Timbro Aziendale

INFORMATIVE FORM FOR PARENTS/LEGAL REPRESENTATIVE

Version 5 of January 15th, 2020

Title of the study: Newborn Screening for Spinal Muscular Atrophy in Lazio and Tuscany: a Two-Year Pilot Project
Protocol code, version and date: NBS_SMA, Version # 2 of June 14th, 2019
Principal investigator and promoting Institution: Prof. Francesco Danilo Tiziano, Istituto di Medicina Genomica, Università Cattolica del Sacro Cuore, Rome
Local principal investigator (on site): *insert name, surname, maternity hospital affiliation*

Principal investigator and coordinator in Regione Toscana: Dr. Maria Alice Donati, Struttura Organizzativa Complessa (SOC) Malattie Metaboliche e Muscolari Ereditarie, Azienda Ospedaliero-Universitaria (AOU) Meyer, Florence

Dear Parents/Legal Representative,

Please read carefully the present form ahead of giving your consent to the participation to this project; be sure of having had an exhaustive counseling with your referral physician, whose staff will dedicate the necessary time to make you fully understand the study.

If you wish, your child could participate to this project, coordinated in Regione Toscana by AOU Meyer, which this maternity hospital has adhered to.

The study encompasses several hospitals in Tuscany and in Lazio.

This information sheet provides you important information about aims and implications of the present project, related to your child's health. If this form would be unclear in any aspect, please ask for further explanations to the medical personnel. Take your time to consider. Your child participation is on a voluntary basis; you may withdraw the consent at any moment.

Once you have read the present form and have got any clarification, if you decide your child to participate, you will be asked to sign an informed consent.

What is the aim of the project?

The project aims to identify patients affected from spinal muscular atrophy (SMA) before the onset of symptoms, i.e. in a very precocious phase, when clinical signs of the condition have not appeared yet. The main goal of the present study is to establish the incidence of SMA among newborns in Lazio and Tuscany.

The study will also provide data to assess the appropriateness of including SMA among genetic diseases suitable for national mandatory newborn screenings.

This study will last 24 months and will involve approximately 120.000-140.000 newborns.

What is SMA?

SMA is a rare neuromuscular disorder characterized, on the clinical point of view, by progressive muscular paralysis due to the loss of the voluntary control of the movement; intellectual development is generally normal.

SMA is classified into three forms, based on the severity and on the age of onset of clinical signs:

- SMA I (about 50-60% of patients) is the most severe form; the onset is within 6 months of age and life expectancy is below 2 years; the most common cause of death is respiratory insufficiency, mainly due to the weakness of the intercostal muscles.

- SMA II (about 30% of patients) is an intermediate form, with onset within 18 months. Affected children do not acquire the ability of walking without support. Even if life expectancy is barely normal or slightly reduced, the quality of life is generally poor, due to the extreme movement limitation. Moreover, almost all patients have a severe scoliosis, often requiring surgical correction.

- SMA III is the less severe and less common form. The onset of symptoms is over 18 months, and the course is highly variable. Patients may lose or not the walking ability. Life expectancy is normal, while the quality is more or less impaired, based on the entity of movement limitation.

SMA is generally present in families as single cases, since it is due to an autosomal recessive genetic defect: in other words, both parents of a patient, albeit completely healthy, are carriers of the genetic defect that will be manifest in children only if transmitted by both parents. It has been estimated that about one SMA child is born every 6-10.000 neonates; healthy carriers are quite common in the general population, about 2-3%.

The gene responsible for SMA is named *SMN1*: while the majority of healthy subjects has two copies of this gene (one from the mother and the other from the father), in 97-98% of SMA patients both copies are lacking. Close to *SMN1*, there is the *SMN2* gene which is almost identical to *SMN1* but only partially functional; in the absence of *SMN1*, the presence of *SMN2* is not sufficient to prevent the onset of SMA symptoms. The number of *SMN2* copies is variable in patients (generally 1-4 copies) and can mostly explain the different severity of the condition.

Which therapeutic opportunities are available today for SMA?

Up to few years ago, the treatments for SMA were limited to some supportive interventions that have been useful to prolong the survival of patients, without consistently modifying the quality of life; SMA was considered an untreatable condition and, in the case of SMA I and some SMA II, extremely severe. Over the last few years, several very promising potential treatments for SMA have been developed: the first effective drug for the treatment of patients has been recently approved; several others are in advanced experimental phases and will be soon available for human use. Scientific data available today have clearly shown a marked improvement of treated patients, although the disease cannot be considered cured yet. However, it is now evident that the recovery of muscle weakness is much higher as earlier the treatment is started. Thus, the timely diagnosis of SMA is of extreme importance for the better recovery of muscle weakness and for the improvement of the quality of life. Some preliminary data indicate that patients with a predicted diagnosis of a severe form of SMA (type I or II), who were treated before the onset of symptoms, have shown a motor development comparable to that of non-affected children.

What does the participation to this research project imply?

Every neonate undergoes to a tiny blood sampling from the heel for the "mandatory newborn screenings", as stated by law in Italy. If you will consent the participation of your child to this project, a small additional amount of blood will be devoted to the identification of the genetic defect responsible for SMA. Thus, this test will be performed together to the mandatory screenings (that will be performed in any case, as by routine).

What will happen to the biological sample of our child?

The sample of your child will be sent to the Institute of Genomic Medicine of the Università Cattolica del Sacro Cuore/Fondazione Policlinico Universitario "A. Gemelli" in Roma, where the genetic test for SMA will be performed on DNA extracted from the blood sample.

The DNA sample will be discarded at the end of the analysis, while the blood sample will be stored for two years after the end of the study at the above mentioned Institution, under the responsibility of Prof. Francesco Danilo Tiziano.

You may require the destruction of the remaining blood sample at any time. Only a limited number of persons will be authorized by the Responsible of the project to access to the biological sample of your child.

How will we be informed about the results of the genetic test?

The results of the genetic test will be available within 7 working days from sampling.

If the test will be negative (normal), no direct communication will be performed, as in the case of the mandatory newborn screenings. Since the genetic test can identify about 98% of SMA patients, there is a small residual risk (<1/300,000) that your child is still affected from SMA. This risk cannot be further reduced, unless your child will present clinical signs suggestive of SMA.

If the genetic test will be positive, thus indicating the genetic diagnosis of SMA, you will be invited to perform a genetic counselling with the physicians of the SOC Malattie Metaboliche ed Ereditarie at AOU Meyer. In that occasion, your child will be clinically evaluated, you will be informed in details about the meaning of the test and provided with all information regarding SMA, the available therapeutic opportunities, and the reproductive risk for you and your relatives. A new aliquot of blood of your child will be sampled for the confirmation of the results of the screening. Based on the results of this latter test, an official report will be provided with the specific diagnosis.

If your child will be confirmed positive, you both will be considered healthy carriers of the condition.

How to proceed if our child is affected from SMA?

The genetic tests available today (absence of *SMN1* and *SMN2* copy number determination) allow to establish the severity of the condition at about 80% accuracy. Thus, these genetic information will be used to identify the most appropriate standards of care for your child at the SOC Malattie Metaboliche e Muscolari Ereditarie AOU Meyer in Florence, where SMA patients are treated according to the International standards of care.

Which benefits can arise from the participation in the project?

As reported above, the early diagnosis of SMA, particularly if performed in the pre-symptomatic phase of the disease, may help to maximize the results of the specific treatment. Thus, if your child would be affected by SMA, particularly in the case of the most severe forms, the most appropriate treatment will be started timely. Further, your relatives and yourselves will take advantage of the opportunity to perform informed reproductive choices, based on the awareness of being healthy carriers of SMA. No reward will be due for the participation to the present project.

Which risks may arise from the participation to the project?

Since the blood specimen required for the present project will be sampled together with that of the mandatory newborn screenings, no additional risks are foreseen from the participation in the project.

Finally, since only the genetic test for SMA will be performed, there is no risk of incidental unrequested information.

What if you decide not to participate to the project?

The participation to this project is on a voluntary basis. No explanation will be required if you will not consent the participation of your child, and no changes will be done to the standard cares of your child. Further, you can decide to withdraw your consent at any moment.

How personal data regarding the identity of our child will be protected?

Your data and the biological sample of your child will be processed only in relation to the objective of the study, in compliance with the current legislation on the protection of personal data, pursuant to art. 13 and 14 of the EU of 27/04/2016, no. 679 ("Regolamento generale sulla protezione dei dati personali – GDPR"). The autonomous holders of data processing are the Azienda Ospedaliero Universitaria Meyer of Florence (as Principal Investigator and Coordinator for the Tuscany Region) and the Università Cattolica del Sacro Cuore in Rome (as Promoter of the study). The maternity hospital will be appointed Responsible for data processing, pursuant to art. 28 of the GDPR. In summary, here are some essential information:

I. **Data Holder and Responsible for data protection**

The Data Holder is the Azienda Ospedaliero Universitaria Meyer, registered office Viale Pieraccini n. 24, 50139 - Florence, PEC meyer@postacert.toscana.it, as research and coordination Center for Tuscany Region. Pursuant to art. 37 of the GDPR, Responsible for the Protection of personal Data (RPD) has been designated that of the Meyer University Hospital, who is available for any clarification at the email address: privacy.dpo@meyer.it.

II. **Purpose and categories of data processing**

The processing of personal data will be carried out:

a) in order to perform the study indicated in the introduction;

b) for the purpose of diagnosis, assistance or therapy, in case of positive genetic test.

Your participation to the study determines the processing of the following categories of personal data:

- General data (e.g. personal information and contacts) including personal identification number.
- Specific categories of personal data referred to in art. 9 of the GDPR (e.g. data related to health condition) and possibly genetic data (i.e. data concerning the hereditary characters of an individual).

III. **Legal basis of the processing and Nature of provision**

The legal basis of the abovementioned processing is to be found mainly in the consent, pursuant to art. 9, 2nd comma, lett. A) of the Regulation. The participation in the present study is on a voluntary basis; the consent to the processing for the aims described above is free and optional; the lack of the provision will not prevent your right to make use of the other medical services provided by the Institution where you are under treatment. However, it is necessary to specify that the consent at item II.a is necessary to participate in the study described here; it will be not possible to participate to the study if data and biological samples indicated for this purpose will be not provided.

In case of positive test as reported in item II.b, a preventive consent will be acquired in order to communicate the results to the Maternity hospital by the Holder of data processing (AOU Meyer). Data provision is necessary to fulfil the request of health assistance to the patient and the legal obligations, regarding the preservation of administrative and health papers.

IV. **Modality of processing**

The aims, as at point II, include the performance of the collection, registration, preservation and managing of personal data through papery and computerised devices, according to logics strictly related to the aims and, in any case, in order to warrant safety and confidentiality of data, according to art. 32 of the GDPR.

The Holder, for the activity of collection of the biological sample and of the study consent, will make use of the support of the Maternity hospitals, mentioned in the study protocol, that will be preventively indicated as responsible of the treatment, according to art. 28 of the GDPR.

The subjects in charge of data processing will pay specific attention in differentiating data collected with medical/clinical aims from those collected with research aims, with respect to the protection of rights and dignity of the patient.

V. **Categories of subjects to whom data can be communicated**

The Holder engages not to diffuse genetic or particular data and not to use biological samples for aims different from those indicated at point II.

The Holder AOU Meyer, with your consent to the participation in the study, is authorized to communicate or transfer data and biological samples of the study, to perform the genetic test, to the *Istituto di Medicina Genomica dell'Università Cattolica del Sacro Cuore*, with registered office at Largo Francesco Vito, n. 1, 00168 - Roma, Study promoter, in its capacity as autonomous and distinct Holder of processing.

The Promoter will not use samples for different aims than those indicated in the study protocol and engages with the Holder AOU Meyer to possibly communicate to third-party uniquely aggregated and anonymized data. Data emerging from the results of the genetic test, if implying a concrete and direct benefit in terms of treatment, prevention or awareness of Your future choices, will be communicated directly to you; only with your consent, data could be make known to different persons, specifically indicated by yourself.

VI. **Preservation of personal data**

Data provided by you will be preserved no longer than the period required to pursuit the finalities for which have been collected and processed. In particular, DNA sample will be discarded at the end of the analysis, whereas blood sample will be preserved for two years after the end of the study, by the Promoter.
The data emerging from the present study will be preserved within the limits established by the laws regulating the specific subject.

VII. **Transfer of personal data outside the EU**

The data object of the study will not be object of processing in Countries outside the European Union.

VIII. **Exercise of rights**

You may exercise your rights under and within the limits of art. 15-21 of EU Regulation 2016/679, including the right to request access to your personal data, their correction or erasure, the limitation of their processing, the objection to processing and data portability.
Any consent here expressed is voluntarily given and can be revoked at any time without any disadvantage or prejudice and without altering the legitimacy of data processing based on the consent given before revocation.
If you decide to withdraw the consent to the data processing for the purposes referred in point II.a, you will obtain the discarding of the biological sample and the erasure of your genetic data unless, in origin or following the processing, sample or information can no longer be assigned to an identified or identifiable subject, and/or unless the data erasure severely impairs the achievement of the project aims.
Requests relating to the exercise of these rights may be submitted to the Data Protection Officer by writing to the e-mail privacy.dpo@meyer.it or by writing to the Data Controller at the address given in point I.
Lastly, if you consider that the processing of personal data of your child is in violation of the EU Regulation 2016/679 or of Legislative Decree no. 196/03 s.m.i., you have the right to complain to the Guarantor, as provided by art. Article 77 of the abovementioned Regulation, or to bring an action to the appropriate courts (Art. 79 of the Regulation).

Additional information

No additional costs will be charged to you and you will not receive any reward for participation in the study. The study was drawn up in accordance with the Norms of Good Clinical Practice and the Helsinki Declaration, and was approved by the Ethical Committee of the Tuscany Region Paediatric Section.
For further information or clarifications about the research project, or if you would like to withdraw your consent for participation in the study and/or have the biological sample of your child discarded, please contact the following numbers:
Tel: 055.5662560 (AOUMeyer Screening Centre Secretariat)
Fax: 055.566.2836 (AOUMeyer Screening Centre Secretariat)
Email: screening@meyer.it

REGIONE TOSCANA

Timbro Aziendale

MEYER Azienda Ospedaliero-Universitaria

UNIVERSITÀ CATTOLICA del Sacro Cuore

INFORMED CONSENT FOR PARENTS/LEGAL REPRESENTATIVE

Version 5 of January 15th, 2020

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Principal investigator and promoting Institution: Prof. Francesco Danilo Tiziano, Istituto di Medicina Genomica, Università Cattolica del Sacro Cuore, Rome

Local principal investigator (on site): *insert name, surname, maternity hospital affiliation*

Principal investigator and coordinator in Regione Toscana: Dr. Maria Alice Donati, Struttura Organizzativa Complessa (SOC) Malattie Metaboliche e Muscolari Ereditarie, Azienda Ospedaliero-Universitaria (AOU) Meyer, Florence

I, the undersigned (mother/representative) _____
born on___/___/_____resident in_____ address _____

Tel._____

Domicile (if different from your permanent address)_____

I, the undersigned (father/representative) _____
born on___/___/_____resident in_____ address _____

Tel._____

Domicile (if different from your permanent address)_____

Of the newborn _____ born on ___/___/_____

resident in _____ address _____

DECLARE that:

- I have received from Doctor_____ comprehensive information about the request for participation in the project, as reported in the information sheet of which I have a copy, given to me on (date) _____ at (time) _____.
- I have received a clear information regarding nature, purpose and potential health implications of this study for my child

I also **DECLARE** that:

1. I have read and understood the information sheet provided on the research project and which is part of this consent;
2. I was given the opportunity to ask any question to the investigator of the study and I received satisfactory answers;
3. I was given enough time to consider the received information and to discuss it with third-party;
4. I have been informed that the study protocol and all forms have been approved by the relevant Ethical Committee;
5. I have been clearly explained that I can decide my child not to participate in the study, without giving any explanation, and that these decisions will not change in any way the relation with the doctors and with the hospital;
6. I have been informed on how the results of this study will be communicated;
7. I have been informed that the results of the study, as aggregated data, will be shared with the scientific community, protecting the identity of the child according to the current law on privacy;
8. the subscription of the present form expresses my consent to the participation of the child in the study, to taking of sample, and to its use together with his/her personal data, as reported in the informative sheet; in case of aims

and use different from those described, the present consent will not have any validity and we will have to be contacted again;

9. We authorize the transfer of the sample and of personal data of our child to the Istituto di Medicina Genomica of Università Cattolica in Roma, aware that, under the responsability of the Promoter and Responsible of the study, all safety measures provided by law will be implemented.

Therefore we **DECLARE** to:

☐**Consent** ☐ **Not consent** - REQUIRED - the participation of the minor in the study

☐**Consent** ☐ **Not consent** - REQUIRED - to be informed about the results of the analysis

_____	___/___/_____	_____	_____
Full name of the mother/legal representative	Date	Time	Signature
_____	___/___/_____	_____	_____
Full name of the father/legal representative	Date	Time	Signature

By subscribing this form, we consent to the processing of personal data of our child for the aims of the research, within the limits and with the modality indicated in the Informative sheet provided with the present document, pursuant the Regulation (EU) 2016/679 and of the D. Lgs. 196/2003 s.m.i., having read the informative regarding personal data processing from the paragraph "How personal data regarding the identity of our child will be protected?".

_____	___/___/_____	_____	_____
Full name of the mother/legal representative	Date	Time	Signature
_____	___/___/_____	_____	_____
Full name of the father/legal representative	Date	Time	Signature

Io sottoscritto Prof./Dr.

…… (Cognome) …… (Nome)

Dichiaro che i genitori/tutori legali del Paziente hanno firmato spontaneamente la partecipazione allo studio

Dichiaro inoltre di:

- aver fornito esaurienti spiegazioni in merito alle finalità dello studio, alle procedure, ai possibili rischi e benefici e alle possibili alternative;
- aver verificato che i genitori/tutore legale abbiano sufficientemente compreso le informazioni fornitegli;
- aver lasciato ai genitori/tutore legale il tempo necessario e la possibilità di fare domande in merito allo studio;
- non aver esercitato alcuna coercizione od influenza indebita nella richiesta del Consenso

_____	___/___/_____	_____	_____
Nome per esteso del medico che ha fornito le informazioni e raccolto il consenso informato	Data	Ora	Firma