1 Publishable Summary

Pre-eclampsia is a complex pathogenesis that requires a personalised medicine approach. The main goal of this project is therefore to develop a clinically robust predictive blood test for pre-eclampsia, using innovative technologies and utilising novel metabolite and protein biomarkers.

Summary description of project context and objectives

The IMPROvED (IMproved PRegnancy Outcomes by Early Detection) project is a multicentre clinical study aiming to assess and refine two innovative prototype screening tests for pre-eclampsia, a common complication of late pregnancy. Approximately 50 million babies are born to first time mothers worldwide every year and almost 1 in 20 of these pregnancies are complicated by pre-eclampsia. The condition is associated globally with 70,000-80,000 maternal and over 500,000 infant deaths annually. For the mother it can lead to acute problems in the liver, kidneys, brain and the clotting system, and pre-eclampsia is the most important cause of maternal death in Europe - accounting for 17-24% of all maternal deaths.

Identification of women at risk of pre-eclampsia is the first step to effective intervention and prevention. Current screening is based on the presence of clinical features however the majority of women who develop pre-eclampsia are first-time mothers, who commonly have no identifiable clinical risk factors in early pregnancy.

Prompted by the current absence of a clinically useful screening test for pre-eclampsia the IMPROvED consortium aims to develop a robust predictive blood test suitable for use in a clinical environment, employing innovative technologies and utilising novel metabolite and protein biomarkers. Project partners Metabolomics Diagnostics (Ireland) and MyCartis (formerly Pronota, Belgium) have developed two prototype screening tests (ProTest & MetTest) for pre-eclampsia which will be further refined and validated in IMPROvED with the aim of ultimately progressing to regulatory approval and clinical use.

5000 first time mothers will participate in the study by attending at least two and up to four visits with an IMPROvED midwife, in four European countries, Ireland, U.K., the Netherlands and Sweden. At each visit comprehensive clinical data, blood, urine and hair samples are collected. A customised IMPROvED Clinical Data and Biobank Management Database, specifically designed for data management in clinical trials and cohort studies, has been developed by project partner MedSciNet. In parallel to participant recruitment and validation of the ProTest and MetTest, project partner University of Groningen, the Netherlands will assess the health economic benefits of screening tests.

An additional primary aim of IMPROvED is to establish a high calibre pregnancy biobank, accessible to pregnancy researchers, housing samples derived from women attending multiple clinical centres at up to four time-points during pregnancy and representative of different healthcare models. An appropriate governance plan in compliance with ethical and data protection regulations will be developed during the project. **Fehler! Verweisquelle konnte nicht gefunden werden.** shows sample movement throughout the project; from collection and processing at each recruitment centre, to shipment of samples to UCC where sample reconfiguration will be performed allowing redistribution of a subset of samples to Metabolomics Diagnostics and MyCartis. The remaining samples will be housed in UCC forming the IMPROvED pregnancy biobank.

Description of the work performed since the beginning of the project and the main results achieved until the end of P2

The quality of both the clinical data and the biobanked samples collected is paramount to realising the aims of the project. The complexities of carrying this clinical study at 6 recruitment centres across four countries necessitated the implementation of a strong study framework to support the numerous work streams required. Consistency across recruitment centres was ensured by the production of standard operating procedures (SOPs), a toolkit of training materials and aids (including webinars and training videos), continuous monitoring of clinical data by local centre monitors (overseen by the Global Clinical Coordinator) and compliance with ICH-GCP and ethical requirements, ensured by the study monitor. In addition an EU tender process was employed to identify suitable consumable and freezer suppliers for the project ensuring consistency in biospecimen collection, processing and storage. Prior to initiation of recruitment study recruitment materials were developed (i.e. banners, posters, flyers) as well as participant information and consent forms. The study monitor ensured that ethical approvals across all centres were consistent and that all participants throughout the study gave the same level of informed consent including consenting to the future use of their samples stored in the biobank.

Recruitment is ongoing at six centre and almost 2,600 participants have been recruited (more than half the recruitment target). Response to the study is positive with almost 70% of women asked to participate, agreeing. Recruitment rates have risen significantly and are aided by women who enter the study, having a positive experience and making other pregnant women and the local community and health care providers aware of the project.

Over 1600 babies have been born to IMPROvED mothers and end of pregnancy outcome data is currently being collected and entered to the database. When a significant number of participants have had all data collected, monitored and signed off by the principal investigator samples will then be transferred to the Metabolomics Diagnostics and MyCartis. Both SMEs have significantly furthered the development of the two tests and are continually optimising and refining the process.

Work has begun on developing a biobank governance structure for the future biobank and this will continue throughout the study with input from the steering committee, the SAB and the EAB.

Initial preparatory work has also begun on the statistical plan and the health economic analysis ensuring that these tasks are primed to begin in earnest when the initial performance data is available for ProTest and MetTest.

Significant progress has been made in the dissemination of the project. A number of peer-reviewed articles have been published; consortium members have presented IMPROvED at numerous national and international conferences. Public awareness has increased through the website and Facebook page, interactions with patient groups and local media coverage (i.e. at the launch of recruitment at each centre). IMPROvED have presented public information stands at events aimed at pregnant women to increase awareness of pre-eclampsia and IMPROvED.

Expected final results and potential impacts

IMPROvED aims to develop a clinically useful screening test for pre-eclampsia which will enable identification in early pregnancy of women at risk of pre-eclampsia, and thus allow closer prenatal monitoring, early diagnosis, and timely intervention. Conservative estimates suggest that the appropriately targeted use of existing therapies (such as low dose aspirin) should reduce the overall incidence of pre-eclampsia by approximately 20%, but importantly with a greater reduction in early onset disease (30%). The reductions in the incidence of pre-eclampsia, particularly in early onset disease, will lead to reduced intrauterine, neonatal, childhood and long-term complications for babies. An effective screening test would facilitate stratification and targeting of limited

resources within healthcare systems and economic assessments of screening for pre-eclampsia have consistently found that screening for pre-eclampsia is cost-effective under various scenarios.

Dissemination activities will lead to greater awareness of the risks of pre-eclampsia and will foster a culture where open discussion is encouraged. Members of the PAB have reported that in certain instances maternity care givers do not discuss pre-eclampsia with pregnant women as they feel it will frighten/stress the women. However other members have reported the effectiveness of open discussion and in the Netherlands all pregnant women are supplied with a leaflet from the Dutch patient group containing pre-eclampsia information. In addition, the availability of a reliable predictive screening test early in pregnancy should encourage maternity care givers to speak more freely about pre-eclampsia.

The residual IMPROvED biobank housed in UCC will be a valuable future resource for pregnancy researchers who would not normally have access to samples from large cohorts of patients. The precursor to IMPROvED, the SCOPE (Screening for Obstetric and Pregnancy Endpoints) study biobank (http://www.scopestudy.net/) is still providing samples to international researchers. Therefore we expect that the IMPROvED study will lead to an expansion in pregnancy research resulting in greater understanding of pregnancy complications and potential strategies to combat these complications.

The publishable summary has also been uploaded in the online forms in the ECAS Participant Portal.