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European Prevention of Alzheimer's Dementia Consortium
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D2.7 Update#1 to the design based on disease risk-model and scientific re-assessment, including analysis of new interventions

WP2 – Statistical/Methodology Engine Room

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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)
- **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.

EXECUTIVE SUMMARY

This report provides an alternative analysis method for the EPAD Proof-of-Concept (POC) phase II study and the statistical operating characteristics associated with this analysis. The proposed primary endpoint in the EPAD POC is the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). Another common endpoint in Alzheimer's disease trials is the Clinical Dementia Rating Scale Sum of Boxes (CDR-SOB). Here we explore an alternative POC analysis method for CDR-SOB, as RBANS and CDR-SOB may quantify different aspects of disease progression. The CDR-SOB model proposed here provides a well-powered analysis method for the POC trial. With further development or used in conjunction with other covariates, this alternative analysis method could supplement the EPAD POC primary analysis.

We explore an innovative analysis method for the Clinical Dementia Rating Scale Sum of Boxes (CDR-SOB) score based on data leveraged from the EPAD Longitudinal Cohort Study (LCS). The innovative analysis method described in this report is a Bayesian ordinal longitudinal disease progression model (tteDPM) that describes the time it takes for participants with Alzheimer's disease (AD) to progress across the different levels of the CDR-SOB score. The tteDPM is a multiple time-to-event model that captures the time that AD participants spend at each CDR-SOB score before progressing to the next higher score. It characterizes the potential treatment effect in slowing the progression of AD using a single parameter, a Disease Rate Ratio (DRR), to capture the rate of disease progression in treated participants relative to placebo participants.

The design of the PoC study is a platform trial in which there is a master protocol that describes the globally specified aspects of the trial that all interventions follow. Design flexibility is enabled through an intervention-specific appendix that allows customization of certain protocol parameters for each intervention. Here we present the operating characteristics for the tteDPM alternative analysis across a range of flexible protocol parameters including the enrolment population, sample size, and length of follow up. These operating characteristics are based on clinical trial simulations that leverage the EPAD LCS data. Virtual patients are simulated within virtual trials, and this simulated data is analysed using the tteDPM. Results of these virtual trials are tabulated and summarized, providing information on the value of supplementing the primary analysis with this alternative analysis.

These simulations use the EPAD LCS data available at time of report and can be updated as data continues to accumulate.

1. INTRODUCTION

The Bayesian ordinal longitudinal disease progression model (tteDPM) is proposed as an alternative analysis in the EPAD POC for the efficacy endpoint, Clinical Dementia Rating Scale Sum of Boxes (CDR-SOB) score. This model describes the time it takes for participants with AD to progress across the different CDR-SOB levels, assuming underlying monotonic disease states, thereby characterizing the progression of the disease. Alternative disease progression modeling approaches include the Alzheimer's Pre-dementia Clinical Trial Enrichment Tool[1] from the Critical Path Institute's Critical Path for Alzheimer's Disease (CPAD) and multi state modeling under a Markov assumption, such as that proposed in Kalbfleisch and Lawless [2]. The tteDPM is similar in nature to the Kalbfleisch and Lawless model with both Markov and semi-Markov assumptions in a Bayesian framework.

The effect of a disease slowing treatment is incorporated into the model using a single parameter, the Disease Rate Ratio (DRR), that captures the rate of disease progression in treated participants relative to placebo participants. Thus, the tteDPM allows for modeling disease-modifying slowing in the decline of AD participants, as measured by CDR-SOB.

Here, we leverage the EPAD LCS data and the tteDPM to model the progression time of AD participants, as measured by CDR-SOB, as a function of amyloid and clinical status. We then calculate trial design power by utilizing the progression modeling in possible future clinical trials, potentially including the EPAD POC.

2. DISEASE PROGRESSION MODEL

Disease progression modeling aligns participants based on where they are within the course of a progressive disease. Specifically, a participant early on in the progression of disease may progress more slowly than a participant with more advanced progression. Disease progression modeling accounts for the difference in progression as a function of underlying disease state. Here, we use a Bayesian ordinal longitudinal disease progression model to capture the time that subjects spend in each disease state before transitioning to a worse disease state, characterizing these states using the ordinal CDR-SOB score.

2.1. CDR-SOB NATURAL PROGRESSION

CDR-SOB scores are collected for participants in the EPAD LCS. We include patients with amyloid status consistent with pathogenesis (Amy+) at baseline in the LCS in our analysis. These Amy+ participants can be further stratified into those without cognitive impairment (Cog-) and those with cognitive impairment (Cog+). We include the Amy+Cog- and Amy+Cog+ subgroups to illustrate the impact of baseline disease state on

disease progression. **Figure 1** summarizes the EPAD LCS data on CDR-SOB as a function of length of follow-up. As expected, participants with cognitive impairment have a consistently higher mean CDR-SOB score than participants without cognitive impairment. Interestingly, the change in CDR-SOB over time does not vary greatly between participants with cognitive impairment and those without cognitive impairment. Measurements of CDR-SOB scores in the Cog+ subgroup are more variable than in the Cog- subgroup, which may be due to the floor effect of CDR-SOB in the Cog- subgroup. Observed CDR-SOB scores range from 0 to 4 in the Cog- subgroup and from 0 to 5.5 in the Cog+ subgroup. Inferences on disease progression are limited by the distribution of the available CDR-SOB data. In this case, inferences are based baseline CDR-SOB values between 0 and 5.5.

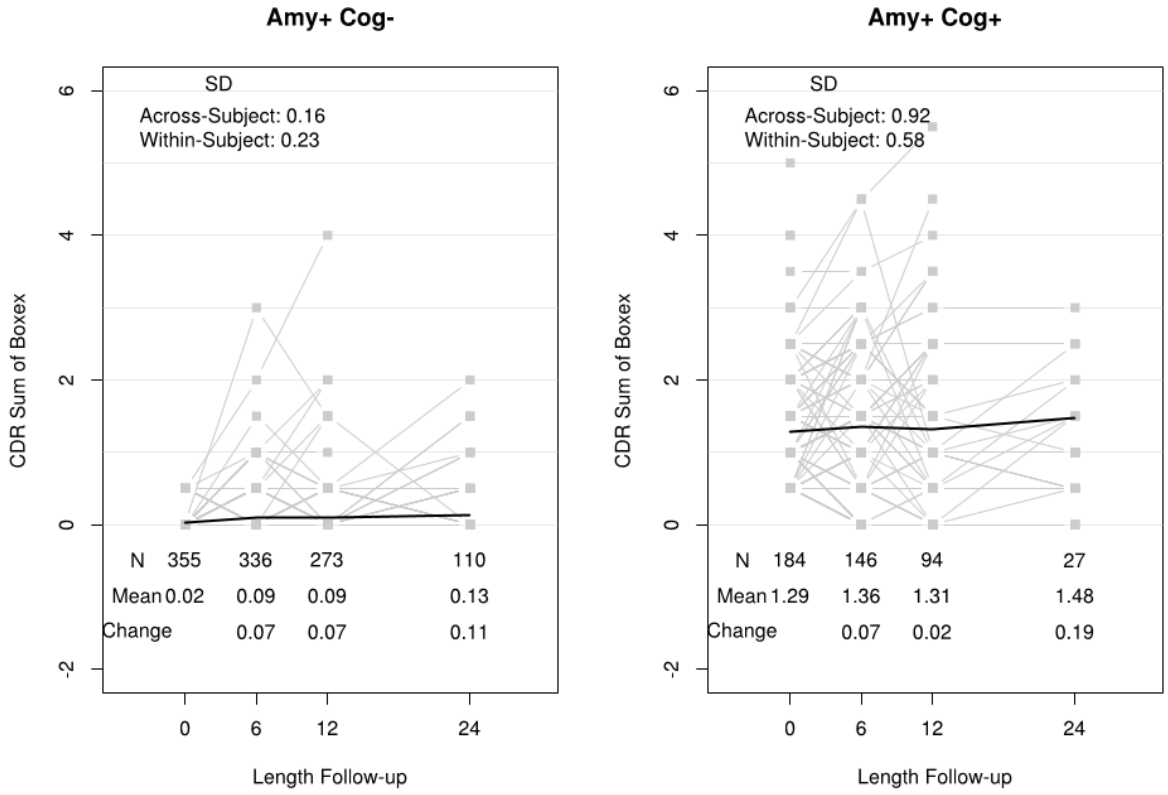

Figure 1. *Natural disease progression measured by CDR-SOB as a function of length of follow-up in the EPAD LCS. Data for participants with amyloid status consistent with pathogenesis but no cognitive impairment (Left) have lower CDR-SOB scores on average than participants with amyloid status consistent with pathogenesis and cognitive impairment (Right). The difference between the Cog+ and Cog- subgroups is less noticeable for the change in CDR-SOB. Additionally, the Cog+ subgroup has more across-subject and within-subject variability compared to the Cog- subgroup.*

We assume that each CDR-SOB score corresponds to an underlying disease state. The CDR-SOB natural progression data is used to estimate the mean time that a participant spends in a given disease state before transitioning to the next higher disease state, and this information is leveraged in the disease progression modeling. Specifically, initial

hazard rate assumptions are based on the total exposure time within a single disease state and the event rate corresponding to transitioning out of that disease state to the next worse disease state, across all participants. **Figure 2** allows us to visualize exposures and events within the EPAD LCS in both participants without cognitive impairment and participants with cognitive impairment. The analysis model assumes monotonicity, and exposures and events were calculated imposing monotonicity. which is further discussed in **Section 2.3**. Additionally, we use the midpoint when summarizing exposure in **Figure 2**, while the analysis model estimates latent states. Details of the model are discussed in **Section 2.2**.

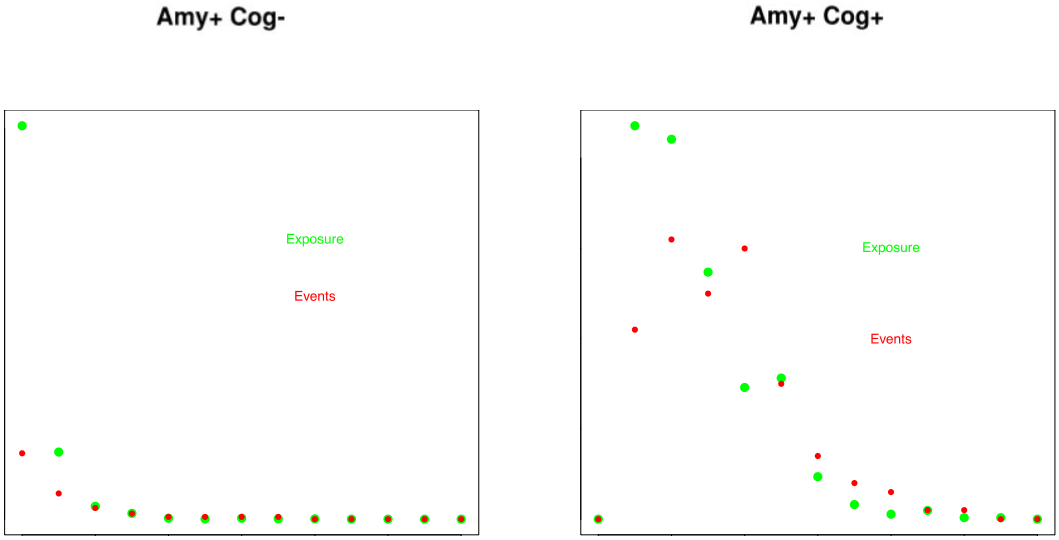

Figure 2. *Total exposure time (in years) and number of events (jumps) observed in the monotonized EPAD LCS data. Participants with amyloid status consistent with pathogenesis but no cognitive impairment (Left) have greater exposure time but fewer events (less disease progression) on average than participants with amyloid status consistent with pathogenesis and cognitive impairment (Right).*

2.2. DISEASE PROGRESSION ANALYSIS MODEL

Here we describe the conceptual and statistical underpinnings of the disease progression analysis model. The Bayesian ordinal longitudinal disease progression model is used to model the CDR-SOB endpoint, where each CDR-SOB score corresponds to an underlying disease state. The tteDPM assumes that the observations of disease states within a participant will be nondecreasing (increasing or staying the same). This assumption of monotonicity is further discussed in **Section 2.3**.

The tteDPM is a multiple time-to-event model where the transitions from each disease state to the next higher disease state are called “jumps”, which characterize events corresponding to a worsening in cognitive function. The time to transition (jump) from

one state to the next state is modeled as having an exponential distribution with differing hazard rates depending on the disease state.

Figure 3 shows hypothetical data from a single participant to describe the conceptual foundation for the progressive disease states modeled by the tteDPM. The state of the disease *k* is not observed continuously. Instead, we observe the state of the disease at each visit. Thus, the precise times when participant *i* transitions from state *k* to state *k+1*, $\gamma_{k,i}$, aren't observed but are modeled as latent variables within the Bayesian structure. We observe the state of a participant at times t_1, t_2,..., t_T up to a final visit at time T. These times may differ by participant. The observed disease states for a participant occur at the visits and are labeled as $x_1, x_2, \ldots, x_T$, which correspond to the CDR-SOB score at that visit. We label the disease states *k=0, 1, 2, ..., 35, 36.* Thus, a CDR-SOB score, x_t, of 0 corresponds to state *k=0*, a CDR-SOB score of 0.5 corresponds to state *k=1*, and so on.

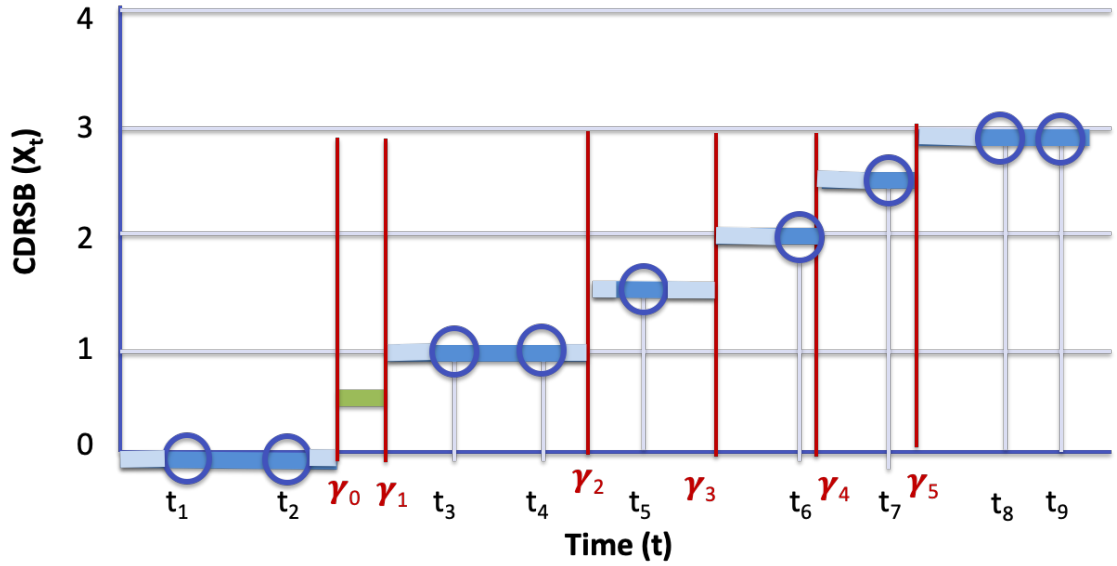

Figure 3. *Hypothetical disease course of a single participant measured by CDR-SOB score as a function of time. The participant i is observed (circle) in a given state when the CDR-SOB score is measured at a clinic visit. The time spent in that state may be known (horizontal blue line) or unknown (horizontal light blue line). The participant may pass through a state altogether between visits (horizontal green line). The participant transitions out of a disease state k and into the next higher disease state k+1 at time* $\boldsymbol{\gamma_{k,i}}$*, represented by a red vertical line. Using this framework, we can capture the time that a participant spends in each disease state and model the hazard rate for each disease state.*

The visit schedule creates a right and left censoring of the values of $\gamma_{k,i}$ between the last point observed in state *k* and the first observation observed at a higher state. The $\gamma_{k,i}$ are modeled as unknown random variables using distributions that balance the survival function of state *k* and the time to event in state *k+1* where $\gamma_{k+1,i} > \gamma_{k,i}$. Let λ_k denote the hazard rate associated with state *k*, and let A_i and B_i denote the right and left censoring time points created by the visit schedule for participant *i*. The model can handle jump sizes greater

than size 1, as shown in **Figure 3** in the interval between $\gamma_{0,i}$ and $\gamma_{1,i.}$ For illustration, the probability density function for sampling the $\gamma_{k,i}$, assuming jump sizes of 1, is defined as

$$f(\gamma_{k,i}|\lambda_k, A, B) = \frac{(\lambda_{k+1} - \lambda_k)\exp[(\lambda_{k+1} - \lambda_k)\gamma_{k,i}]}{\exp[(\lambda_{k+1} - \lambda_k)B_i] - \exp[(\lambda_{k+1} - \lambda_k)A_i]}$$

The full course of disease consists of transitions from states *k = 0, 1, 2, … , 36* and occur at times $\gamma_{0,i}$, $\gamma_{1,i}$,…, $\gamma_{34,i}$, $\gamma_{35,i}$. The true times of transition are unobserved latent variables. The model incorporates the censoring of the latent times by observing the state for a participant at each visit.

Let $\zeta_{k,i}$ be the amount of time that participant *i* spent in state *k*, where:

$$\zeta_{k,i} = \begin{cases} \gamma_{0,i} & k = 0 \\ \gamma_{k,i} - \gamma_{k-1,i} & k = 1, \dots, 35 \\ \infty & k = 36 \end{cases}$$

State 36 is an absorbing state, as participants cannot transition out of it and into a worse disease state.

The times-to-transition in each state are constructed as independent exponential random variables,

$$\zeta_{k,i} \sim \text{Exponential}[exp(\theta_d)\lambda_k] \text{ for } k=0,\dots,35;\ d=0,1.$$

The hazard rate for transitioning from state *k* to state *k+1* in the placebo arm is λ_k. Parameter θ_1 is the log hazard ratio of the transition times for an active treatment (d=1) compared to the placebo control (d=0 and $\theta_0 = 0$). The parameter $\exp(\theta_1)$ is the DRR of the treatment compared to the placebo.

The prior distribution for the placebo hazard rate in each interval is taken as nearly non-informative, with independent Gamma(0.1, 1) prior distributions (using the days scale). The log-hazard ratio also has a nearly non-informative prior distribution: $\theta_1 \sim N(0, 10^2)$.

The calculation of the joint posterior distribution is conducted using Markov chain Monte Carlo (MCMC) techniques successively sampling from each of the parameters in the model. Calculation for the latent variable approach is very straightforward in the Bayesian framework. The Bayesian approach appropriately accounts for uncertainty in the latent transition times. The MCMC algorithm has the following steps:

1. Sample values of λ_0, λ_1,…, λ_{36} from their complete conditional distribution
2. Sample value of θ_1 from its complete conditional distribution
3. Sample the latent jump times γ_{35}, γ_{34}, …, γ_0 for each participant known to have exposure in the respective state.

2.3. MONOTONICITY

The model assumes that the underlying latent states within a participant will be non-decreasing (increasing or staying the same). This is a reasonable assumption given the progressive nature of Alzheimer's disease. All data are simulated as monotonically increasing. However, observed trial data could decrease due to measurement error. To address this and model the underlying monotonic latent states, we use the simple convention that any observed decreases are ignored until the point of an observed increase. Enforcing monotonicity in this way corresponds to assuming the worst case of progression for participants. It is unclear what the most appropriate convention is to model the underlying latent monotonic states. Additional sensitivity analyses, using alternative conventions for monotonicity, will help explain how the defined monotonicity convention affects estimates of disease progression. Potential sensitivity analyses include alternative conventions to imputing the true underlying monotonic state, considering both single imputations and multiple imputations[3]. We are investigating the monotonicity assumption, the monotonicity convention, and their impacts on modelling results in ongoing work.

3. SIMULATIONS

We present example power calculations for trials with various sizes of the participant intervention cohort, enrolment subgroups, and lengths of follow-up. Each trial is simulated with 3:1 randomization of participants to treatment vs. control, visits every 6 months, and baseline CDR-SOB scores motivated by distributions based on observed data from the EPAD LCS. The exact distributions used can be found in **Table 3.2.1** for the Cog- population and in **Table 3.2.2** for the Cog+ population. The simulations also assume a proportional treatment effect. A variety of scenarios are simulated, and the operating characteristics are summarized in **Section 4**.

3.1. TRIAL DESIGN SPECIFICATIONS

The operating characteristics presented in this document are based on some of the protocol specifications in the Master Protocol. However, in this report, rather than conduct the primary analysis using the primary analysis method outlined in the Master Protocol, we explore an alternative analysis of the CDR-SOB efficacy endpoint using the tteDPM. Placebo borrowing or early interims for success or futility are not addressed here.

- **Randomization**: All subjects randomized to an intervention are in a 3:1 fashion for active to placebo.
- **Length of Follow-Up**: The maximum length of follow-up for any research participant is 4 years.
- **Frequency of Visits:** The cognitive endpoint, CDR-SOB score, will be collected every 6-months for all research participants.
- **Alternative Analysis Model:** The alternative analysis is based a Bayesian ordinal longitudinal disease progression model. The model has a single parameter for

each intervention that represents the proportion of cognitive slowing for an intervention. This parameter, the disease rate ratio (DRR; the rate of the rate of decline for the intervention to placebo) is used for the analysis of each intervention in the POC study.

3.2. SIMULATION ASSUMPTIONS

In particular, we make the following assumptions for our simulations:

- **Number of participants per intervention cohort**: 100, 200, 300, 400, and 500 with 3:1 Randomization (Active to Placebo)
- **Enrolling subgroups**: Cognitive impairment + only, cognitive impairment – only
- **Maximum trial duration**: 2, 3, or 4 years after last participant is enrolled
- **Post-baseline follow-up per participant**: Visits every 6 months for the duration of the trial with a maximum of 4 years follow-up per participant
- **Disease Rate Ratio (DRR)**: 1.00, 0.90, 0.80, 0.70, 0.60 and 0.50

For each of the enrolling subgroups (Cog- and Cog+), we assume 1) different CDR-SOB scores at trial entry and 2) different hazard rates. Entry CDR-SOB scores and hazard rates are based on observed data from the EPAD LCS. Entry CDR-SOB scores are based on the distribution of CDR-SOB scores for participant entry in the LCS, and hazard rates are based on observed disease progression across CDR-SOB scores in the EPAD LCS data. Monotonically increasing hazard rates were chosen using the observed EPAD LCS data as a guide. The distribution assumptions for CDR-SOB entry score can be found in **Table 3.2.1** (Cog-) **and 3.2.2** (Cog+), while the hazard rate assumptions can be found in **Table 3.2.3** (Cog-) and **Table 3.2.4**(Cog+).

Table 3.2.1: CDR-SOB entry score; Cognitive Impairment - Subgroup

CDR-SOB score	Probability of CDR-SOB score at trial entry
0	0.95
0.5	0.05

Table 3.2.2: CDR-SOB entry score; Cognitive Impairment + Subgroup

CDR-SOB score	Probability of CDR-SOB score at trial entry
0	0
0.5	0.31
1	0.3
1.5	0.18
2	0.1
2.5	0.07
3	0.02
3.5	0.01
4	0.01

Table 3.2.3: Initial Hazard Rate Assumptions; Cognitive Impairment - Subgroup

CDR-SOB score	Assumed Mean Days in State	Assumed Hazard Rate, λ_k	CDR-SOB score	Assumed Mean Days in State	Assumed Hazard Rate, λ_k
0	2000	0.0005			
0.5	1000	0.001	9.5	250	0.004
1	400	0.0025	10	250	0.004
1.5	400	0.0025	10.5	250	0.004
2	400	0.0025	11	250	0.004
2.5	250	0.004	11.5	250	0.004
3	250	0.004	12	250	0.004
3.5	250	0.004	12.5	250	0.004
4	250	0.004	13	250	0.004
4.5	250	0.004	13.5	250	0.004
5	250	0.004	14	250	0.004
5.5	250	0.004	14.5	250	0.004
6	250	0.004	15	250	0.004
6.5	250	0.004	15.5	250	0.004
7	250	0.004	16	250	0.004
7.5	250	0.004	16.5	250	0.004
8	250	0.004	17	250	0.004
8.5	250	0.004	17.5	250	0.004
9	250	0.004	18	∞	0

Table 3.2.4: Initial Hazard Rate Assumptions; Cognitive Impairment + Subgroup

CDR-SOB score	Assumed Mean Days in State	Assumed Hazard Rate, λ_k	CDR-SOB score	Assumed Mean Days in State	Assumed Hazard Rate, λ_k
0	1000	0.001			
0.5	750	0.00133	9.5	100	0.01
1	500	0.002	10	100	0.01
1.5	400	0.0025	10.5	100	0.01
2	400	0.0025	11	100	0.01
2.5	400	0.0025	11.5	100	0.01
3	250	0.004	12	100	0.01
3.5	150	0.00667	12.5	100	0.01
4	150	0.00667	13	100	0.01
4.5	150	0.00667	13.5	100	0.01
5	100	0.01	14	100	0.01
5.5	100	0.01	14.5	100	0.01
6	100	0.01	15	100	0.01
6.5	100	0.01	15.5	100	0.01
7	100	0.01	16	100	0.01
7.5	100	0.01	16.5	100	0.01
8	100	0.01	17	100	0.01
8.5	100	0.01	17.5	100	0.01
9	100	0.01	18	∞	0

3.3. PARTICIPANT SIMULATION

An individual participant is simulated as follows for each disease subgroup (Cog- & Cog+):

1) A **baseline CDR-SOB score** is simulated using the distribution for the appropriate subgroup. These distributions are provided in **Table 3.2.1** and **Table 3.2.2**.
2) **CDR-SOB disease progression** is simulated based on the time spent in each disease state, which is calculated using an exponential distribution with mean corresponding to the appropriate subgroup hazard rate for the given CDR-SOB disease state. The hazard rates are provided in **Table 3.2.3** and **Table 3.2.4.**

3.4. MISSING DATA

Missing data does not occur in these simulations but can occur in two primary ways using real data. First, a participant could miss a visit but return for a subsequent visit. The model naturally handles this case by utilizing the subsequent visit and censoring of times between observed visits. Second, if a participant is lost to follow up, their data will be censored at the last observed visit. In the primary analysis, assuming missing data are missing at random (MAR), participants will be censored at the dropout time and all data followed up to that point will contribute to the disease progression calculation. Additional sensitivity analyses to explore the MAR assumption may be warranted given that participants may drop out due to disease progression.

4. OPERATING CHARACTERISTICS

In each scenario we simulate 500 virtual trials. For each model evaluation 4,000 draws from a single Markov chain Monte Carlo (MCMC) algorithm are used to create the relevant posterior probabilities, following a 200 draw burn-in period. This number of MCMC draws is used for speed of simulations. In a Phase 3 trial setting, one would need to do extensive simulations with an adequate number of draws to ensure Type I error control and a well-powered design.

The following hypotheses concerning the DRR are tested when summarizing the design operating characteristics using the alternative tteDPM analysis method:

- H_0 (null): $DRR \geq 1$, indicating that treatment does not proportionally slow disease progression relative to placebo control
- H_1 (alternative): $DRR < 1$, indicating that treatment proportionally slows disease progression relative to placebo control

If the posterior probability that the DRR<1 is greater than a (prespecified) threshold S_n, then a conclusion of superiority will be made indicating that active treatment slows disease progression relative to placebo control. The success threshold S_n is determined through simulation to maintain adequate Type 1 error.

The success declaration is made if:

$$P(DRR < 1) > S_n$$

Results provided in **Table 4.1** and **Table 4.2** assume a success threshold of 0.975.

4.1. ENROLLING COGNITIVE IMPAIRMENT – (Cog-)

Assuming enrolment of participants with amyloid status consistent with pathogenesis and without cognitive impairment, we generate the operating characteristics shown in **Table 4.1**. This alternative analysis with the tteDPM provides good power for 30% - 40% slowing in disease progression, depending on sample size and length of follow up.

Table 4.1: Probability of Success; Enrolling Cognitive Impairment – Subgroup

DRR	Follow 2 Years					Follow 3 Years					Follow 4 Years				
	N					N					N				
	100	200	300	400	500	100	200	300	400	500	100	200	300	400	500
1.00	0.03	0.02	0.03	0.03	0.03	0.03	0.02	0.03	0.03	0.03	0.03	0.03	0.04	0.03	0.03
0.90	0.05	0.06	0.1	0.11	0.12	0.07	0.1	0.11	0.14	0.15	0.09	0.1	0.14	0.16	0.19
0.80	0.12	0.14	0.24	0.25	0.31	0.16	0.23	0.33	0.38	0.44	0.16	0.29	0.4	0.5	0.56
0.70	0.19	0.3	0.43	0.49	0.6	0.23	0.46	0.59	0.71	0.79	0.36	0.6	0.73	0.86	0.93
0.60	0.29	0.47	0.66	0.74	0.86	0.41	0.69	0.84	0.92	0.97	0.56	0.84	0.95	0.99	0.99
0.50	0.41	0.68	0.87	0.92	0.95	0.58	0.87	0.96	0.99	1	0.74	0.96	1	1	1

4.2. ENROLLING COGNITIVE IMPAIRMENT + (Cog+)

Assuming enrolment of participants with amyloid status consistent with pathogenesis and with cognitive impairment, we generate the operating characteristics shown in **Table 4.2**. This alternative analysis with the tteDPM provides good probability of success for 20% - 30% slowing in disease progression, depending on sample size and length of follow up.

Table 4.2: Probability of Success; Enrolling Cognitive Impairment + Subgroup

DRR	Follow 2 Years					Follow 3 Years					Follow 4 Years				
	N					N					N				
	100	200	300	400	500	100	200	300	400	500	100	200	300	400	500
1.00	0.01	0.02	0.02	0.03	0.03	0.02	0.03	0.03	0.03	0.04	0.02	0.01	0.02	0.03	0.03
0.90	0.08	0.13	0.2	0.22	0.27	0.13	0.19	0.29	0.39	0.42	0.16	0.29	0.41	0.49	0.55
0.80	0.23	0.41	0.56	0.67	0.77	0.37	0.61	0.79	0.85	0.93	0.5	0.78	0.91	0.97	0.99
0.70	0.44	0.74	0.91	0.96	0.99	0.7	0.94	0.99	0.99	1	0.84	0.98	1	1	1
0.60	0.69	0.95	0.99	0.99	1	0.91	1	1	1	1	0.98	1	1	1	1
0.50	0.88	1	1	1	1	0.98	1	1	1	1	1	1	1	1	1

Probability of success is higher in the Cog+ subgroup than in the Cog- subgroup, although the biological question of when an intervention will be effective is also relevant. Based on these results a well-powered 3-year trial for a 20% slowing in cognitive decline (0.85) in the Cog+ subgroup could be run with 400 participants using the tteDPM analysis. In the Cog- subgroup, a well-powered 4-year trial (0.86) for a 30% slowing in cognitive decline could be run with 400 participants.

5. CONCLUSIONS

The tteDPM described here indicates potential as an innovative analysis method in Alzheimer's disease. Model specification is consistent with the course of disease progression, and model results have clinical interpretability. The simulations presented here suggest that the tteDPM could be used in a well-powered future clinical trial. This approach leverages natural history data from the EPAD LCS and could be used as a supporting analysis for the EPAD POC primary RBANS analysis. Future efforts could investigate the potential benefit of combining the RBANS and CDR-SOB models.

6. REFERENCES

1. Rogers JA, Polhamus D, Gillespie WR, et al. Combining patient-level and summary-level data for Alzheimer's disease modeling and simulation: a β regression meta-analysis. *J Pharmacokinet Pharmacodyn*. 2012;39(5):479-498. doi:10.1007/s10928-012-9263-3

2. Kalbfleisch JD, Lawless JF. The Analysis of Panel Data Under a Markov Assumption. *J Am Stat Assoc*. 1985;80(392):863-871. doi:10.2307/2288545

3. Jackson CH, Sharples LD, Thompson SG, Duffy SW, Couto E. Multistate Markov models for disease progression with classification error. *J R Stat Soc Ser Stat*. 2003;52(2):193-209. doi:10.1111/1467-9884.00351

7. PUBLIC SUMMARY

This report describes the WP2 Trial Design work done by Berry Consultants for EPAD Deliverable 2.7. We have used the EPAD LCS data to inform our modelling assumptions for the simulation-based design of potential future clinical trials, such as the EPAD POC. To date, no interventions have entered the EPAD POC trial. As a result, no analysis of new interventions is included in this report.