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CASE STUDY

Reducing control arm sizes in Alzheimer's disease clinical trials: A case study in collaboration with Roche

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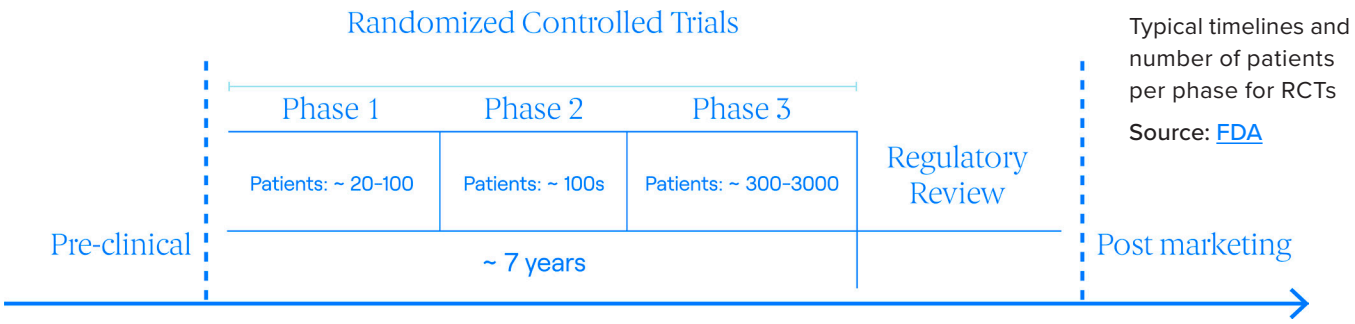
THE CHALLENGE

Long clinical trial timelines delay patient access to novel therapies

Bringing a drug to market requires multiple clinical trials with increasingly larger numbers of patients. For clinical trials in complex neurodegenerative diseases like Alzheimer's disease (AD), longer trial timelines translate to delays in bringing new treatments to patients who need them most. By using machine learning to leverage the wealth of existing patient data from completed clinical trials, we can significantly reduce control arm sizes and accelerate trial timelines. Smaller trial sizes shorten typical enrollment timelines by months, enabling patients to access new treatments sooner.



Typical timelines and number of patients per phase for RCTs

Source: FDA

Here we demonstrate how Unlearn's technology can be used to reduce the size of a control arm up to 35% while generating regulatory-suitable evidence for a completed Phase 2 AD clinical trial.

This analysis was done in partnership with Roche for determining potential use cases in their existing AD clinical programs.

THE SOLUTION

TwinRCTs™— Smaller trials with robust, regulatory-suitable evidence

A TwinRCT is a randomized controlled trial that generates regulatory-suitable clinical evidence with a smaller study. TwinRCTs are powered by prognostic digital twins, machine-learning generated predictions of a patient's prognosis as if they were randomized to the control arm.

Digital twins are created using baseline data collected at the beginning of a trial from all enrolled patients regardless of randomization assignment, and are used as baseline covariates in the primary analysis, allowing for precise estimates of treatment effects.

- Make trials more attractive to patients
- Attain faster enrollment periods
- Achieve a higher probability for success

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IMPACT

TwinRCTs reduce the control arm size by up to 35% in AD trials

How will this patient's disease progress?

Age (years): 74
Sex: Female
Region: Northern America
Years of education: 18

ApoE e4 Count: 1
Amyloid status: Positive
Total Tau (pg/mL): 219
p-Tau181 (pg/mL): 22

History of hypertension: Yes
History of type 2 diabetes: No
Height (cm): 165
Taking AChEI or memantine: Yes

Time (months)	Baseline	3	6	9	12	15	18
ADAS Commands	1	0.1 ± 0.4	0.1 ± 0.4	0.1 ± 0.4	0.1 ± 0.4	0.1 ± 0.4	0.1 ± 0.4
ADAS Comprehension	0	0.0 ± 0.2	0.0 ± 0.2	0.1 ± 0.3	0.1		± 0.3
ADAS Construction	0	0.3 ± 0.5	0.3 ± 0.5	0.4 ± 0.6	0.4 ± 0.6	0.4 ± 0.6	0.5 ± 0.6
ADAS Ideational	0	0.1 ± 0.3	0.1 ± 0.3	0.1 ± 0.3	0.1 ± 0.4	0.1 ± 0.4	0.1 ± 0.4
ADAS Naming	0	0.1 ± 0.3	0.1 ± 0.3	0.1 ± 0.4	0.1 ± 0.4	0.1 ± 0.4	0.2 ± 0.4
ADAS Orientation	0	0.6 ± 0.8	0.6 ± 0.9	0.8 ± 1.1	0.9 ± 1.2	1.1 ± 1.4	1.2 ± 1.5
ADAS Remember Instructions	0	0.1 ± 0.4	0.1 ± 0.4	0.1 ± 0.4	0.1 ± 0.4	0.2 ± 0.5	0.2 ± 0.5
ADAS Spoken Language	0	0.0 ± 0.1	0.0 ± 0.2	0.0 ± 0.2	0.0 ± 0.2	0.0 ± 0.2	0.0 ± 0.2
ADAS Word Finding	0	0.2 ± 0.4	0.2 ± 0.4	0.2 ± 0.4	0.2 ± 0.4	0.2 ± 0.5	0.2 ± 0.5
ADAS Word Recall	4	4.6 ± 1.1	4.6 ± 1.1	4.5 ± 1.2	4.7 ± 1.3	4.7 ± 1.3	4.7 ± 1.5
ADAS Word Recognition	3	4.1 ± 2.4	4.4 ± 2.6	4.6 ± 2.8	4.8 ± 2.9	4.7 ± 2.9	4.8 ± 3.0
ADAS Delayed Word Recall	8	6.4 ± 2.1	6.6 ± 2.1	6.5 ± 2.3	6.5 ± 2.3	6.7 ± 2.5	6.6 ± 2.5
ADAS ancellation	0	1.6 ± 0.9	1.1 ± 0.9	1.6 ± 1.1	1.5 ± 1.0	1.6 ± 1.1	1.6 ± 1.1
ADAS og11 Total	8	10.3 ± 0.9	10.6 ± 0.9	11.0 ± 1.0	11.6 ± 1.1	11.8 ± 1.1	12.2 ± 1.2
CDR munity	0.5	-	0.5 ± 0.3	-	0.7 ± 0.4	-	0.8 ± 0.4
CDR e + Hobbies	0	-	0.6 ± 0.3	-	0.7 ± 0.4	-	0.8 ± 0.5

Digital twins are created using baseline data from each enrolled patient whether they are assigned to the active or control arm. A patient-specific prognostic score is derived from a patient's digital twin.

In partnership with Roche, Unlearn evaluated digital twins on the ABBY study, a completed, randomized, double-blind, placebo-controlled, multi-center Phase 2 study on the use of low-dose subcutaneous Crenezumab in patients with mild-to-moderate AD. The goal of the analysis was to use a previously completed trial to evaluate our TwinRCT solution for reducing the number of required control patients.

Endpoint	Correlation between subject outcome and digital twins for the score change from base-line at 18 months	Prospective sample size reduction (maintaining a 1:1 randomization ratio)	Prospective control arm size reduction (starting from a 1:1 randomization ratio)
ADAS-Cog12	0.46	21%	35%
CDR-SB	0.37	14%	24%

The prognostic value of digital twins can be used to reduce sample sizes in prospective studies; the larger the correlation, the greater the reduction in control arm size. This table shows the correlation between observed outcomes and the digital twin predictions for the ADAS-Cog12 and CDR-SB change from baseline at 18 months and the resulting prospective sample size or control arm reductions from a 1:1 randomized study. For ADAS-Cog12, the control arm size reduction is 35%.

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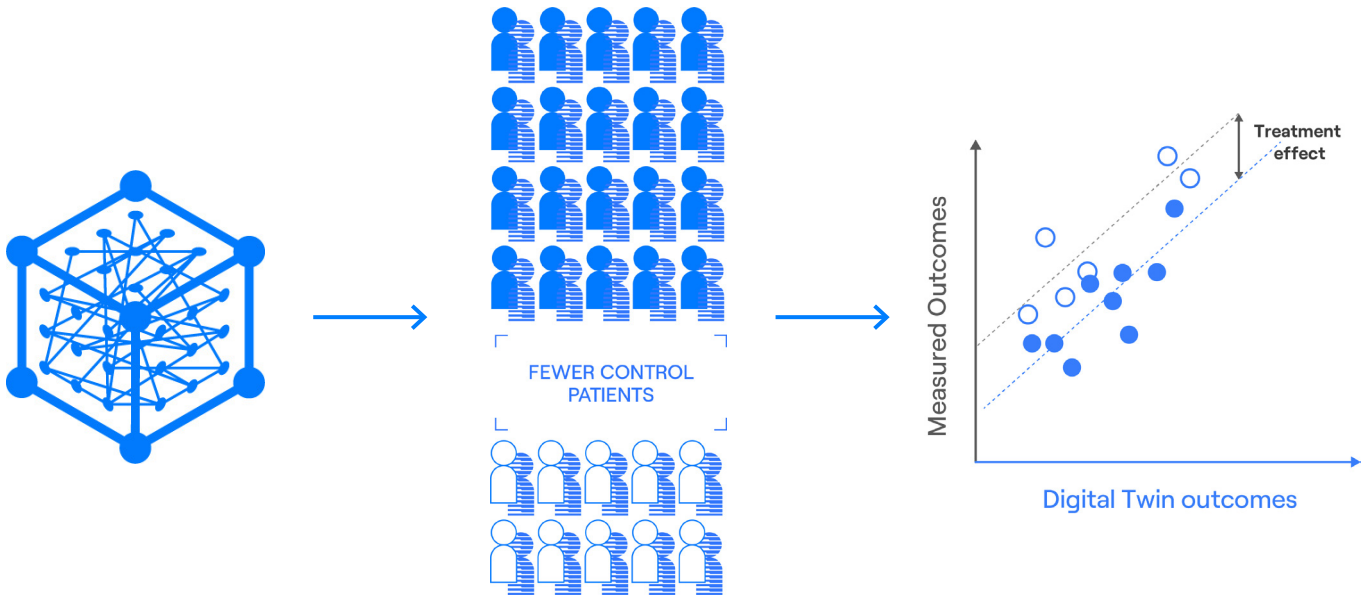
PROCOVA

Our three-step regulatory framework

In March 2022, the European Medicines Agency published a draft qualification opinion using our PROCOVA™ procedure. PROCOVA provides the regulatory framework for implementing our TwinRCT solution and ensures robust clinical evidence is generated by decreasing uncertainty in treatment effect estimates and strictly controlling type-I error rates.



1. Train and evaluate the prognostic model
2. Estimate sample size and design the trial
3. Execute the trial and estimate treatment effect

PROCOVA consists of three steps:

1. Training a prognostic machine learning model on historical data and then evaluating the model by comparing digital twin outcomes to measured outcomes.
2. Estimating the sample size required for a prospective study and then designing the primary analysis of the TwinRCT.
3. Executing the TwinRCT and then estimating the treatment effect from the completed study. Digital twins are used as a covariate in an adjusted analysis of the trial data.

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Partner with us

TwinRCTs enable smaller, more efficient clinical trials—significantly accelerating timelines and helping to bring effective therapies to patients sooner. In this case study, we've shown how digital twins reduce the control arm size up to 35% for a Phase 2 study on the use of low-dose subcutaneous crenezumab in mild-to-moderate AD. Based on this analysis, we estimate a reduction of 175 control arm patients for a 1000 patient Phase 3 study with an initial 1:1 randomization ratio. This reduction translates to subtracting over a year from a typical clinical trial timeline.

With programs in neurology and immunology and inflammation (I&I), Unlearn will continue to expand into new therapeutic areas. We are seeking partners to adopt this novel approach and accelerate clinical development programs across different disease areas.

TwinRCTs seamlessly integrate into clinical trial protocols and have applications at multiple stages of clinical development.

We partner with sponsors to run TwinRCTs and help get novel therapies to patients sooner.

Selected areas of research:

CNS

- Alzheimer's Disease
- Multiple Sclerosis
- Amyotrophic Lateral Sclerosis
- Huntington Disease
- Parkinson's Disease

I&I

- Systemic Lupis Erythematosus
- Rheumatoid Arthritis
- Psoriasis
- Crohn's Disease
- Ulcerative Colitis

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METHODS

Using a previously developed machine learning model of AD progression, Unlearn created digital twins using baseline data for 184 patients from the placebo arm of the ABBY study. The digital twins consisted of trajectories describing the time evolution of a number of variables used to evaluate safety and efficacy in three-month intervals starting from baseline. Outcomes were computed for the 12-component Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog12), and the Clinical Dementia Rating Sum-of-Boxes (CDR-SB).

After digital twins were created blind to patient outcomes, they were compared to observed outcomes across visits, and prognostic scores derived from digital twins were used as covariates in the final analysis to estimate control arm size reductions for this Phase 2 RCT.

The reduction in the required number of patients assigned to the placebo arm depends on the correlation coefficients in change scores between actual subjects and digital twins. Using the 18-month outcomes for the change in ADAS-Cog12 and CDR-SB scores from baseline, the digital twin predictions had a correlation of 0.46 (ADAS-Cog12) and 0.37 (CDR-SB) with the observed values from subjects that took placebo. These values suggest that in similarly designed studies, this approach can yield 21% (ADAS-Cog12) or 14% (CDR-SB) smaller studies when maintaining a 1:1 randomization ratio, or 35% (ADAS-Cog12) and 24% (CDR-SB) smaller control arms when maintaining treatment arm size.

Visit us at unlearn.ai to learn more.

partnerships@unlearn.ai