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D4.9 Establishment of the DSMB

WP4 – EPAD Cohort and EPAD Trials

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Confidential Information (please indicate here if any sections contain confidential information and should NOT be made publically available)


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DEFINITIONS

- Partners of the EPAD Consortium are referred to herein according to the following codes:
 - **Janssen.** Janssen Pharmaceutica NV (Belgium)
 - **UEDIN.** The University of Edinburgh (United Kingdom)
 - **UOXF.** Masters and Scholars of the University of Oxford (United Kingdom)
 - **BBRC.** BarcelonaBeta Brain Research Center (Spain)
 - **SYNAPSE.** Synapse Research Management Partners S.L (Spain)
 - **KI.** Karolinska Institutet (Sweden)
 - **VUMC.** Stichting VUmc (Netherlands)
 - **UCAM.** Masters and Scholars of the University of Cambridge (United Kingdom)
 - **MRC.** Medical Research Council (United Kingdom)
 - **BERRY.** Berry Consultants LLP (United Kingdom)
 - **UNIGE.** Université de Genève (Switzerland)
 - **RUMC.** Stichting Katholieke Universiteit (Netherlands)
 - **CU.** Cardiff University (United Kingdom)
 - **CHUT.** Centre Hospitalier Universitaire de Toulouse (France)
 - **IQVIA.** IQVIA, Ltd (United Kingdom)
 - **AE.** Alzheimer Europe (Luxemburg)
 - **EMC.** Erasmus Universitair Medisch Centrum Rotterdam (Netherlands)
 - **APHP.** Hôpital de la Salpêtrière (France)
 - **INSERM.** Institut National de la Santé et de la Recherche Médicale (France)
 - **ULEIC.** University of Leicester (United Kingdom)
 - **IXICO.** IXICO Technologies Ltd (United Kingdom)
 - **ARACLON.** Araclon Biotech S.L (Spain)
 - **FRAUNHOFER.** Fraunhofer-Gesellschaft zur Förderung der angewandten Forschung e.V. (Germany)
 - **Eisai.** Eisai Inc (United States)
 - **SARD.** Sanofi-Aventis Recherche & Développement (France)
 - **NOV.** Novartis Pharma AG (Switzerland)
 - **BI.** Boehringer Ingelheim International GmbH (Germany)
 - **Eli Lilly.** Eli Lilly and Company Ltd (United Kingdom)
 - **HLU.** H. Lundbeck A/S (Denmark)
 - **Takeda EU.** Takeda Development Centre Europe Ltd (United Kingdom)
 - **AC Immune.** AC Immune SA (Switzerland)
 - **Biogen.** Biogen Idec Limited (United Kingdom)
 - **Amgen.** Amgen NV (Belgium)
 - **Pfizer.** Pfizer Limited (United Kingdom)
 - **UCB.** UCB Biopharma SPRL (Belgium)
 - **ARIDHIA.** Aridhia Informatics Ltd (United Kingdom)
 - **ROCHE.** F. Hoffmann - La Roche (Switzerland)
 - **UKK.** University Hospital of Cologne (Germany)
 - **MSD.** Merck Sharp & Dohme (United States)


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- **Grant Agreement.** The agreement signed between the beneficiaries and the IMI JU for the undertaking of the EPAD project (115736).
- **Project.** The sum of all activities carried out in the framework of the Grant Agreement.
- **Work plan.** Schedule of tasks, deliverables, efforts, dates and responsibilities corresponding to the work to be carried out, as specified in Annex I to the Grant Agreement.
- **Consortium.** The EPAD Consortium, comprising the above-mentioned legal entities.
- **Project Agreement.** Agreement concluded amongst EPAD participants for the implementation of the Grant Agreement. Such an agreement shall not affect the parties' obligations to the Community and/or to one another arising from the Grant Agreement.

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EXECUTIVE SUMMARY

This document describes the progress made towards establishment of the data safety monitoring board for the EPAD Proof of Concept trial. The position of the DSMB within the PoC platform is outlined along with the high level roles and responsibilities of the DSMB. A proposed data flow for the DSMB is presented. Finally materials for the selection of the DSMB chairperson were prepared. It was not possible to complete the establishment of the DSMB because the PoC trial was not initiated with an intervention.

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1. Introduction

The purpose of this deliverable is to document the progress made towards establishment of the data safety monitoring board (DSMB) for the EPAD Proof of Concept (PoC) trial. The following work was undertaken:

- Establishing the position of the DSMB within the PoC Platform
- High level roles and responsibilities of the DSMB
- Proposed data flow for the DSMB
- Preparation of materials for selection of the DSMB chairperson

It was not possible to complete the establishment of the DSMB because the PoC trial was not initiated with an intervention.

2. Position of DSMB

The DSMB was included in the PoC platform set-up as shown in Figure 1 to act as an independent advisory board on safety for the PoC trial, reporting to the Appendix Steering Committee (ASC). It was planned that one DSMB would serve all active Appendices but with flexibility in membership numbers and required experts depending on the interventions and any specific safety considerations.

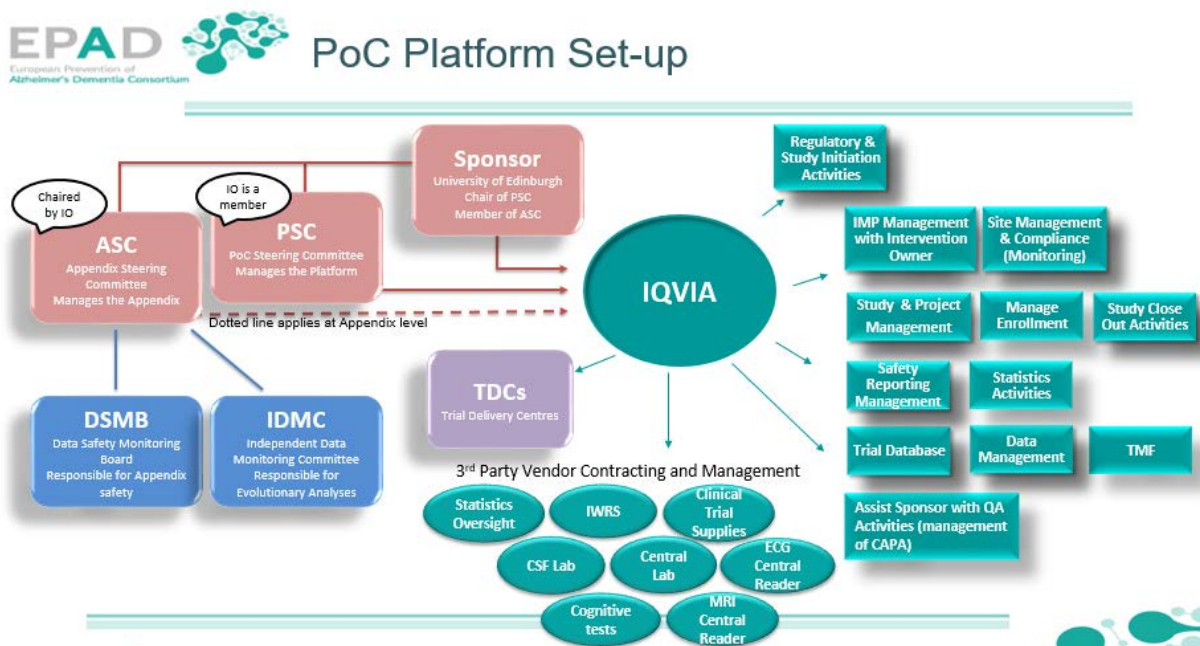



Figure 1. PoC Platform Set-up, showing DSMB in blue box with reporting line to ASC.

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3. DSMB Role and Responsibilities

The DSMB was planned to be an expert advisory group who function as a review committee independent from the sponsor and study team to review study data to ensure the safety of subjects enrolled in the EPAD PoC trial. As such, the primary objective of the DSMB is to review the available clinical data and provide recommendations regarding the continuation of the study, from a safety perspective to the study team. It was planned that these reviews would occur approximately quarterly throughout each year, as well as on an ad hoc basis, if needed. The DSMB would be responsible for providing recommendations related to Appendix safety to the relevant Appendix Steering Committee. The recommendation should indicate the appropriateness of continuing the study, from a safety perspective, as well as any other recommendations relevant to study conduct and/or patient safety. If recommendations related to Appendix safety may impact the Master Protocol or PoC platform, the DSMB should also report to the PoC Steering Committee.

Although no direct review of efficacy data by the DSMB was planned, as this was to be the responsibility of the IDMC, if required for an individual Appendix, the DSMB may also be asked to review clinical and biomarkers outcomes and provide recommendations accordingly.

The DSMB was to be composed of five members: one Chairperson, and four additional individuals who collectively have experience/expertise in the management of patients with Alzheimer’s disease and/or geriatrics and in the conduct and monitoring of randomised clinical trials. The DSMB chairperson would provide leadership, ensure the board operated according to the charter and be responsible for all DSMB communications and recommendations, supported by an administrative coordinator. The Chairperson should also assist in the selection of the other members.


3.1. ASC Role and Responsibilities

The ASC was to be responsible for ensuring the required data was made available to the DSMB for their review. The preparation of the datasets was to be done by the IQVIA, see section 4 for a description of the data flow for the DSMB.

It was to be the responsibility of the ASC to implement any changes required to the ISA as a result of the DSMB recommendations. The ASC was also to be responsible for reporting to the PSC if any intended changes to the ISA may impact other Appendices.

4. DSMB Data Flow

The data flow begins with at the trial delivery centre with the data being entered in the eCRF and then reaching IQVIA database (see Figure 2). Data required for the DSMB reviews would then be transferred by the IQVIA data management team to the IQVIA statistical analysis team (IQVIA SSG in diagram). The IQVIA SSG will then prepare and transfer the pre-defined datasets to the DSMB. The specifications for

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these datasets and transfers was to be outlined in an Appendix specific DSMB charter and data transfer agreement.

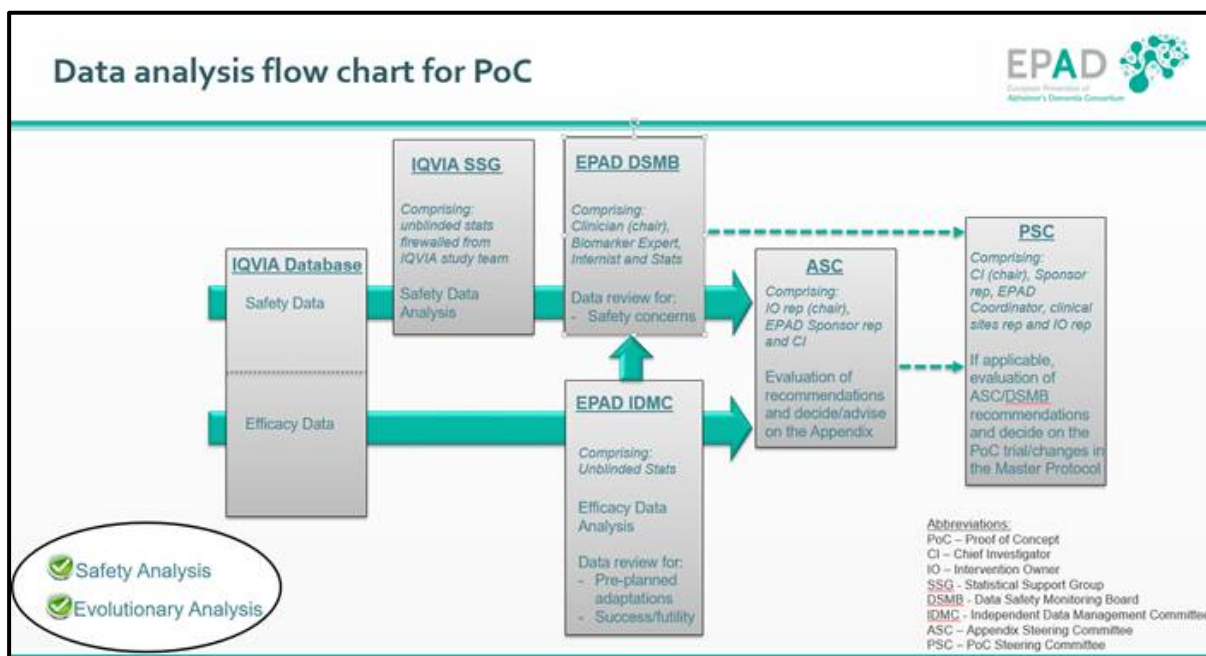




Figure 2. Data flow, showing DSMB data flow and reporting lines across top of figure.

5. Materials to aid selection of DSMB chairperson

A one page summary overview of the DSMB chairperson requirements (see Annex 1) was prepared as well as a presentation on the DSMB remit. The purpose of these documents was to inform potential candidates for DSMB chairperson about the position, role and purpose of the DSMB but they were not used because an intervention for the PoC trial was not secured.

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ANNEXES

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Annex I. Data Safety Monitoring Board – Chairperson Requirements for the EPAD Proof of Concept Trial

A double-blind, randomized, placebo-controlled, adaptive, Proof-of Concept (PoC) platform clinical trial of multiple interventions for the secondary prevention of Alzheimer’s Dementia in subjects from preclinical to prodromal stages of Alzheimer ’s disease.

Introduction: EPAD PoC Protocol

The EPAD PoC trial is an adaptive clinical trial with an aim to assess the efficacy and safety of multiple interventions for the secondary prevention of Alzheimer’s dementia. The interventions can be tested simultaneously, with the potential for new interventions to be added sequentially, and will be compared to common placebo data. The primary objective of the trial is to evaluate the potential for a reduction in the rate of clinical decline as measured by the primary cognitive clinical endpoint.

EPAD PoC DSMB Responsibilities

The EPAD PoC DSMB is an expert advisory group who function as a review committee independent from the sponsor and study team to review study data to ensure the safety of subjects enrolled in the EPAD PoC trial. As such, the primary objective of the DSMB is to review the available clinical data and provide recommendations regarding the continuation of the study, from a safety perspective to the study team. It is planned that these reviews will be scheduled to occur quarterly throughout each year, as well as on an ad hoc basis if needed.

Composition of EPAD PoC DSMB, Experience and Commitment

The DSMB is planned to initially be composed of five members: one Chairperson, and four additional individuals who collectively have expertise in the:

- management of patients with Alzheimer’s disease;
- statistical methods for clinical trials;
- sequential analysis of trial data.

The DSMB Chairperson will serve in a leadership role to the DSMB therefore the person selected should have previous experience of chairing a DSMB or have extensive experience as a member of a DSMB, in the field of Alzheimer’s disease. The DSMB chairperson will provide input into identifying and selecting other members of the committee. The DSMB will be supported by an administrative coordinator for meeting set-up, minute taking etc. This may be the chairperson’s own administrator or an already established EPAD administrator.

DSMB meetings are initially planned to be quarterly throughout the duration of the trial, predominantly via webex/teleconference. Although the DSMB members should be prepared to meet face to face on occasion, if necessary. The time commitment for the DSMB chairperson is initially expected to be one day per quarter to the DSMB activities, with appropriate payment outlined in a contract. If making use of their own administrator, it is anticipated this would be recompensed at approx. 1 day per year. The chairperson and all DSMB members are asked to make an initial commitment of 5 years to the committee.