Meeting: Consortium Meeting		**Location:** Uppsala Universitet, Sweden
Date: 15-16 September 2015	**Duration:** 2 days	**Recorders:** Bridget Glaysher

Attendees

Name	Initials	Organisation	Role
Colin Palmer	CP	UNIVDUN	Coordinator
Moneeza Siddiqui	MS	UNIVDUN	Participant
Myra White	MWh	UNIVDUN	Participant
Cyrielle Maroteau	CM	UNIVDUN	Participant
Bridget Glaysher	BG	UNIVDUN	Participant
Anke-Hilse Maitland-van der Zee	AHM	UU	Participant
Folkert Asselbergs	FA	UU	Participant
Hamid Mahmoud Pour	HM	UU	Participant
Ekaterina Baranova	EB	UU	Participant
Ana Alfirevic	AAl	UOL	Participant
Dan Carr	DC	UOL	Participant
Kate Bloch	KC	UOL	Participant
Mia Wadelius	MWa	UUP	Participant
Malgorzata Karawajczyk	MK	UUP	Participant
Mathias Brännvall	MB	UUP	Participant
Ulrica Ramqvist	UR	UUP	Participant
Ann-Christine Syvänen	ACS	UUP	Participant
Ulrika Liljedahl	UL	UUP	Participant
Niclas Eriksson	NE	UUP	Participant
Leif Nordang	LN	UUP	Participant
Sofie Collin	SC	UUP	Participant
Hugo Kohnke	HK	UUP	Participant
Alun McCarthy	AM	PGXIS	Participant
Anu Aaspõllu	AAa	ASPB	Participant
Eva Rye Rasmussen	ERR	Univ Copenhagen	Participant
Mikko Niemi	MN	Univ Helsinki	ESAB

Apologies: Panos Deloukas (ESAB), Olivier Delrieu (PGXIS)

Actions

ID	Description	Owner	Deadline
150916-01	UNIVDUN to send control data to UOL	CM (UNIVDUN)	ASAP
150916-02	Check literature to review if/how to include pilot samples in main sequencing runs	WP3	ASAP
150916-03	Investigate extension requirements	BG	Next TC
150916-04	Collate patient info into one spreadsheet	WP1/WP2	End September

Meeting Summary

Day 1: 15th September 2015

Plenary Session 1 – *Prefekten in Akademihotellet*

Welcome to Uppsala: Mia Wadelius
MWa welcomed everyone to the meeting and explained the agenda and housekeeping issues for the meeting.

Welcome to the Consortium: Colin Palmer (CP)
CP provided a detailed overview of the project, covering all aspects including the consortium partners, the main objectives of the project and how the Work Packages (WPs) fitted together to deliver these.

WP1
AAl introduced WP1 and gave a recap of the standardised phenotype determined by the consortium to define patient inclusion. This definition was finalised at the phenotype standardisation workshop and subsequently published.

Myopathy recruitment update (Ana Alfirevic)
AAl outlined the wide range of strategies employed in terms of patient recruitment. 260 cases had been recruited for the project as a whole, with 57 more from UOL identified as potential recruits. MS said that UNIVDUN had 16 new cases to contact and expected to have more when the next download of GoSHARE takes place. MWa said that UUP had 1 new case with from whom DNA had been collected, and three further cases for potential recruitment.

The low rate of patient recruitment via the Clinical Practice Research Datalink (CPRD) route (approximately 20% success rate) attending was discussed and it was noted that in the first phase of the statin myopathy patient recruitment in 2010 collection of saliva had a lower rate of participation (17%) than collection of blood (35%).

AAl then gave details of number of patients already recruited who had taken various

different types of statin and how this compared to the control groups.

Replication cohort from Bruce Psaty USA (Ana Alfirevic)

AAl gave details of samples sequenced in the US by Bruce Psaty's group. 429 patients had been sequenced and they expected to have 96 more. This should give enough collectively to stratify the analysis for individual statins.

FA asked if a gene based analysis had been carried out, AAl replied that it had but no results were available yet.

AAl mentioned that 10 samples sequenced in the US will also be sequenced by PREDICTION for comparison. There was discussion around how to analyse the two different cohorts.

MN asked about statin dose and drug:drug interactions. CP/AAl replied that patients were stratified by statin type and a minimum dose for inclusion in the study had been set. There is data available on all the medications each participant had taken. It was also noted that if too many measures were taken into account the analysis would lose statistical power.

WP2

Angioedema recruitment progress (Mia Wadelius)

MWa introduced WP2 and recapped the background to the study and current understanding of the way ACE inhibitors work. MWa then described the current state of patient recruitment. 250 cases and 250 controls have been recruited for the discovery cohort. Recruitment for the replication cohort is ongoing. UUP have identified 58 cases and have DNA from 11 of these. MWh said that UNIVDUN have identified 3 additional cases and expect to have more through contact with centres in Aberdeen. EB said UU have 4 additional cases and AAl mentioned UOL have 20. A discussion of the difficulties in recruiting followed, the main difficulties being patients not turning up or their case not passing adjudication.

MWa then gave details of a pre-PREDICTION study carried out at UUP which had found two clinical and one genetic possible risk factors. There was discussion around the best approach for getting this study published. It was suggested that qPCR analysis could easily be done in the PREDICTION samples from UU, UNIVDUN, UOL and Univ Copenhagen to replicate the genetic variant that is located in an intron and thus may not be detected by exome sequencing.

Replication cohort from Denmark (Eva Rye Rasmussen)

ERR outlined her interest in the PREDICTION project and gave details of the recruitment and sample collection she had carried out in Denmark. ERR has identified 45 patients with ACE inhibitor angioedema, and has written consent from 35 of them. So far 14 patients have provided a blood sample. She has approval to recruit many more, however, time and funding constraints mean it is unlikely this will be done. ERR will focus on collecting samples and data from those patients

already recruited.

There was discussion around patient recall, patients in Denmark all had relatively recent disease so their ability to recall details was good. The type of sample collected from each patient was also discussed.

WP5

WP5 update (Anke-Hilse Maitland)
AHM introduced WP5 and mentioned 2 publications which had come from clinical record studies. AHM also mentioned the main challenge for WP5 was to decide which phenotypes to choose.

Statin Intolerance replication (Moneeza Siddiqui)
MS presented studies carried out at UNIVDUN investigating variants of the CKM and LILRB5 genes in relation to statin intolerance. Carriers of a particular variant of the CKM gene are unable to produce high levels of CK, calling in to question the use of CK as a biomarker. Carriers of a rare allele of the LILRB5 gene are more likely to tolerate statins.

There was discussion around the controls used for these studies.

ACEI Intolerance replication (Hamid Mahmoud Pour)
HMP presented studies carried out at UU. An investigation patterns of ACEi prescriptions revealed that those suffering heart or renal failure were most likely to discontinue treatment. A study investigating continuation of ACEi therapy after angioedema found that almost half of those suffering angioedema continue ACEi therapy and the risk of a subsequent angioedema was much higher in these patients.

There was discussion around how subsequent angioedema was defined, as opposed to a second visit about the original event. ERR asked how the patients were defined. HMP replied they were GP patients specifically coded for angioedema.

Day 2: 16th September 2015

Plenary Session 2 –*Clasonsalen*

WP3

WP3 introduction (Colin Palmer)
CP introduced WP3 and mentioned extensive work that had been carried out on harmonisation. Agilent SureSelect Human All Exon v5 had been selected as the method and had proved very consistent between centres. 4 different pipelines had been considered for calling and a decision was still to be made on which to use. It is intended to get the full dataset to PGXIS by November.

Sequencing progress Dundee (Cyrielle Maroteau)
CM presented data on harmonisation work that had been done at UNIVDUN and gave an update on the progress of sequencing stain and ACEI cases.

There was discussion around control matching. It was agreed that **UNIVDUN would send details of the controls to UOL for comparison**. There was also discussion of the different number of variants identified at the different centres.

Sequencing progress Liverpool (Kate Bloch)
KB presented data on harmonisation work that had been done at UOL and gave details of the different pipelines used.

There was discussion of the differences between variants, and the best method for doing the analysis. AAl mentioned that UOL had a site licence for the Ingenuity software. AM asked what data would be sent to PGXIS. It was agreed that the consensus dataset would be sent, giving fewer variants, but ones which are found in all analyses.

Sequencing progress Uppsala (Ulrika Liljedahl)
UL gave an introduction on the UUP sequencing facility and an update on the progress of sequencing the PREDICTION samples.

There was discussion around re-running the pilot samples as an overall control. Different opinions were expressed on whether it would be better to run them during sequencing, after the sequencing and whether either would be a useful exercise. AAl suggested **checking the literature to see how similar studies had approached this**.

WP4, WP6, WP7 and Management

WP4 (Alun McCarthy)
AM gave an explanation of the taxonomy3 analysis and presented data on a recent study of RA carried out using this method of analysis. AM explained that WP4 was awaiting data from WP3 before it could really begin, however some work had gone into determining a suitable format for the data to be transferred in.

There was discussion around the mathematical principles involved in the analysis and how this differs from other methods of analysing this type of data.

WP6 (Colin Palmer)
CP gave an overview of the work that would be covered by WP6, the aim of which is to make biological sense of the genetic markers found. This work package would not be able to start until data was available from other work packages. Preliminary data suggested that immune system may be involved so WP6 may involve investigating these T cells.

WP7 (Anu Aaspõllu)
AAa mentioned that WP7 was waiting for input from the other work packages before work could get underway. AAa gave an update on work that ASPER had done for other projects including developing a test for a SLCO1B1 variant which has been associated with Statin-induced myopathy.

There was discussion of how much interest this test had generated, and the types of other tests that ASPER was developing.

Management (Bridget Glaysher)
BG mentioned the two main management tasks for the remainder of the project were to submit the remaining deliverables and to co-ordinate the final report.

Remaining deliverables were discussed one-by-one and expected delivery dates were reviewed. It was agreed that deliverables 1.4, 2.2 and 7.3 could be submitted as soon as possible, deliverable 3.1 would be delayed until the end of Oct 15, and 3.2 end of November 15. It was also foreseen that D4.1 and 4.2 would probably not be complete until the end of May16. Other deliverables should be submitted on time as detailed in the grant agreement.

There was general concern however about the likelihood of all the deliverables to be submitted in the final month being completed on time. The possibility of applying for an extension was raised. CP/BG noted that work done in the extension period would have to be funded from the existing budget. BG would **look into this and it would be discussed at the next TC**.

BG concluded the session with a brief overview of the requirements for final

reporting.

Wrap up discussions

The final discussion involved two main areas:

Firstly, it was agreed that all the patient information should be **brought together into one single file by the end of September/ beginning of October.** This should include only the basic information required for adjudication of cases. There discussion on the variant analysis. AAl suggested it was important to make the analysis plan which will take into consideration several clinical characteristics of our patients and controls. AAl was willing to write an outline and send it round to all those involved after the full data sets become available. There was also discussion of stratification. A TC would then be set up to discuss this further.

Secondly, the possibility of future funding was discussed. Two calls under H2020 were of potential interest to the consortium. After discussion it was felt that the most appropriate call was 'New concepts in patient stratification'. There was preliminary discussion around how to make the proposal unique, and sufficiently innovative and visionary.

CP thanked everyone for attending and thanked MWa for making the arrangements for the meeting. The meeting was then closed.

Next Meeting

Location: TBC	**Date:** TBC