

#### Publishable Summary

The AMYPAD Prognostic and Natural History Study (PNHS) submissions and approvals procedure followed a similar 2-step strategy as the EPAD LCS, in which the first activation of Sites included all the partners (Wave-1), and then subsequently all the subcontractor Sites (Wave-2). This shared strategy was also in line with the original plan of having AMYPAD PNHS sponsored by the University of Edinburgh, when the study was expected to be approved as a direct amendment to the EPAD LCS protocol. However, after delays in establishing the sponsorship role, in July 2018 the sponsorship of the study was moved to VUmc and submission could commence.

In line with the VUmc sponsorship and the expertise of Wave-1 sites, the submissions were undertaken by each individual site with the supervision of VUmc. In specific situations, sites led national submissions and/or amendments to include additional sites within the same country. The Sponsor role is to lead the submission process by sharing standard documents, providing guidance and maintaining oversight.

For the PNHS, the AMYPAD partners who are potential Wave-1 centres for the study consist of the following: UEDIN, CHUT, BBRC, VUmc, KI, UNIGE and UKK. In addition, a number of Wave-2 sites are considered, with the majority originally aligned with the EPAD Trial Delivery Centres (TDCs), but in view of study timelines, slow recruitment into EPAD LCS and slow start of PNHS, additional sites which are not in EPAD but can bring in parent cohorts are also considered. This expansion in the number of study sites is also directly related to the results of the IMI Mid-term review, where the risks of not achieving recruitment goals have been highlighted and initiated mitigation strategies.

Considering the above, this document will outline the processes of undergoing submission and obtaining approvals in both Wave-1 and Wave-2 Sites, detail any challenges that led to delays, and provide expected timelines for remaining Sites. In short, at the time of writing, all Wave-1 Sites with the exception of UKK have been approved and are actively recruiting, and 7 Wave-2 Sites have also received approvals and will be activated soon.

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