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Subject: 2018 mid-year progress report Vision Grant 2016 – **addendum July 2018**

July, 2018

Dear Mrs. Tsigas, members of the board of directors and members of the medical advisory board of the Preeclampsia foundation,

We would like to thank the Preeclampsia Foundation for the opportunity to investigate maternal cerebrovascular health after preeclampsia. Herewith our *extended* 2018 mid-year progress report for the Vision Grant 2016, for which a one-year no-cost extension of the “cerebrovascular health after preeclampsia project” has been granted. In spring 2017, our project protocols received approval from the Medical Ethics Committee of the Erasmus Medical Center Rotterdam after which we started with the MRI brain scans and cognitive tests May 2017. The study is “on track” and we expect to complete the project, i.e. finish the scanning process, 31 December 2018. Here after we will start with the complex process of analyzing and interpreting of the MRI scans and cognitive tests. After which we will start publishing the results. We estimate that the first analyses of the MRI scans and cognitive tests will be completed in May 2019, that is two years after start of the study. Our goal is to report results to you in the 2019 mid-year report Vision Grant.

Project goal:

The incidence of vascular brain diseases, such as dementia and stroke, is increasing. This is often due to damage to small blood vessels in the brain. This is mainly caused by risk factors for cardiovascular disease (CVD) including hypertension. Preeclampsia is a specific hypertensive disorder, which occurs during pregnancy. Preeclampsia is also an important risk factor for CVD later in life and might therefore also be associated with the development of damage to small blood vessels in the brain. This may then lead to an increased risk for vascular brain diseases. This study investigates the relationship between preeclampsia and damage to small blood vessels in the brain.

Study objectives:

1. To investigate cerebrovascular health in young women by examining the overall incidence of asymptomatic cerebral small vessel disease (cerebral white matter lesions, microbleeds and lacunar infarcts), which might be related to dementia and stroke in later life (neurodegenerative small vessel disorders).
2. To compare cerebrovascular health in women with a history of an uncomplicated pregnancy with cerebrovascular health of women with a history of preeclampsia.
3. To investigate specific risk factors for asymptomatic cerebral small vessel disease after a pregnancy complicated by preeclampsia.

Progress:

The “cerebrovascular health after preeclampsia project” is a sub-project of the ongoing Generation R study. Generation R is a prospective, population based, ongoing large birth cohort study from early pregnancy onwards. Almost ten thousand pregnant women and their children were included. All women gave birth between 2002 and 2006 in Rotterdam, the Netherlands. All data about their pregnancy and any complications, such as hypertension or preeclampsia are known and available in a structured database. Additional information about covariates encompassing for example smoking, parity and use of medication are also available.

For the current project, we use a nested case-control design in which women with a pregnancy complicated by preeclampsia (case group) will be matched with women with an uncomplicated pregnancy on age (control group), ethnicity and educational level and will be on average 13-14 years after the index pregnancy. All women will receive an MRI brain in the Sophia Children Hospital, Rotterdam. Together with the MRI brain scan, multiple cognitive tests and blood pressure measurements will be performed.

After acknowledgment of the Preeclampsia Foundation Vision Grant 2016 in September 2016 we finalized the study protocols regarding MRI sequences and the cognitive functioning tests in close collaboration with Departments of Epidemiology and Radiology of the Erasmus Medical Center Rotterdam. In spring 2017, our project protocols received approval from the Medical Ethics Committee of the Erasmus Medical Center Rotterdam.

We have started inviting eligible women for the MRI brain scan in April 2017. In May 2017 we actually performed the first MRI brain scans and cognitive tests. Of the 436 women with preeclampsia in our cohort, 43 are loss to follow-up (13-14 years after pregnancy) and 120 women decided not to participate in the MRI study. One woman sadly died and one woman could not be scanned due to medical problems. This results into a remaining maximum number of 297 includable women with preeclampsia. By the end of the study period we aim to have scanned 594 women (cases + controls). Until now May 2018, 60% of women have been scanned. The study is “on track” and we expect to complete the project, i.e. finish the scanning process, 31 December 2018.

The following sequences will be scanned to investigate asymptomatic cerebral small vessel disease:

- T1
- Diffusion Tensor Imaging (DTI)
- FLAIR
- T2-star
- 3D Phase Contrast
- enhanced Arterial Spin Labeling (eASL)

The T1 weighted scan is arguably the most important image we collect. The data collected from this scan is usually used in analyses with the other images. DTI measures water diffusion in the brain and is well suited to measure white matter tissue structure. FLAIR can give a much clearer view of the structures close to the cerebrospinal fluid, in example the periphery of the hemispheres and the periventricular regions. The images can be used to assess certain pathologies like white matter lesions and lacunar infarcts. T2-star is performed to assess cerebral microbleeds. 3D Phase Contrast allows the assessment of the total cerebral blood flow. eASL allows for the quantification of cerebral blood flow.

All participants have given written informed consent for the MRI brain scan and additional cognitive functioning tests. The total visit takes 1.5 hour. Every MRI scan will be checked within two months for any abnormalities by a dedicated team of doctors. In the unfortunate case of incidental findings that are of main importance, these will be reported to the participant and her own general practitioner. The participant will then be referred to the Department of Neurology of the Erasmus Medical Center Rotterdam.

We expect to start with the complex process of analyzing and interpreting of the MRI scans and cognitive tests in January 2019. After this we will start publishing the results. We estimate that the first analyses of the MRI scans and cognitive tests will be completed in May 2019, that is two years after start of the study. Our goal is to report results to you in the 2019 mid-year report Vision Grant.

(expected) Timeline:

- April 2017 approval from the Medical Ethics Committee of the Erasmus Medical Center Rotterdam
- May 2017 first MRI brain scans and cognitive tests and actual start of the study
- December 2017 participation rate of 30%
- May 2018 participation rate of 60%
- December 2018 *expected* completion of MRI brain scans and cognitive tests
- January 2019 *expected* start of analyzing and interpreting of the MRI scans and cognitive tests
- May 2019 *expected* first results and reporting of those results to the Preeclampsia foundation through 2019 mid-year report Vision Grant.

Some delay in the project has been caused by the premature delivery (after placental abruption) of the son of the main investigator in this project, Sarah Schalekamp-Timmermans. Her son died after delivery. One year no cost extension to complete the work was granted thereafter in May 2017.