PROBIOTICS AND THE NEURODEVELOPMENT IN THE PREMATURE INFANT <32 WEEKS GESTATIONAL AGE AND <1500G

UNIQUE PROTOCOL ID: HCB/2021/0454

INFORMED CONSENT- ENGLISH VERSION

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PATIENT INFORMATION LEAFLET

STUDY TITLE: Probiotics and the neurodevelopment of the extreme premature infant <32 weeks and <1500g
PROMOTOR: Benjamin J Baucells, Giorgia Sebastiana and Òscar García-Algar
PRINCIPAL INVESTIGATOR*: Benjamin J Baucells, Neonatology service BCNatal Hospital, phone 932275400 extension 7503 (secretaria del servicio de Neonatos)*
CENTRE: Hospital Clínic seu Maternitat

INTRODUCTION
The researchers are addressing to the participant to inform them of a research study to which they have been invited to participate. The study has been approved by the Ethics Committee, in accordance with current legislation, Order SAS/3470/2009, of 16th December, that contain directorates about studies post authorisation of an observational nature for drugs used in humans.

The intention of the researchers is that you receive the correct and adequate information for the participant to evaluate and judge if they want to participate or not. For that reason, please read this information leaflet with special care and the investigators will answer any queries after the explanation. Moreover, the participant can seek advice to any person they consider.

VOLUNTARY PARTICIPATION
The participant must know that enrolment in this study is voluntarily, and they can decide to participate or decide otherwise and revoke consent at any point, without it having any impact in their relationship with the clinicians or being detrimental to their treatment.

GENERAL DESCRIPTION OF THE STUDY*:*
It is know that the extreme premature infant (under 32 weeks gestation) or low weight (under 1500g) has an increased risk of neurodevelopment impairment, linked to immaturity paired with the challenges in the neonatal unit and the neonatal period, as opposed to the full term neonate. For those circumstances, during their admission in the neonatal and later on during infancy, the premature infant will receive interventions that aim to diminish and palliate the impact of prematurity in their development. Although premature infants are assessed during their early life, there is current evidence that shows that some of the neurodevelopment impairment is not seen until the start of school and even in adulthood.

As per probiotics, they were defined by the WHO as those microorganisms that when administered in adequate amounts, confer a health benefit for the host. Different studies in premature infants have brought forth the theory that when probiotics are given routinely to neonates less than 32 weeks gestational age they can contribute to reducing the risk of necrotising enterocolitis (an intestinal disease that tends to affect premature infants and can entail gut destruction and high mortality) and therefore the risk of death. Following this line of thought, at BCNatal Hospital Clinic there was the administration of routine probiotics

Lactobacillus acidophilus and *Bifidobacterium bifidum*, in the premature infants under 32 weeks gestational age and less than 1500g during the years 2014-2016.

The aim of this study is to assess the ability of probiotics to impact the neurodevelopment of the premature infant <32 weeks gestation that were treated at BCNatal Hospital Clinic, comparing them to those that did not receive probiotics. The researchers will proceed to collect data and to practice neurodevelopment assessment tests at 24 months corrected age (Bayley test) and a further assessment at 6 years of age, evaluating intelligence (WISC-V test) and evaluating behaviour and social interaction (CBCL-6 and BRIEF-2). Additionally, the investigators would collect results from the Cerebral magnetic resonance of any patient that might have received one. Finally, the researchers also intend to collect plasma samples (blood test) to study biological biomarkers of neuronal plasticity and neurodevelopment.

The intention of the researchers is to try and recruit a total of 150 patients and follow them up at 24 months corrected age (routine follow-up for any premature infant <32 weeks and <1500g) and another follow-up check at 6 years in a global assessment in one visit, less than 1 hour duration.

During the study, the participant or any of the legal guardians can contact the researchers to notify any incidence in the neurodevelopment of the participant (new diagnose, behaviour problems at school or at home, etc.).

BENEFICITS AND RISKS OF THE PARTICIPATION IN THE STUDY

The results of the study will allow to determine the paper of probiotic administration, intervention with very low reported risks, in the neurodevelopment of premature infants. Nevertheless, the identification of biomarkers will help identify those patients that may require posterior follow-up and neurolodevelopmental support to enhance their performance. There is also the possibility of not finding any benefit from the administration of probiotics.

Potential risks associated to the participation in the study are derived from blood sampling, in general mild, that could entail pain during extraction and in the site of extraction, as well as a haematoma from the procedure that self-resolve in a few days.

CONFIDENCIALITY

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The Hospital Clinic of Barcelona, with CIF 0802070C, as the responsible institution for the treatment of your data, informs you that the treatment, communication and cession of personal identifiable data will be done in accordance to the EU Ruling 2016/679 of the European Parliament and the Council of the 27th of April 2016, related to the protection of physical people, and the treatment of their personal data and free circulation of data, being of mandatory compliance by the 25th of May 2018. The legal frame that justifies the treatment of your data and consent to this act are in accordance to what has been established in article number 9 of the EU Ruling 2016/679.

All data collected will be identified with a code and will not contain any data that allows the identification of participants. Only the clinician and their collaborators with specific permission will be granted access to your clinical history.

Your identity or any personal data will not be made available to any third party unless legal requirement or medical emergency. Health authorities, Ethics Committee and authorised personnel may access your data if it is necessary for data quality check and review of study procedures, always ensuring preservation of confidentiality in accordance with existing law.

Only codified deidentified data will be made available to third parties if required for the purpose of the study and always ensuring confidentiality. Personal data such as name, initials, date of birth, hospital identification number, address, etc. will never be made available to third parties.

If any data is to be transferred out of the European Union, whether it is to related bodies to the Health Centre where you were cared for, or other healthcare providers or researchers in collaboration with the current project, it will be protected by contract and any other adequate mechanisms established by data protection authorities.

A part from the aforementioned rights (access, modification, denial and cancellation and suppression of data following the new Ruling) the participant will be able to limit the use of data that is incorrect, request a copy and transfer of any data to a third party that the participant wishes. To be able to carry out these rights, or to clarify any doubts about confidentiality, the investigators encourage the participant to contact the Principal Investigator or the delegate of Data Protection of BCNatal Hospital Clinic through the email protecciodades@clinic.cat. The participant is also entitled to contact the Data Protection Agency if they are unsatisfied.

Collected data will not be eliminated, even if you abandon the study, to guarantee the internal validity of the study and to ensure compliance with legal requirements of drug research regulators. However, no new data will be collected if the participant stop participating.

The researcher and the promotor are obliged to preserve collected data for the study for up to 5 years after finalisation. Afterwards, personal information will only be stored by the Healthcare provider to care for the participant and by the promotor for other scientific research purposes if the participant has given consent, and current legislation allows it

ECONOMIC COMPENSATION

The participation in the study will not incur in any costs for the participant and their family with the exception of the costs to attend the appointments at the Centre for their assessment given that it is a limited budget study, and the majority of patients live in the catchment area of the centre. The assessments will aim to coordinate efforts to minimise the impact of the study in the legal guardian´s work and private life.

OBTENTION AND USE OF BIOLOGICAL SAMPLES

Participation in the study entails the collection of plasma samples. In accordance to the established practises in Law 14/2007 for biomedical research and the Royal Decree 1716/2011 that regulates the use of biological samples for research, the participant agrees by signing this document to the use of any biological samples for the purpose of this study.

The biological samples will be stored in the laboratory of the Institut d'Investigacions Biomèdiques August Pi I Sunyer (IDIBAPS) until the use for the purpose of the study. Once finalised, the samples will be destroyed.

A code will be used to identify the biological samples without any data that may reveal the participants´ identity. Only the clinician of the study and the collaborators will be able to relate that sample to the participant.

Any data obtained from the processing of the samples will be treated in the same mode as the rest of collected data for the study.

The cession of biological samples for this study is free of cost and voluntary. That means the participant will not have any rights to commercial benefits of the discoveries thqt could derive from the biomedical research.

If relevant information that could impact the health of the participants or family members is obtained, they will be notified. In the circumstance that contact is required, contact data from your clinical history will be used. However, if the participant decides not to be informed of the results, this will be respected, please fulfil the necessary box in this form.

If any genetic results are obtained, the participant nor their doctor will be informed. If they wish to know the results, they may get in contact with the promotor of the study. Taking into account that these are exploratory studies, said information cannot be used for guiding treatment or diagnostics.

OTHER RELEVANT INFORMATION

Any new information relevant to the treatment used in the study, that can affect the participants involvement in the study, discovered after enrolment, will be communicated as soon as possible by the researchers.

If the participant wishes to withdraw consent to participant in the study, no new data will be added to the database, and any identifiable samples obtained can be destroyed to prevent new analyses.

The participant must also be informed that they may be excluded from the study if the promotor or researchers find it adequate, may it be for security, or any other side effect related to the medication being studied o if they deem there has been a breech in protocol. Under any circumstance the participant will be informed of the withdrawal and the reason behind it.

Once signing the consent form, the participant agrees to fulfil all the procedures expressed in this leaflet and communicated to them.

Once participation has ended, the participant will receive the most adequate available treatment and that their clinician deems appropriate to treat their illness, although continuing the medication of the study may not be possible. Therefore, neither the researchers nor the promotor have a legal requirement to continue the treatment out of the study.

CONSENT FOR PARENTS OR LEGAL GUARDIANS OF UNDER AGED PARTICIPANTS

Title of the study: "Probiotics in the neurodevelopment of the premature infant under 32 weeks and less than 1500g"

I, *(name and surname of participant)*
as …….. of ……..
(tutor, parent or legal guardian) (name of minor)

- I have read the information leaflet that I have been handed in about the study.
- I have been able to ask questions about the study.
- I have received sufficient information about the study
- I have spoken to (researcher name) ……
- I understand the voluntary role
- I understand I can withdraw from the study:
    - Whenever I want
    - Without giving explanations
    - It will not impact the medical care.

In line with what has been established in the 2016/679 EU Ruling of the European Parliament and the counsel of 26th April 2016 in relationship to the protection of physical people, data circulation and data treatment, I declare I have been informed of the existence of a file o treatment of personal identifying data, of the need to compile these and the uses of such information.

I hereby accept that …… participates in the study
(name of minor)

□ Boths parents

Father signature
Date……./……../…… Signature: …….

Mother signature
Date……./……../…… Signature: …….

In the situation where only one of the parents gives authorisation, the necessary requirements have to be fulfilled:

□ I confirm that the other parent does not oppose to the inclusion of our child in the study

Signature of the parent (specifiy mother or father)
Date……./……../…… Signature: …….

□ I am the sole legal tutor

Signature of legal tutor
Date……/……../…… Signature: ……

Researcher signature
Date……/……../…… Signature: ……