's adjustment abilities, and also of the level of stimulation and the type of care received during the first days of life. Since it has been shown that the effect of low birth weight and of gestational age can be modulated by socio-environmental factors (Dezoete e MacArthur, 2000; Gross et al., 2001), a longitudinal study which helps to clarify the role of factors such as the early experiences of life on the development of the premature infant, would enable us to program interventions aimed at preventing the negative consequences of a non-optimal early environment. It has already been documented that it is possible to promote the reduction of stress behaviors and the increase of self-adjustment behaviors by the infant (Als, 1986). In line with this perspective, the relative knowledge of the way in which individual, environmental and relationship factors interact, could lead to interventions in the method of treatment and in the environmental stimuli in the Neonatal Intensive Care Unit.

With regard to the relationship aspects as well, an intervention which involves the parents aimed at promoting contact and early interaction between the mother and newborn could enable the mother-child dyad to develop a relationship based on reciprocal involvement and responsiveness (Field et al., 1980). Adequate self-regulation ability by the infant and a good relationship with the mother represent important protective factors in respect of the subsequent development of the premature infant.

From the point of view of intellectual development, evaluating the cognitive performances of a premature infant could be an opportunity to plan early interventions which would prevent delays in development and promote learning even before the infant starts school (Achenbach et al., 1993).

Concrete implications deriving from the analysis of the socio-economic impact attributable to the pre-term birth are constituted by the availability – through this study – (i) of a support tool for the decision-making process (local, regional and ministerial) for the allocation of the resources provided in the neonatal context; (ii) of a tool which can identify exactly what part the cost of the different items plays in the overall impact of pre-term birth and the existing connection between the costs incurred and the effect that these investments can have on the levels of quality of life.

2.0 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

Longitudinal phase

1. Evaluate any existing differences between the quality of life in healthy infants born pre-term Vs healthy infants born full term at different times of their development (at 18 and 30 months; at 3, 5 and 7 years).

2.2 SECONDARY OBJECTIVES

Cross-sectional phase

2. Describe the main structural and care characteristics of the NICUs.

Longitudinal phase

3. Evaluate the impact of the *quality of the care* on the quality of life of healthy infants born pre-term
4. Evaluate the existing correlation between the different categories of cost, the quality of life and the quality of treatment.
5. Compare the principal outcomes as regards cognitive competence, behavioral function and emotional development of infants born pre-term with those born full term.

3.0 PLANNING THE STUDY

3.1 STUDY DESIGN

This is a multi-center, longitudinal observational study. Approximately 30 Italian Neonatal Intensive Care centers will be participating in the study. Two cohorts (“cases” and “controls”) will be selected during enrolment. The first corresponds to “healthy” pre-term newborns (**VLBW**) and the second to “healthy” full term newborns (**TERM**).

The two groups selected according to the methods described in section 3.2 will be followed in parallel for the whole duration of the follow-up, currently set at seven years. In the event of excessive mortality of the control sample, new controls will be recruited at the time of the corresponding check-up and paired up according to age and to the other

inclusion criteria.

In compliance with the scientific content of the observational protocol, it is not envisaged that any interventions which might lead to variations in routine medical practice will be used.

3.2 ENROLMENT METHOD

During the agreed enrolment period (6 months), all the infants born pre-term (“cases”) at the Specialist Centre who comply with the criteria set forth at section 4.1 at the 36th postconceptional week will be enrolled consecutively.

Subsequently for each VLBW infant, the corresponding TERM newborn, who complies with the criteria set forth at section 4.1 (“controls”), must be enrolled at the 40th week of the pre-term birth point (+/-2 weeks). The two cohorts will be followed up for a period of 7 years.

In order to limit sample problems, the enrolment of the infants will start from the study start up date for each NICU and continue until the set number has been reached (no longer than the 6 months already set).

In the event that the enrolled population has to be assigned to a treatment, this will be based only on the judgment of the physician. The protocol must not be a hindrance to the specialist in the choice of the therapeutic diagnostic route to follow.

Given the observational nature of the study, no randomization procedure will be carried out during enrolment.

3.3 SCHEDULE OF VISITS

Type of Visit	Birth/ Discharge	6 months	18 months	30 months	3 years	5 years	7 years
No. Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Time	0 Months	6 Months	18 Months	30 Months	3 years	5 years	7 years

3.4 EVALUATION PROCEDURES

This contains the description of the entries to be made at each visit and also of the questionnaires to administer at each phase of the project (see tables 1a and 1b below).

The time sequence of the visits should not differ from normal clinical practice in the management of a patient with the characteristics listed in section 4.0.

The brief summary of the phases and evaluation times is given in Appendix 1.

Table 1a. Brief summary of the areas of evaluation, the evaluation tools used and the phases of evaluation of the pre-term infants

Subject of the evaluation	Areas of investigation	BIRTH - DISCHARGE	6 MONTHS	18 MONTHS	30 MONTHS	3 YEARS	5 YEARS	7 YEARS
CHILD	<i>Temperament</i>		QUIT 1-12		QUIT 13-36		QUIT 3-6	
	<i>Cognitive area</i>		Griffiths/Bayley	Griffiths/Bayley MacArthur Questionnaire	Griffiths/Bayley	Language test	WPPSI Prerequisites of learning	Learning level
	<i>Adjustment and behavior</i>	NNNS		CBCL/1½-5		CBCL/1½-5		CBCL/4-18
	<i>Quality of life</i>			TAPQOL	TAPQOL	TAPQOL	TAPQOL	TACQOL
MOTHER	<i>Mother's emotional state</i>	Edinburgh Scale; Parental Stress Scale: NICU	BDI STAI PSI	BDI STAI PSI	BDI STAI PSI	BDI STAI PSI	BDI STAI PSI	BDI STAI PSI
	<i>Child perception</i>		Child perception questionnaire	Child perception questionnaire		Child perception questionnaire		Child perception questionnaire
	<i>Perception of the quality of treatment</i>	Nurse Parent Support Tool						
ENVIRONMENT/ TREATMENT		Neonatology sheet (Medical history); Questionnaire about the Care; Environment evaluation sheet	Social/personal details sheet (supplemented)	Social/personal details sheet (supplemented)	Social/personal details sheet (supplemented)	Social/personal details sheet (supplemented)	Social/personal details sheet (supplemented)	Social/personal details sheet (supplemented)
		Informed consent letter; General Pediatrician's letter	General Pediatrician's letter	General Pediatrician's letter	General Pediatrician's letter	General Pediatrician's letter	General Pediatrician's letter	General Pediatrician's letter
RESOURCE CONSUMPTION	<i>Direct Medical/non-medical costs</i>	NICU sheet: Section A Section B1	Section B2 Section C	Section B2 Section C		Section B2 Section C	Section B2 Section C	Section B2 Section C

Table 1b. Brief summary of the areas of evaluation, the evaluation tools used and the phases of evaluation of the full term infants

<i>Subject of the evaluation</i>	<i>Areas of investigation</i>	BIRTH - DISCHARGE	6 MONTHS (postal delivery and telephone conversation)	18 MONTHS (visit)	30 MONTHS (postal delivery and telephone conversation)	3 YEARS (visit)	5 YEARS (visit)	7 YEARS (visit)
CHILD	<i>Temperament</i>		QUIT 1-12		QUIT 13-36		QUIT 3-6	
	<i>Cognitive area</i>		Griffiths/Bayley	Griffiths/Bayley MacArthur Questionnaire	Griffiths/Bayley	Language test	WPPSI Prerequisites of learning	Learning level
	<i>Adjustment and behavior</i>			CBCL/1½-5		CBCL/1½-5		CBCL/4-18
	<i>Quality of life</i>			TAPQOL	TAPQOL	TAPQOL	TAPQOL	TACQOL
MOTHER	<i>Mother's emotional state</i>	Edinburgh Scale	BDI STAI PSI	BDI STAI PSI	BDI STAI PSI	BDI STAI PSI	BDI STAI PSI	BDI STAI PSI
	<i>Child perception</i>		Child perception questionnaire	Child perception questionnaire		Child perception questionnaire		Child perception questionnaire
	<i>Perception of the quality of the treatment</i>							
ENVIRONMENT/ TREATMENT		Medical History sheet; Social/personal details sheet (supplemented)	Social/personal details sheet (supplemented)	Social/personal details sheet (supplemented)	Social/personal details sheet (supplemented)	Social/personal details sheet (supplemented)	Social/personal details sheet (supplemented)	Social/personal details sheet (supplemented)
		Informed consent letter; General Pediatrician's letter	General Pediatrician's letter	General Pediatrician's letter	General Pediatrician's letter	General Pediatrician's letter	General Pediatrician's letter	General Pediatrician's letter
RESOURCE CONSUMPTION	<i>Direct Medical/non-medical costs</i>	Day-care center sheet; Section A Section B1	Section B2 Section C	Section B2 Section C		Section B2 Section C	Section B2 Section C	Section B2 Section C

4.0 INCLUSION AND EXCLUSION CRITERIA

4.1 INCLUSION CRITERIA FOR THE VLBW

The cases were recruited from amongst the newborns hospitalized at the Neonatal Pathology and Neonatal Intensive Care Units participating in the study.

In order to minimize the impact of complications linked to any perinatal suffering on the subject's global functioning, all the pre-term infants with no major pathologies, excluding those born as part of a multiple birth, will be taken into consideration, with reference to the following inclusion criteria (evaluated at the 36th postconceptional week):

1. pre-term infants according to the Vermont Database criteria (weight between 401 and 1500 grams and/or gestational age between 22 weeks and 29 weeks + 6 days - www.vtoxford.org);
2. pre-term in-born;
3. no documented neurological pathology:
 - a. negative brain ultrasound (periventricular leukomalacia (PVL) max. stage 1, intraventricular hemorrhage (IVH) max. stage 1 and 2);
 - b. neurological examination within the norm (clinical evaluation used in the individual centers);
4. no sensory deficits:
 - a. retinopathy (ROP) max. stage 1 and 2
 - b. neonatal hearing screening (ABR or Otoemission – within the norm at the 34th week. If pathological, request confirmation at the 37th-40th week)
5. no malformation syndromes and/or major malformations, even if isolated (see Vermont Database – birth defects code - www.vtoxford.org)
6. parents of Italian nationality
7. mother aged over 18 years, with no manifest psychiatric and cognitive pathologies, not a drug addict.
8. no single-parent families
9. informed consent by the families to participation in the study

4.2 INCLUSION CRITERIA FOR THE FULL TERMS

With regard to the control group, each participating NICU undertakes to recruit, for each infant born pre-term, an infant born full term in the same Hospital, excluding those born as part of a multiple birth, with the following characteristics:

1. born in the period corresponding to the 40th postconceptional week of the pre-term infant (+/- two weeks);
2. no pre- or perinatal complications (Apgar 5' ≥ 8);
3. social-personal profile superimposable onto that of pre-term infant:
 - sex,
 - mother same age (+/- 3 years) and with the same characteristics:
 - same school attendance (number of years)
 - same working conditions (employed or unemployed)
 - with no psychiatric and/or cognitive pathologies
 - not a drug addict;
 - similar family social-economic level (referring to Hollingshead's classification).

5.0 UNDESIRABLE MEDICAL EVENTS

5.1 MANAGEMENT OF THE UNDESIRABLE EVENTS

The Investigator is responsible for correctly registering all the undesirable events which occur during the period of observation of the patients, according to the standards of normal clinical practice and for informing the competent Medical Authorities (Pharmaco vigilance Department of the same Hospital).

6.0 STATISTICAL METHODS

6.1 DATA MANAGEMENT

All the CRFs sent to the MediData DPC (Data Processing Center) will be registered and filed.

In order to eliminate macroscopic Data Entry errors, all data will be compared with a range of plausible values when being entered in the database.

Checks will be carried out on the data after it has been entered; the checks will be defined beforehand in order to evaluate legibility, any internal inconsistencies or wrong data.

A Query will be automatically added to the "Query Form" for each inconsistent/illegible/wrong data and this will be sent to the Investigator. When all the "Query Forms" have been returned to the MediData Data Processing Center (DPC), the relevant corrections will be entered in the database. At the end of the validation process, the database will be "frozen" and used for the statistical analysis.

6.2 DESCRIPTION OF THE ENROLLED CASES

All the patients enrolled in the study will be described, except for those with violations of the inclusion/exclusion criteria.

6.3 CALCULATION OF THE SAMPLE SIZE

6.3.1 Longitudinal phase

The primary objective of this study is to evaluate any existing differences between the quality of life in infants born pre-term vs. infants born full term at different stages of development (at 18 and 30 months and at 3, 5 and 7 years).

In order to estimate the sample number we can formulate the hypothesis that there is a difference in the quality of life between infants born pre-term and infants belonging to the control group and that this difference is quantifiable in terms of mean scores relative to the quality of life (Dixon et al, 1983; O'Brien et al. 1983).

A study, which is in the literature, has been carried out on a sample of Dutch children aged between 1 and 4 years aimed at evaluating the relationship between pre-term birth and the quality of life (Theunissen N. et al, 2001). The TAPQOL questionnaire, completed by the parents, was used to evaluate the children's quality of life. The worst quality of life of the 65 pre-term children with a gestational age of less than 32 weeks compared to children in the control group (consisting of 50 children of pre-school age extracted from the population of Dutch children, similar as to sex, age and other social-demographic variables) was highlighted by the scores per subject field of the questionnaire, and on average was always lower in the first group than in the second. From amongst the scores which turned out to be statistically significant, from a conservative viewpoint, we took into consideration

the smaller score, the one relative to motor function. It is attested that this value was on average (SE) -10.5 (2.7).

A sample of 200 children per group would mean that this expected difference for the score of the motor function subject field in the TAPQOL questionnaire between children born pre-term and children born at full term, could be evaluated with a degree of statistical reliability as 95% (type 1 error = 0.05) and a power of 85%, supposing there is a 30% drop out rate.

The fact that this study takes into consideration children with a lower gestational age than the children in the study by Theunissen et al. should guarantee the conservativity of the sample size estimation.

With regard to the power of the sample relating to the evaluations above 5 years of age, there is no known data in the literature at the moment with which to predict any expected differences. The study will therefore provide the possibility of evaluating them for the first time.

6.4 STATISTICAL ANALYSIS

An Analysis Plan will be defined as a basis from which to conduct the study analyses. It will contain a detailed description of the evaluability criteria for the analyses relating to the enrolled children.

The first step in the evaluation of the collected data will be an exploratory analysis aimed at describing the general characteristics of the study sample as well as the qualitative and quantitative characteristics of the data. To this end, the scores relative to the various subject fields and the total score (should one be necessary) will be extracted for each scale, using the calculation algorithms proposed by the authors; moreover, the mean, standard deviation, minimum and maximum will be calculated for the quantitative variables envisaged by the case report form and the questionnaires, whereas the distribution of absolute and relative frequency will be calculated for the qualitative variables.

The evaluation of the primary and secondary objectives of the study will then be conducted as follows:

Primary objective

The evaluation of any existing differences between the quality of life in children born pre-term vs. children born at full term shall be carried out on the individuals, evaluable at 18 and 30 months and at 3 years from the discharge visit through the subject fields of the TAPQOL questionnaire, suitably summarized with the descriptive statistics envisaged. These scores will then be compared by way of statistical tests using a significance level $\alpha=0.05$.

Any difference between the groups at 5 and 7 years from discharge will be evaluated in a similar way. The TACQOL questionnaire will be taken into consideration for the last visit.

Secondary objectives

The main structural and treatment characteristics of the NICUs will be noted at the birth of the infant and summarized through frequency distributions and descriptive statistics relative to the items in the case report form.

The presence of any depressive symptoms in the mothers will be noted at all the visits in both groups (TERM and VLBW) by comparing the scores of the specific scales (Edinburgh scale, BDI, STAI, PSI questionnaires).

The evaluation of the quality of the treatment will be carried out by referring only to the population of pre-term infants and considering the data collected at the discharge visit by the NICU staff, with regard to the presence of the parents in the NICU (access to the NICU

by father and/or mother and the fact that conversations with the parents are envisaged), the personal care of the infant (containment, postural care, nesting in the cot, reduction of touch stimuli - *minimal touch*, clustering of the samples, personalization of the treatment routine, KMC practice and any conditions limiting it), breastfeeding (understood as being the possibility of the mothers breastfeeding their infants). In order to evaluate whether the treatment has had an impact on the infants' quality of life, the quality of the treatment will be compared with the quality of life of the infants born pre-term, measured via the TAPQOL questionnaire at 18 and 30 months and at 3 and 5 years from the discharge visit and the TACQOL questionnaire at 7 years from the discharge visit. The relationship between quality of life and quality of the treatment will be evaluated by comparing the scores obtained from the TAPQOL/TACQOL questionnaires at each visit, with the variables relating to the quality of the treatment described above.

The cost relating to the different items of expense (visits, admissions, tests, therapies...), the expenses incurred by the family and the loss of productivity due to looking after the children (both pre-term and not) will be calculated per individual patient (average cost per child) and as an aggregate cost (total cost). Once estimated, a relationship will be established between these costs and the variables relating to the quality of the treatment (TAPQOL and TACQOL questionnaires) of the infants born pre-term and those born at full term.

The two groups of infants will also be compared in the medium and long term for cognitive competence, behavioral attitude and emotional development, through the creation of a stratified distribution per group of the items in the questionnaires relating to mental development (Griffiths and Mac Arthur questionnaires at 18 months; language test at 3 years, WPPSI – the prerequisites of learning at 5 years and level of learning at 7 years), to the behavior profile (CBCL scale) and the child's temperament (QUIT questionnaires).

Other "ad hoc" analyses will be carried out where necessary on the basis of the results of the exploratory analyses.

6.5 APPLICATION OF THE GRIFFITHS AND BAYLEY SCALES IN THE NEO-ACQUA PROJECT

Both the scales taken into consideration are commonly used in studies on premature infants as a tool for evaluating the cognitive outcomes linked to pre-term birth in the first years of life.

Evaluation of the level of development of the infant born pre-term at 6, 18 and 30 months of corrected age was introduced as a secondary objective in the context of the NEO-ACQUA longitudinal project. The aim of administering a development scale during the abovementioned follow-ups, was to help trace the general psychomotor and cognitive development trend for this group of children. Although the Griffiths scale and the Bayley scales do not provide totally equivalent scores, as some studies conducted on clinical samples have shown, they can both be considered suitable for the purpose of achieving this objective. It is therefore deemed that each Neonatal Intensive Care Unit participating in the project can choose independently, based on its own requirements and availability, which of the two scales to use to evaluate the level of development.

In order to limit any possible disharmony deriving from the use of different tools however, it appears appropriate to make specific corrections to the scores obtained. The quotients of development obtained from administration of the Griffiths in particular, are obtained by way of a transformation of the rough scores, on the basis of which the mental age obtained is divided by the chronological age and multiplied by 100. In this way, the mean quotients calculated and the standard deviations are found to be different for each of the sub-scales of the test. The Griffiths scale for the 2-8 years age band for example, has a mean general quotient of 100.18 with a standard deviation of 12.76. As suggested by

Ivens and Martin, these discrepancies can reduce the possibility of comparing the Griffiths' scores with those obtained through other development scales. In order to remedy this problem, the authors suggest two methods: first of all it is possible to convert the scores obtained in standard points (with mean 100 and standard deviation 15) through an algorithmic transformation; secondly, one can refer to descriptive categories which correspond to the range of scores used by other tests as well (including the Bayley scale): a level of development which is considered to be very low, for example, corresponds to standard points lower than 70 and to general quotients of the Griffiths lower than 75, a low level identifies standard scores of between 70 and 79 inclusive and quotients obtained with the Griffiths of between 75 and 82 inclusive, and so on (Ivens and Martin, 2002).

7.0 QUALITY ASSURANCE/QUALITY CONTROL PROCEDURES

7.1 MONITORING THE STUDY

So that the Investigators may correctly implement the procedures required by the study, the following activities are envisaged:

- Study start up meeting, coordinated by the Advisory Board, with the objective of sharing the operative procedures, training the Investigators to complete the data collection tools, and standardize the methods of clinical evaluation of the patients included;
- Monitoring visits
- Specific Help Desk telephone service for the project;
- All the Centers will have a Methodological Guide enabling correct understanding of the study tools.

8.0 ETHICAL ASPECTS

8.1 ETHICAL STANDARDS

The protocol complies with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and subsequent amendments laid down by the 29th (Tokyo, 1975), the 35th (Venice, 1983), the 41st (Hong Kong, 1989) and by the 52nd (Edinburgh, 2000) World Medical Assemblies.

8.2 INFORMED CONSENT FORM

It is the Investigator's (Local Study Head) responsibility to provide the subjects with the written informed consent form and the patient information sheet. The information sheet, which contains a clear and thorough definition of the objectives, must be read by the patient before s/he is included in the study.

The information sheet for the families and the informed consent forms are attached to each Case Report Form. The informed consent must be kept by the Investigator at the Center, whereas the copy of the information sheet must be given to the families.

9.0 ADMINISTRATIVE AND INSURANCE AGREEMENTS

9.1 INSURANCE

No insurance agreements are envisaged due to the absence of any treatment or of any diagnostic tests not included in standard clinical practice.

9.2 PUBLISHING RULES

The publications deriving from the collected data will be coordinated and authorized by the Advisory Board. The results will be published in the name of the “NEO-ACQUA Study Group” giving the names of the Center Monitors in diminishing order based on the numbers of the patients enrolled at the birth/discharge visit (for the relative publications) and of the subsequent follow-ups.

The Centers which complete the transverse and longitudinal phases of the study limited to a number of Cases lower than 5 and Controls lower than 5 will not be mentioned in the relevant publications.

9.3 DATA OWNERSHIP

The group of Supporting Bodies represented by the respective members of the Advisory Board shall have the right of ownership of all the study data collected at all the participating Centers, without prejudice to the right of each research Center to use the data collected at its own Center.

10.0 STUDY CONDUCT

10.1 ADVISORY BOARD

The study is coordinated by a scientific board consisting of:

1. Massimo Agosti MACCHI FOUNDATION AND HOSPITAL, VARESE
2. Roberto Bellù “A. MANZONI” HOSPITAL, LECCO
3. Renato Borgatti “E. MEDEA” SIRHHC BOSISIO PARINI (LC)
4. Guido Calciolari MACCHI FOUNDATION AND HOSPITAL, VARESE
5. Maria Caterina Cavallo COMMERCIAL UNIVERSITY “L. BOCCONI”-CERGAS, MILAN
6. Irene Colangelo COMMERCIAL UNIVERSITY “L. BOCCONI”-CERGAS, MILAN
7. Alberto Del Prete “A. MANZONI” HOSPITAL, LECCO
8. Rosario Montiroso “E. MEDEA” SIRHHC BOSISIO PARINI (LC)
9. Rinaldo Zanini “A. MANZONI” HOSPITAL, LECCO

The Board’s duties are as follows:

- the scientific coordination of the project
- the evaluation of the results
- the harmonization of the overall results in scientific communications

10.2 CENTER PARTICIPATING IN THE STUDY

It is the duty of each Center participating in the study:

- to enroll the cohorts as defined by the Study Protocol
- to collect all the variables envisaged by the Case Report Forms
- to administer the tools
- to send the forms to MediData using the special pre-stamped envelopes
- to cooperate in the quality control of the data
- to keep a copy of its own Data Report Forms until the study is finished and the statistical processing complete.

10.3 MEDIDATA

Medidata provides a technical scientific organizational support for the conduct of the study. It will also support the activities at the Centers, providing them with all the necessary material for the conduct of the study, and in particular:

- Copy of this Study Protocol
- Case Report Forms (CRF)
- Methodological Guide
- Data Entry
- Data Base Management
- Quality control of data
- Statistical Analysis
- Telephone Help-desk

11.0 STUDY TIMING

Year 2005	
May	Investigator Meeting
July - November	Activations of the NICUs
December – January 2006	Beginning of recruitment
Year 2006	
June - July	End of the recruitment - Visit 1
June - July	Beginning Visit 2 (infant 6 months old)
September – October	Data cleaning
November - December	Statistical Report (cross-sectional phase)
December	End of Visit 2
Year 2007	
June - July	Beginning Visit 3 (infant 18 months old)
December	End of Visit 3
Year 2008	
June - July	Beginning Visit 4 (infant 30 months old)
December	End of Visit 4
January - February	Data cleaning
March	Statistical Report (longitudinal phase)
Year 2009	
January	Beginning Visit 5 (infant 3 years old)
June	End of Visit 5
Year 2011	
January	Beginning Visit 6 (infant 5 years old)
June	End of Visit 6
Year 2013	
January	Beginning Visit 7 (infant 6 years old)
June	End of Visit 7
September – October	Data cleaning
November - December	Final statistical report

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APPENDIX 1 Summary of the assessment time and phases

<i>Assessment phase</i>	<i>Instruments</i>	<i>Preterm group</i>	<i>Full-term group</i>	<i>Who does the evaluation</i>	<i>Assessment time</i>
Birth - Discharge	NNNS	H		Neonatologist	
	Edinburgh Scale	H	H	Mother	10 min.
	Parental Stress Scale: NICU	H		Mother	10 min.
	Nurse Parent Support Tool	H		Mother	10 min.
	Neonatology sheet	H		Neonatologist	
	Questionnaire about the Care	H		NICU operator	
	Anamnestic sheet	H	H	Neonatologist	
	Environmental evaluation sheet	H		Operator	
	Section A	H	H	Neonatologist	
	Section B1	H	H	Neonatologist	
6 months	Griffiths/Bayley	H		Psychologist	
	QUIT 1-12	H	P	Mother	10 min.
	BDI	H	P	Mother	10 min.
	STAI	H	P	Mother	10 min.
	PSI	H	P	Mother	20 min.
	Child perception questionnaire	H	P	Mother	10 min.
	Social/personal details sheet	H	P	Mother	5 min.
	Section B2	H	P	NICU operator/ Mother	10 min.
	Section C	H	P	Mother	10 min.
18 months	Griffiths/Bayley	H	H	Psychologist	
	MacArthur questionnaire	H	H	Psychologist	
	CBCL/1½ -5	H	H	Mother	10 min.
	TAPQOL	H	H	Mother	10 min.
	BDI	H	H	Mother	10 min.
	STAI	H	H	Mother	10 min.
	PSI	H	H	Mother	20 min.
	Child perception questionnaire	H	H	Mother	10 min.
	Social/personal details sheet	H	H	Mother	5 min.
	Section B2	H	H	NICU operator/ Mother	10 min.
	Section C	H	H	Mother	10 min.

H = observation/data collecting made at hospital

P = Questionnaire posted at home or phone interview

Assessment phase	Instruments	Preterm group	Full-term group	Who does the evaluation	Assessment time
30 months	Griffiths/Bayley	H		Psychologist	
	QUIT 13-36	H	P	Mother	10 min.
	TAPQOL	H	P	Mother	10 min.
	BDI	H	P	Mother	10 min.
	STAI	H	P	Mother	10 min.
	PSI	H	P	Mother	20 min.
	Social/personal details sheet	H	P	Mother	5 min.
3 years	Language test	H	H	Psychologist	
	CBCL/1½ -5	H	H	Mother	10 min.
	TAPQOL	H	H	Mother	10 min.
	BDI	H	H	Mother	10 min.
	STAI	H	H	Mother	10 min.
	PSI	H	H	Mother	20 min.
	Child perception questionnaire	H	H	Mother	10 min.
	Social/personal details sheet	H	H	Mother	5 min.
	Section B2	H	H	NICU operator/ Mother	10 min.
Section C	H	H	Mother	10 min.	
5 years	WPPSI	H	H	Psychologist	
	Learning prerequisites	H	H	Psychologist	
	QUIT 3-6	H	H	Mother	10 min.
	TAPQOL	H	H	Mother	10 min.
	BDI	H	H	Mother	10 min.
	STAI	H	H	Mother	10 min.
	PSI	H	H	Mother	20 min.
	Social/personal details sheet	H	H	Mother	5 min.
	Section B2	H	H	NICU operator/ Mother	10 min.
Section C	H	H	Mother	10 min.	
7 years	Learning level	H	H	Psychologist	
	CBCL/4-18	H	H	Mother	15 min.
	TACQOL	H	H	Mother	10 min.
	BDI	H	H	Mother	10 min.
	STAI	H	H	Mother	10 min.
	PSI	H	H	Mother	20 min.
	Social/personal details sheet	H	H	Mother	5 min.
	Section B2	H	H	NICU operator/ Mother	10 min.
	Section C	H	H	Mother	10 min.