Comparing randomized trial designs to estimate treatment effect in rare diseases with longitudinal models: a simulation study showcased by Autosomal Recessive Cerebellar Ataxias using the SARA score

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Abstract

Parallel designs with an end-of-treatment analysis are commonly used for randomised trials, but they remain challenging to conduct in rare diseases due to small sample size and heterogeneity. A more powerful alternative could be to use model-based approaches. We investigated the performance of longitudinal modelling to evaluate disease-modifying treatments in rare diseases using simulations. Our setting was based on a model describing the progression of the standard clinician-reported outcome SARA score in patients with ARCA (Autosomal Recessive Cerebellar Ataxia), a group of ultra-rare, genetically defined, neurodegenerative diseases. We performed a simulation study to evaluate the influence of trials settings on their ability to detect a treatment effect slowing disease progression, using a previously published non-linear mixed effect logistic model. We compared the power of parallel, crossover and delayed start designs, investigating several trial settings: trial duration (2 or 5 years); disease progression rate (slower or faster); magnitude of residual error ($\sigma=2$ or $\sigma=0.5$); number of patients (100 or 40); method of statistical analysis (longitudinal analysis with non-linear or linear models; standard statistical analysis), and we investigated their influence on the type 1 error and corrected power of randomised trials. In all settings, using non-linear mixed effect models resulted in controlled type 1 error and higher power (88% for a parallel design) than a rich (75% for a parallel design) or sparse (49% for a parallel design) linear mixed effect model or standard statistical analysis (36% for a parallel design). Parallel and delayed start designs performed better than crossover designs. With slow disease progression and high residual error, longer durations are needed for power to be greater than 80%, 5 years for slower progression and 2 years for faster progression ataxias. In our settings, using non-linear mixed effect modelling allowed all three designs to have more power than a standard end-of-treatment

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analysis. Our analysis also showed that delayed start designs are promising as, in this context, they are as powerful as parallel designs, but with the advantage that all patients are treated within this design.

Keywords Non-linear Mixed effect models, Simulation study, Rare disease, Clinical trial design, Model-based analysis

Background

Randomized parallel designs are the gold standard used for clinical trials, and the statistical analysis is then usually a comparison of change from baseline or end of treatment measurements [1]. Rare diseases however involve small target populations with heterogeneous presentation of the condition, progression, severity of symptoms or response to treatment. Other designs may then be considered such as single arm trials, or designs using natural history data, such as patient registries, to inform the design or to use as an external control [2]. Furthermore, analysing longitudinal data using linear or non-linear mixed effect models has been shown to improve the power of those trials compared to standard approaches [3, 4].

Autosomal recessive Cerebellar Ataxias (ARCA) are a group of ultra-rare, progressive neurodegenerative disorders. They mainly affect the cerebellum but also induce other multi-systemic damage to other neurological systems, causing impairment to gait, balance, speech and fine motor movements [5]. More than 100 genotypes have been identified [5] and symptoms usually emerge during childhood or early adulthood. ARCAs are prime candidates for targeted molecular therapies or gene therapies due to their genetic etiology. While there is currently no approved disease-modifying treatment for most ARCAs, multiple clinical trials are ongoing, which aim to quantify the treatment effect of such therapies. However, the settings of those clinical trials can be very different depending on the genotype or kind of drugs, and there are still statistical challenges to design randomised clinical trials for these diseases [6]. Among ARCA genotypes, disease severity at onset and disease progression rate can vary [7–9], which have an influence on the designs. Other randomized trial designs have been explored for neurodegenerative diseases. For example the FDA just approved a drug for Niemann-Pick disease type C [10], where a crossover design was used to demonstrate the effect of the compound. Delayed start designs are also being investigated to show the effect of disease-modifying drugs for instance in Parkinson's and Alzheimer's disease [11, 12]. Crossover and delayed start designs could be used to account for individual progression rates, but modelling approaches are needed to account for temporal change in the outcome or carryover effect. Due to the genetic diversity of this disease, there are currently no universally applicable biomarkers, and clinician-reported composite scores such as the Scale for Assessment for the Rating of Ataxia (SARA) [13] are commonly used as endpoints.

In this work, we propose to explore the advantage of model-based analyses of trials compared to more standard statistical analyses through a simulation framework. We evaluate several clinical trial designs that could be used to quantify a disease-modifying treatment effect according to their power and type 1 error. We simulated data using a longitudinal non-linear mixed effect model (NLMEM) [14] that we built to describe– as a showcase example for our methodological approach—the SARA score over the time since onset of symptoms in patients included in the ARCA registry [15] and diagnosed with Autosomal Recessive Spastic Ataxia of Charlevoix Saguenay (ARSACS), introducing a hypothetical treatment effect slowing down the disease progression rate. We explored two disease progression rates, a "slow progression rate" and a "fast progression rate" to reflect the diversity of progression rates more generally in ARCAs and to assess its impact on clinical trial design. We also explored other clinical settings of interest, such as the duration of the trial, the number of patients and the magnitude of residual error.

Methods

We performed a simulation study to evaluate and compare the performance of several clinical trial designs for ARCAs in order to quantify a disease-modifying treatment effect. We investigated several settings, such as the design, the estimation model, the number of patients, the magnitude of residual error and the duration of the trial.

Simulation model

Data was simulated using a previously published NLMEM [14] describing the evolution of the total SARA score for an exemplary specific subgroup of patients in the ARCA registry [15], namely patients with a genetically confirmed diagnosis of Autosomal Recessive Spastic Ataxia of Charlevoix Saguenay (ARSACS) [16]. The jth total SARA score y_{ij} observed at time t_{ij} since symptoms onset in individual i was described using the following equations:

$$\begin{aligned} y_{ij} &= f\left(t_{ij}, \psi_i\right) + \sigma \times \epsilon_{ij} \\ log\left(\psi_{ik}\right) &= log\left(\mu_k\right) + \eta_{ik} \end{aligned} \quad (1)$$

where $f\left(t_{ij}, \psi_i\right)$ represents the structural model, a function of t_{ij}, ψ_i, the vector of individual parameters for individual i (of dimension K), μ the vector of fixed effects.

Table 1 Parameters of the logistic model on the ARSACS population on the ARCA registry used in the simulation study for the slow progression scenario in the control (untreated) group. For the fast progression scenario, α was set to 0.22 and for the low standard error σ was set to 0.5. δ represents the SARA score at TSO $= -\infty$, γ represents the amplitude of the logistic (maximum SARA score $= \delta + \gamma$). α ($year^{-1}$) represents the disease progression rate and β represents the location parameter (inflexion point reached at TSO $= \frac{\beta}{\alpha}$). ω_* represents the standard deviation of the distribution of the random effects of parameter $*$. For example, individual δ_i follow a log-normal distribution of parameters: LN($log(\delta), \omega_\delta^2$)

Parameter	Value
δ	6.16
γ	28.75
β	3.94
α (yr^{-1})	0.11
ω_δ	0.31
ω_γ	0
ω_β	0.20
ω_α	0.09
σ	2

The random effects η_i were assumed to follow a joint multinormal distribution with variance–covariance matrix Ω. For the residual error model, σ was the standard deviation of the residual error, and $\epsilon_{ij} \sim N(0,1)$. The population parameters for this model were $\theta = (\mu, \Omega, \sigma)$.

The structural model for the evolution of the SARA score, f was a four-parameter logistic model [14]:

$$f(t_{ij}, \psi_i) = \delta_i + \frac{\gamma_i}{1 + \exp(\beta_i - \alpha_i \times t_{ij})} \qquad (2)$$

where $\psi_i = (\delta_i, \gamma_i, \beta_i, \alpha_i)$. This model was developed previously to describe the evolution of the SARA score in the ARCA registry [7]. As a bounded, non-linear model it was able to represent the evolution of SARA scores over the course of the disease, and we found it outperformed other alternatives that we tested (sigmoid, Gompertz, 3 parameter logistic models). The parametrisation was then changed in [14] to introduce a treatment effect. In the model, δ represents the SARA score at TSO $= -\infty$, γ represents the amplitude of the logistic (maximum SARA score $= \delta + \gamma$). α (year^{-1}) represents the disease progression rate and β represents the location parameter (inflexion point reached at TSO $= \frac{\beta}{\alpha}$).

A Drug Effect (DE) parameter was introduced on α, reducing the disease progression rate after the inclusion in the clinical trial in the treatment group, in order to mimic a disease-modifying treatment effect. Therefore, under treatment, we assumed $\alpha_{trt} = \alpha(1 - DE \times TRT)$, with TRT (treatment) an indicator function ($= 1$ if the patient is treated, 0 if the patient is in the control group). Hence, with a drug effect
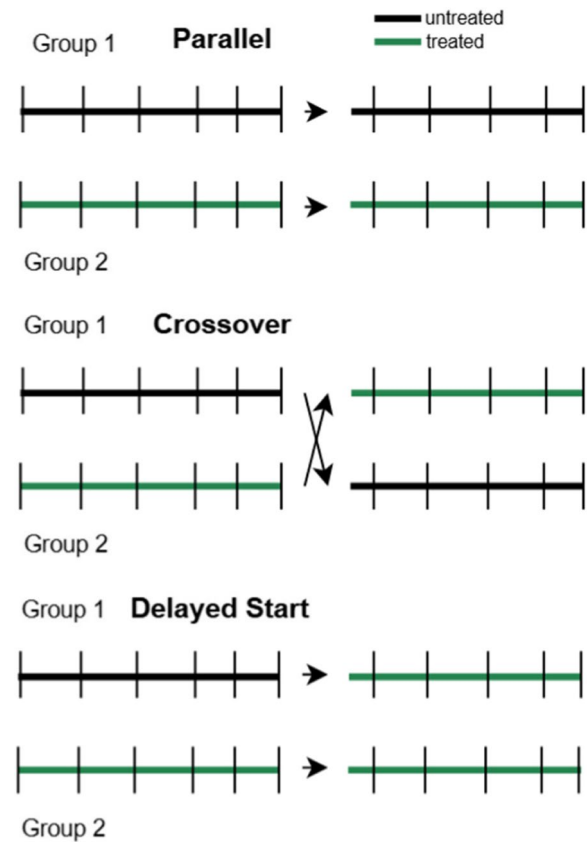

Fig. 1 Schematic representation of the parallel, crossover and delayed start designs for a trial, with a change mid-trial in the cross-over and delayed start designs

of 0, the equation is equal to [2], which is equivalent to natural progression with no drug, with a DE of 1, there is no progression, and with DE > 1, the SARA score decreases. In this study we assumed that the treatment effect is DE = 0.5 hence dividing by 2 the disease progression rate. The parameters used for the simulation are given in Table 1.

Trial designs

Three clinical trial designs were investigated: 1, parallel design where patients are randomized to the control (untreated) group or treatment (treated) group; 2, crossover, where patients switch group mid-trial; 3, delayed start, where patients are randomized in control or treatment group, and the patients in the control group receive the treatment at mid-trial, as shown in Fig. 1. For each design, N patients were included with an allocation ratio of 1:1, and we generated one observation at inclusion in the trial and then every 6 months for the duration of the trial. The details of the equations for the cross-over and delayed start designs are shown in Supplementary Materials 2.

Simulation scenarios

We define a simulation scenario as a combination between the parameters of the model used for the simulation, the duration of the trial and the number of patients in the trial. For each scenario, we generated 500 datasets under each of the three trial designs investigated.

In this work, we considered two reference scenarios. The slow progression reference scenario (A) used the parameters previously estimated on the ARSACS population (Table 1). In a previous study [14], a trial duration of 5 years for the ARSACS population yielded adequate power, so we set the same duration. The fast progression reference scenario (B) assumed a faster disease progression rate than the first, by multiplying the α parameter by 2 (the other parameters remaining unchanged). The faster progression rate means there is a stronger signal which would make it possible to reduce the trial duration and still achieve the same target power (because, in our model, the treatment effect is assumed to slow the disease progression rate). Therefore, we investigated a shorter trial duration in our fast progression scenario (2 years). The number of observations in each patient is hence 11 for the 5-year trial and 5 for the 2-year trial.

DE was simulated at 0 and 0.5 (for the type 1 error and power assessment, respectively). Figure 2 shows the graph of the logistic model using the population parameters for the slow and fast progression, for treated and untreated patients at three different times since disease onset at inclusion (5, 15 and 25 years).

In each of the reference scenarios, we varied other settings to study the impact on the type 1 error and power of such trials. First, we investigated the influence of the duration of the trial, by using a shorter trial for the slow progression reference (2 years) and a longer trial for the fast progression reference (5 years). We also considered a lower magnitude of the residual error (σ=0.5 with a 2 year and 5-year trial for the slow progression reference, and σ=0.5 with a two-year trial for the fast progression reference).

Time Since Onset (TSO) at inclusion was assumed to follow a uniform distribution between 0 and 30 years [14]. All scenarios were evaluated with N = 100 patients (50 per arm). If, in a scenario, there is at least one design where one model has more than 99% power, all designs and models within that scenario were simulated again with 40 patients. In this additional simulation (with 40 patients), the simulated patients were stratified in each arm on their time since onset at inclusion to ensure a balanced distribution of TSO (30%: 0–10 years, 30%: 10–20 years, 40%: 20–30 years). The data of the first simulated data set is shown for all designs (slow progression, 5-year duration, 100 patients, with σ=2 and σ=0.5) in Fig. 3.
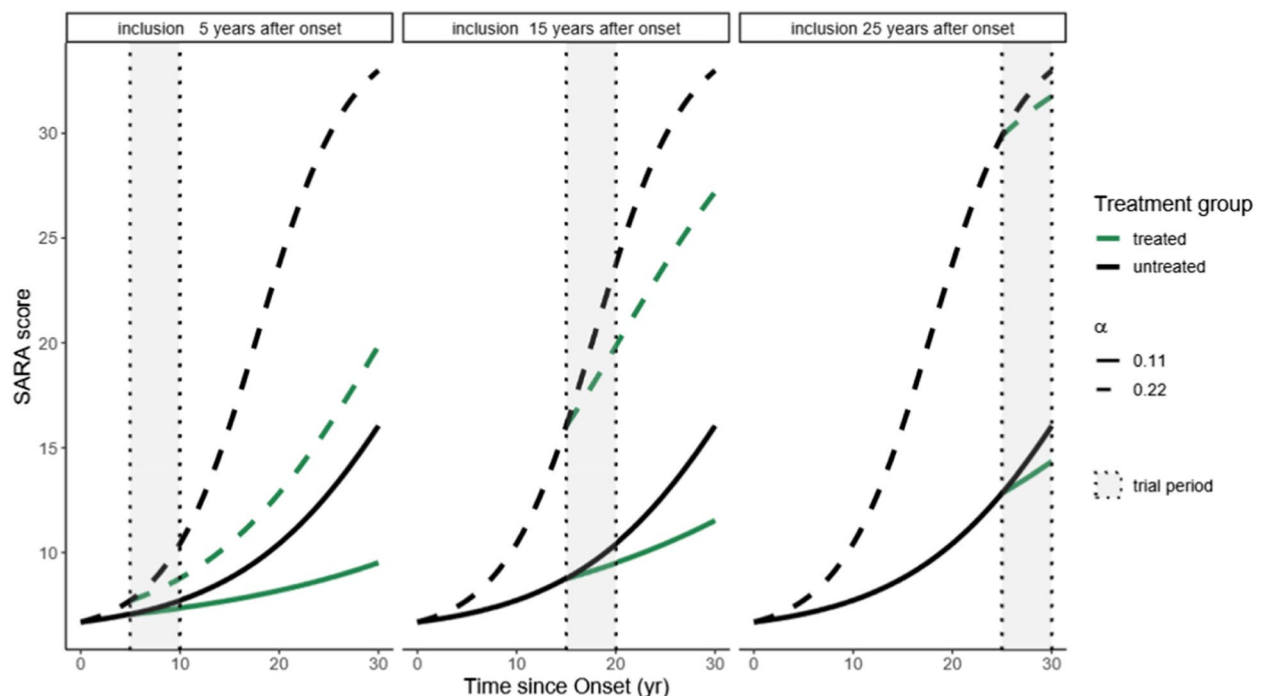

Fig. 2 Evolution of Sara score versus time since onset with the logistic model using the population parameters. Each panel represents a time since onset at inclusion (5, 15 and 25 years), full or dashed lines represent two different progression rates (α = 0.11 or 0.22 respectively), the black and green colours represent if the patient is untreated or treated (assuming a drug effect of 0.5), and the grey box represents the trial period
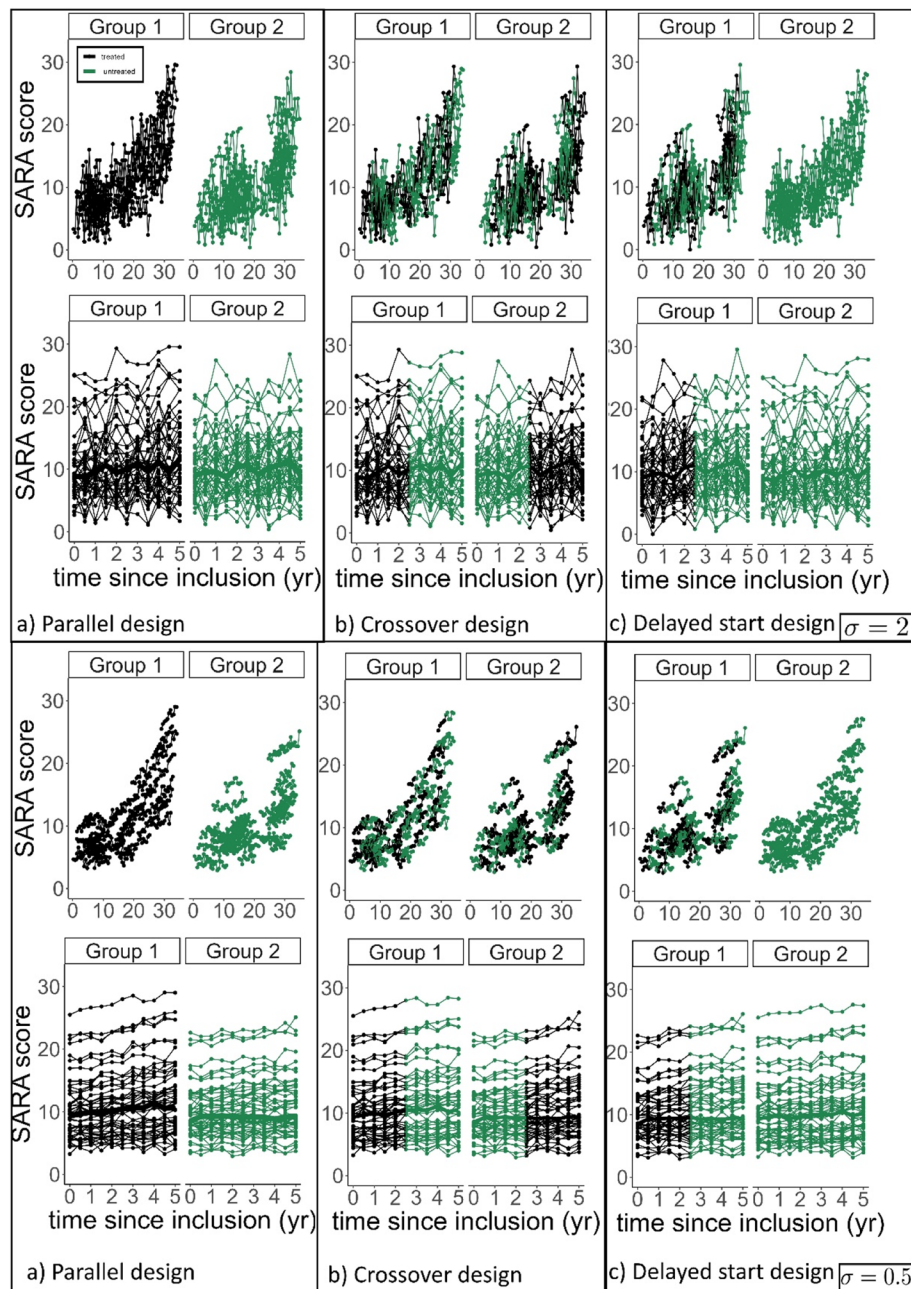
Fig. 3 Simulated data set with a parallel (left), crossover (middle) or delayed start (right) design, with a duration of 5 years, $N = 100$ patients. The top two rows represent $\sigma = 2$, and the bottom two rows $\sigma = 0.5$, as a function of time since onset of symptoms (top row) or time since inclusion (bottom row). Each panel represents a randomization group, lines join the observations of a patient. Treatment status is differentiated by colour (black: patients that are not under treatment; green: patients under treatment). In the graph versus time since inclusion, the bold line represents the median observation at each time point in each panel

Estimation models

Each simulated trial was analysed using all observed data with 2 models, the logistic model used for the simulation and a simpler model assuming a linear evolution of the SARA score. For the logistic model, DE was estimated with no random effect and it was fixed to 0 for the crossover and delayed start designs when patients were untreated. Also, to ensure the identifiability of all parameters, γ was fixed to its estimated value in the ARSACS population and its random effect was fixed to 0. For the linear model (with slope and intercept, both with random effects and a covariance), a fixed effect DE was introduced on the slope parameter. Time since inclusion was used as the independent variable, with the time since onset at inclusion as a covariate on the base and slope.

In the slow progression reference scenario, we also assessed the performance of a sparser linear model, which we call sparse linear model. In this approach, we used the same linear model, but only the first, mid-trial and last observations were kept for each patient. It was made to mimic an end-of-study approach, while keeping the mid-trial point, which is needed for the crossover and delayed start designs.

Evaluation

For each scenario, we evaluated the empirical type 1 error of the Likelihood Ratio Test (LRT) comparing a model with and without treatment effect (type I error of 0.05), in a simulation where DE = 0. We also evaluated the power based on the LRT, corrected for the empirical type 1 error (i.e., with a statistical significance threshold chosen such that the type 1 error is 5% at that threshold), by simulating a drug effect of 50% (DE = 0.5). For each estimated proportion of significant LRT over the 500 replicates, its 95% confidence interval was constructed using an exact binomial test (using the Pearson-Clopper method).

Implementation

Simulations were performed using NONMEM 7.5.0 [17], via the sse command in Pearl Speaks NONMEM (PsN) 5.3.1 [18]. Parameter estimation was performed using the SAEM [19] algorithm for the logistic and linear model, and using the FOCE [20] algorithm for the sparse linear model. Data analysis and visualisation were performed using R 4.1.2 [21]. NONMEM and PsN code for a scenario of the simulation study are available in a Zenodo repository (https://doi.org/10.5281/zenodo.14755801).

Results

Simulation study: slow-progression case

Figure 4 shows the type 1 error for the three designs (parallel, crossover and delayed start) and three models (logistic, linear and sparse linear) in the slow progression reference scenario (N = 100, duration 5 years and σ = 2). The type 1 error of the logistic model was controlled for the parallel and delayed start design, and slightly inflated for the crossover design. Type 1 error was controlled in every design for the linear model. For the sparse linear model, the type 1 error was controlled for the crossover and parallel designs but inflated for the delayed start design. Figure 5 shows the power corrected for the empirical type 1 error for the three designs. For the parallel design, the linear model had lower power than the logistic model (75.4%) and the sparse linear much lower power (49.2%), whereas the logistic model had the highest power (88%). If we were to apply a two-sample t-test with change from baseline, the type 1 error would be controlled and the power would be even lower than the sparse linear model, at 35.8%. The difference in power for the three designs was even more marked for the delayed start design. For the logistic model, the corrected power was highest for the parallel design (88.0%), closely followed by the delayed start design (83.4%), while the
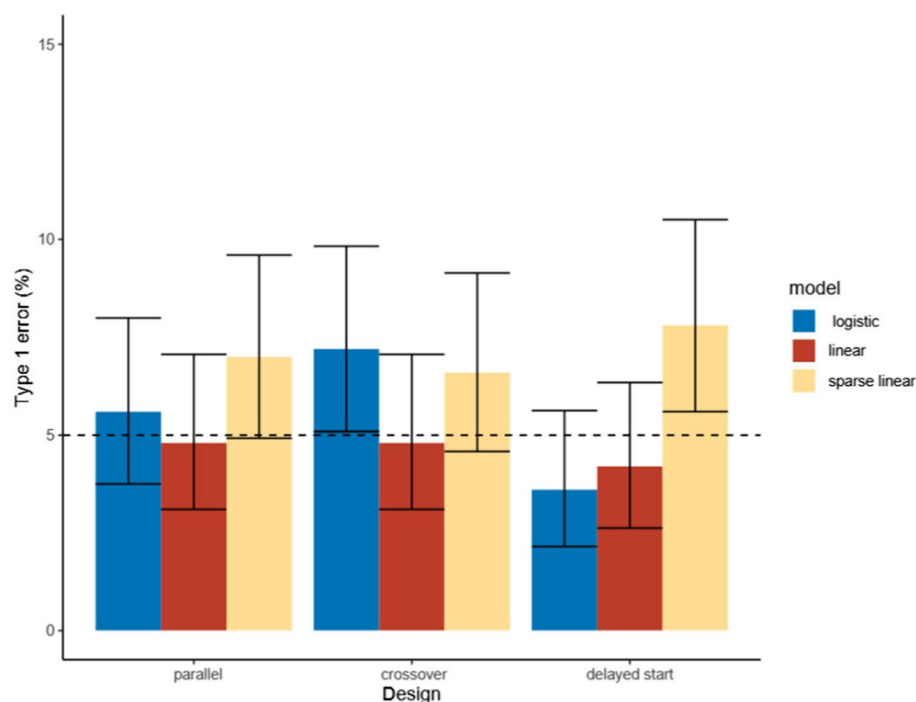

Fig. 4 Type 1 error for the three designs and three analysis models on the slow progression scenario without a drug effect (DE = 0%), *N* = 100 and assuming a trial duration of 5 years. The colours of the bars correspond to the model used for estimation
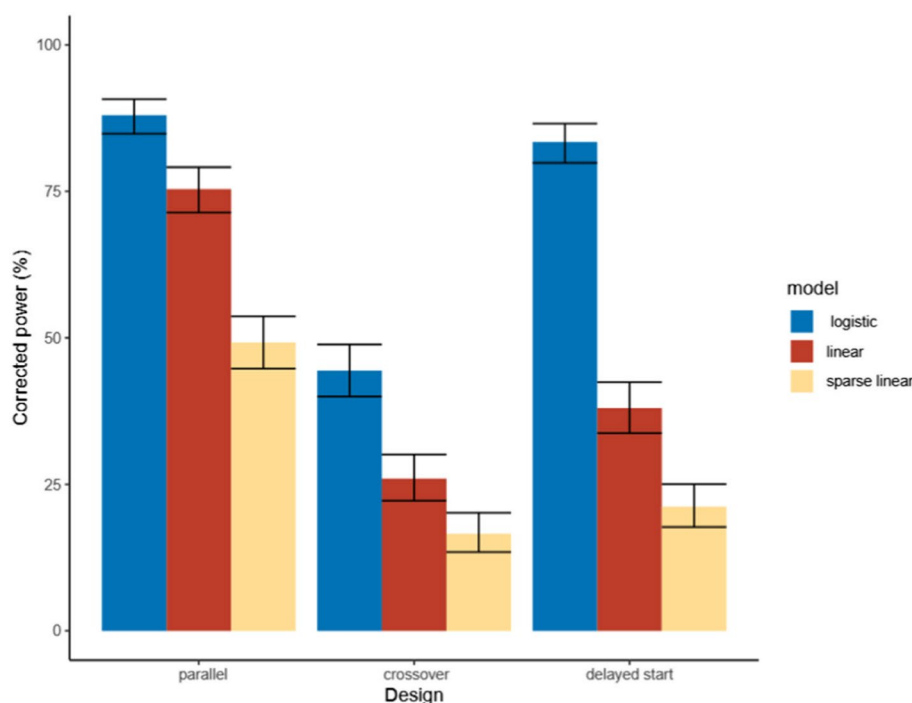
Fig. 5 Corrected power for the three designs and three analysis models on the slow progression scenario assuming a drug effect DE = 50%, *N* = 100 and a trial duration of 5 years. The colours of the bars correspond to the model used for estimation

crossover design (44.4%) performed much worse. The two other models followed a similar trend across all three designs. In the supplementary material, Figs S1–1 and S1-2 show the violin plots of the error in the estimation of the treatment effect in the slow and fast progression case, with the nonlinear mixed effect model which were adequate both for DE = 0 and DE = 0.5.

We then investigated the influence of a smaller magnitude of residual error (σ=0.5 and a duration 5 years) and the influence of a shorter trial duration (2 years and σ=0.5) on the type 1 error and corrected power. Type 1 error (Fig. 6) was controlled in most scenarios for the logistic model and it was inflated in some scenarios for the linear model. In Fig. 7, we show the corrected power for those scenarios. With a duration = 5 years and σ=0.5, the power was close to 100% for the logistic model in all designs. All designs were therefore re-evaluated with 40 patients to better compare the relative performance of each design. The corrected power is also close to 100% in almost all designs for the linear model. With a shorter duration of 2 years and a lower residual error, we observed powers similar to the slow progression reference scenario, with power going from 90% for the parallel and delayed designs to 57.2% for the cross-over design. In this scenario, the linear model had lower power than the logistic model, and the delayed start design performed as poorly as the cross-over design with power dropping by half compared to the parallel design.

Simulation study: fast-progression case
In the fast progression reference scenario, the type 1 error was controlled for all designs for both the logistic and the linear models (Fig. 8 bottom-left panel). The corrected powers (Fig. 9 bottom-left panel), were similar to the slow progression reference case, with the highest power found for the parallel and delayed start designs, and a marked decrease for the crossover design. The corrected power for the linear model was much lower in all designs.

Varying the magnitude of residual error (σ=0.5) or considering a longer trial duration of trial did not impact type I error (Fig. 8) which remained controlled in almost all scenarios for both the logistic and linear models. In Fig. 9, we show the corrected power for those scenarios. For the logistic model, the power was close to 100% in all scenarios with 100 patients, and remained high with 40 patients for the parallel and delayed start design, decreasing by 5 to 15% for the crossover design. For the linear model, the corrected power was close to 100% with 100 patients when σ=0.5 for all 3 designs but was much lower with 40 patients than the logistic model.

Discussion
In this work, we performed a simulation study to evaluate the type 1 error and power to detect a treatment effect through longitudinal modelling for different designs, progression rates, durations and magnitudes of residual error. The settings for the simulation study were derived
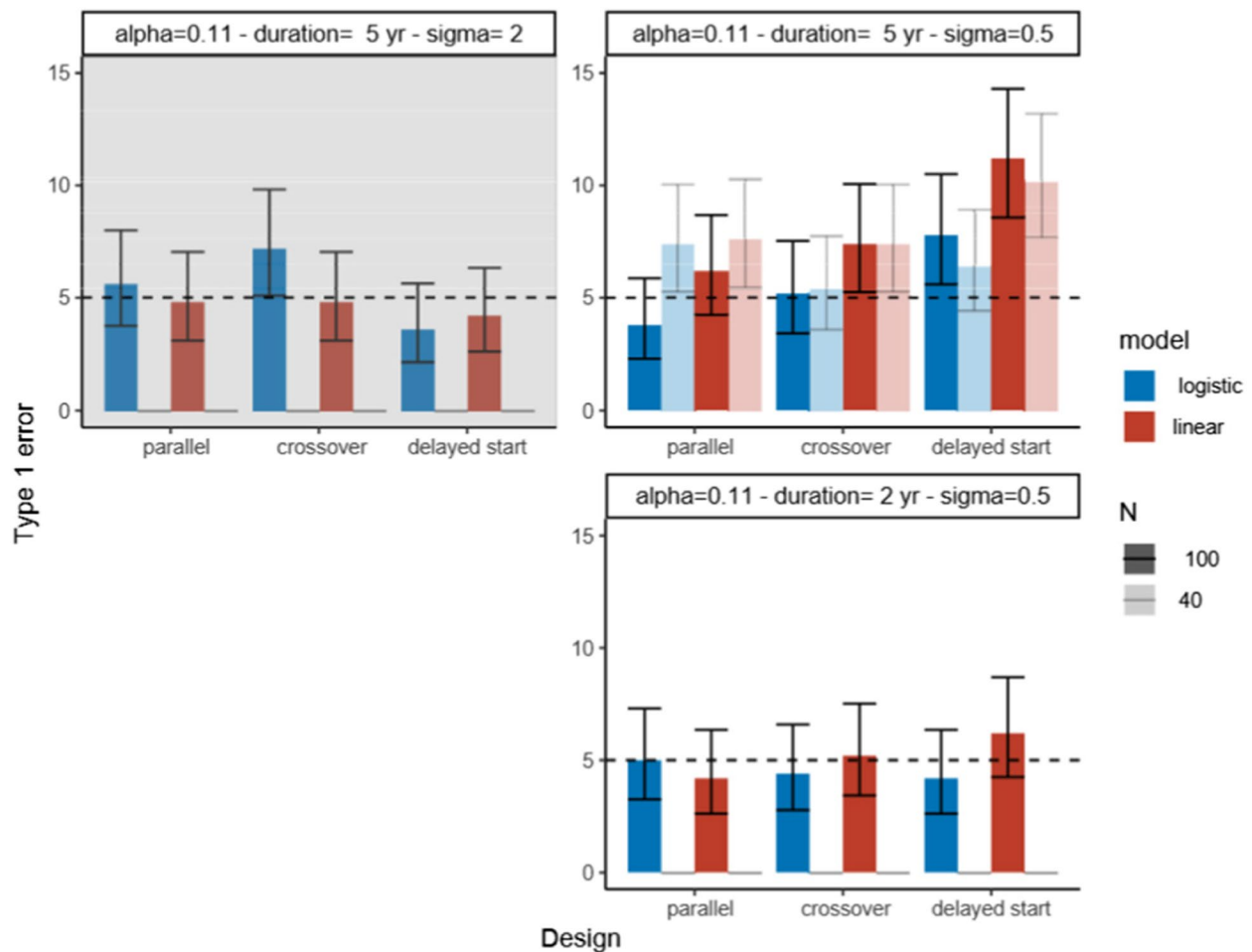
Fig. 6 Type 1 error for the slow progression reference and the scenarios with duration = 5 years/σ=0.5 and duration = 2 years/σ=0.5. The colours of the bars correspond to the model used for estimation. The grey background (upper left panel) highlights the reference scenario (slow progression). In Darker and lighter shades represent N=100 and N=40, respectively

from a model describing the evolution of SARA scores in patients with ARCA [15]. We compared the modelling approach with an end-of-treatment analysis evaluating change from baseline.

In our settings, we used a sparse linear model to mimic an end-of treatment analysis, adding the mid trial point required for the crossover and delayed start designs to keep the same number of observations for all designs. The sparse linear model was outperformed by the logistic model. For the parallel design, using longitudinal modelling with non-linear mixed effect models enabled the power of the trial to go from 50 to 88% (and from 38 to 88% with a two-sample t-test with a change from baseline). The linear mixed effect model that uses all individual observations also performed worse than the logistic model, even when informing the base and slope parameters with the time since onset at inclusion in the study, although, in most scenarios, the power of the linear model was still relatively high when using a parallel design. This shows that part of the loss of power is

attributable to model misspecification since data was simulated using a logistic model.

In this study, we found that, in both the slow and fast progression case, the parallel design performs the best, followed by the delayed start design which had almost identical power in all scenarios. The crossover design had lower power than the other two. The poor performance of the crossover design was unexpected, as, in some settings, such as bioequivalence studies, it was shown to have better performance in terms of power than a parallel design [22], due to the fact that it allows to identify treatment effect using each patient as its own control. This loss of power was not due to a bias in the estimation of the treatment effect as shown in Supplementary Figures S1–1 and S1-2. In our case, the underperformance of the crossover design could be explained by the fact that neurodegenerative ataxias are slowly progressive diseases. Even though using non-linear models accounts for the temporal and carry-over effect, the identification of the treatment effect relies on the observation of a progression
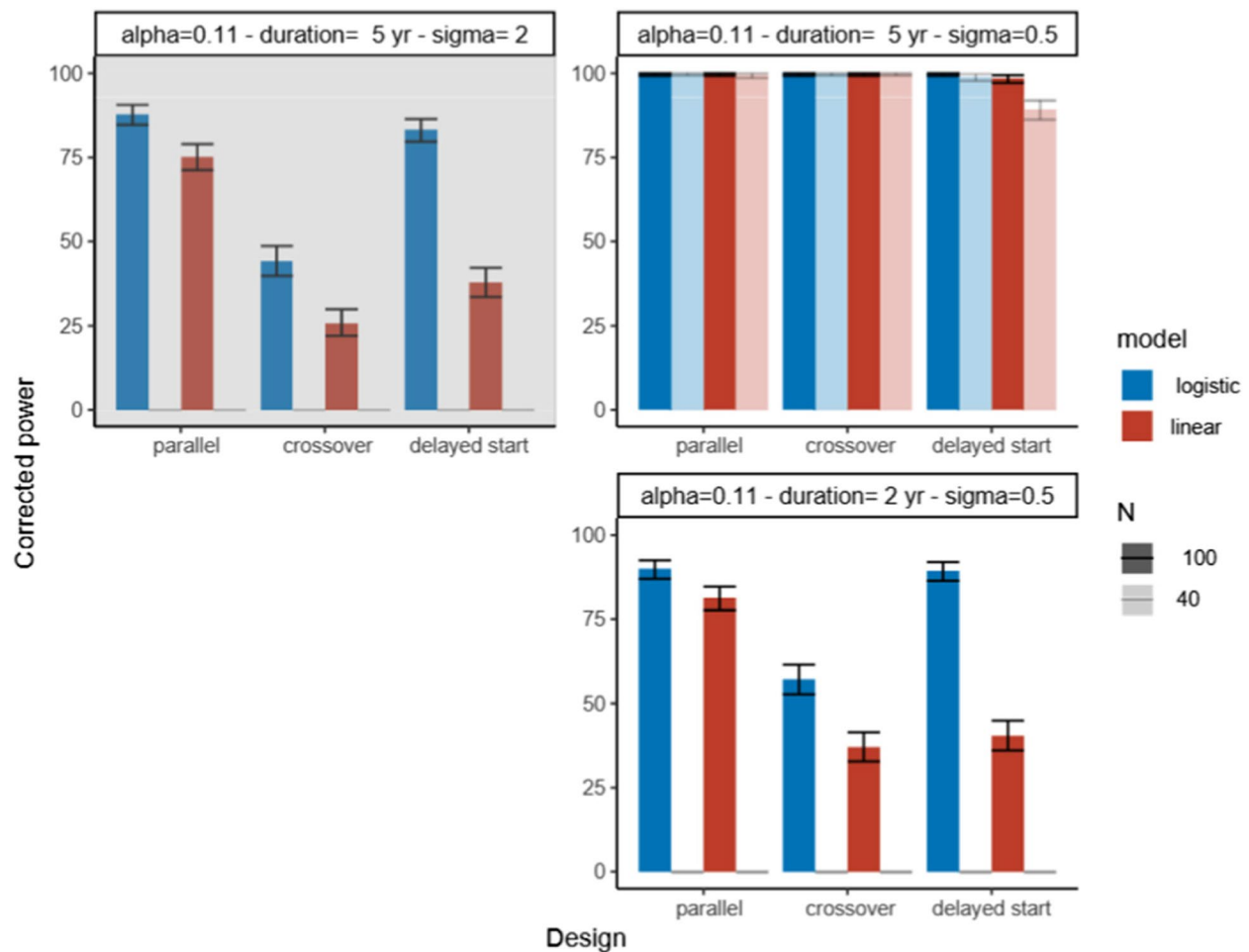
Fig. 7 Corrected power for the slow progression reference and the scenarios with duration = 5 years/σ = 0.5 and duration = 2 years/σ = 0.5. The colours of the bars correspond to the model used for estimation. The grey background (upper left panel) highlights the reference scenario (slow progression). Darker and lighter shades represent N = 100 and N = 40 respectively

under treatment. In the particular context of ARCAs we found (Hendrickx et al.) [7] that for the ARSACS population which we used as a basis for the slow-progression scenario, the change in SARA score was very progressive and variable depending on disease stage (from 0.05 to 1 point/year). The SARA score also increases especially slowly in the earlier stages, and here with uniform inclusion in the first 30 years after onset of symptom we expect SARA to progress by less than 0.25 points per year in half of the subjects included. This should also be contrasted with the high residual error (σ = 2), implying that to identify a disease modifying treatment effect, it is important to observe the disease progression for a long period of time. In our simulation settings, the total duration was the same for all designs, so that disease progression was only followed for 2.5 years under treatment for each patient in the cross-over design. Furthermore, here the variability in progression rate is termed quite low (< 30%), whereas the strength of a crossover trial is to

differentiate between the variability in disease progression (α) and the treatment effect.

In our settings, the delayed start design performed almost as well as the parallel design. An advantage is that all patients eventually get treated, just like in single arm trial, while preserving the ability to identify untreated progression within the trial. A delayed start design was evaluated by Wang et al. [12] for its ability to detect a drug-induced disease modification in neurodegenerative disorders, as with a lasting effect on disease progression, patients who receive the treatment only in the second period won't catch up to the patients who received the treatment earlier, resulting in parallel curves between the two treatment groups. We believe that, in our settings, the delayed start design outperforms the crossover design because in one group, patients are observed under treatment for the full duration of the trial, unlike the crossover design. Also, the delay duration was chosen to be the mid-trial observation (at 1 year for 2-year trials and
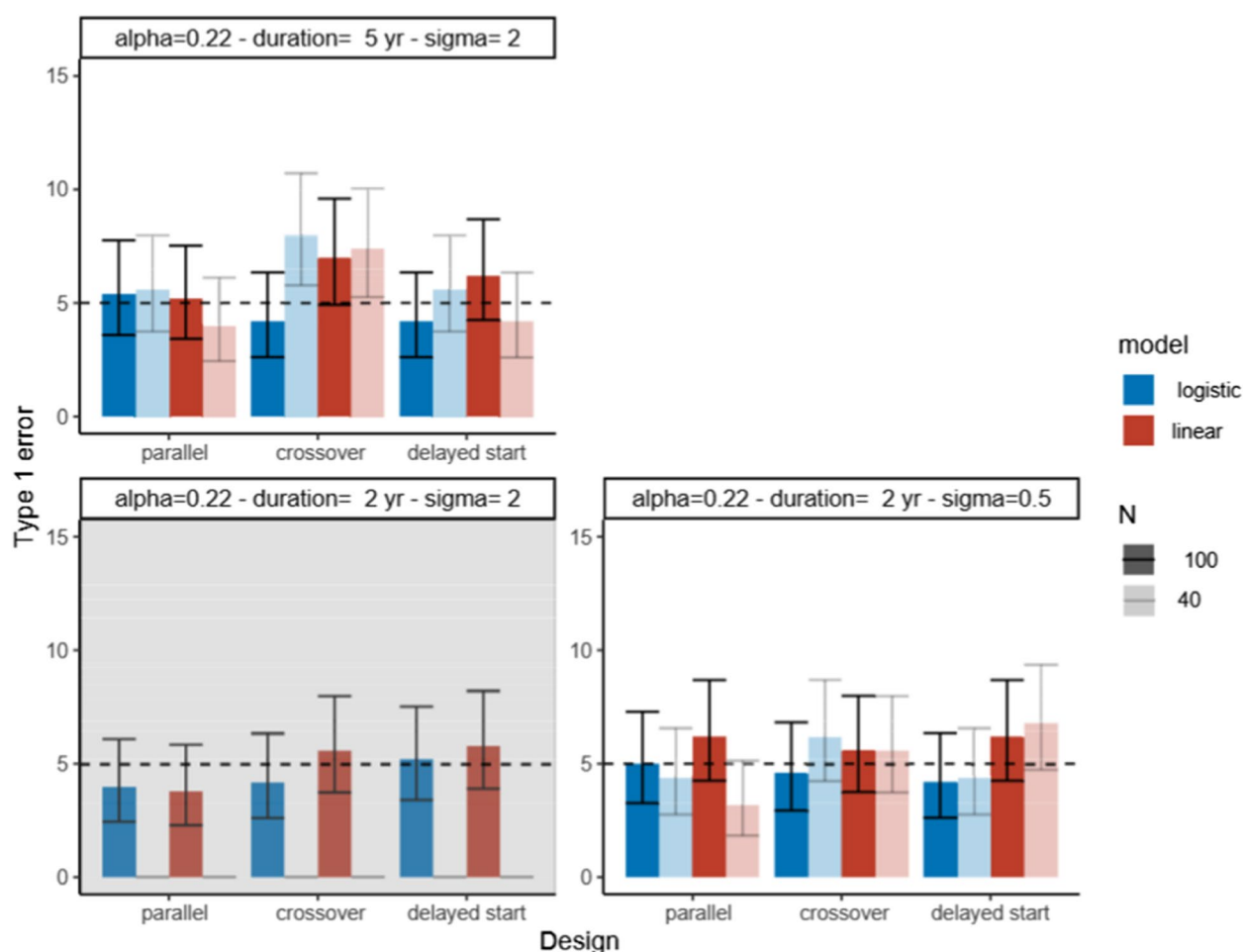
Fig. 8 Type 1 error for the fast progression reference and the scenarios with duration = 5 years/σ=2 and duration = 2 years/σ=0.5. The colours of the bars correspond to the model used for estimation. The grey background (lower left panel) highlights the reference scenario (fast progression). Darker and lighter shades represent N = 100 and N = 40 respectively

at 2.5 years for 5-year trials), but the delay duration could be further optimised with regards to power or feasibility.

In this work, we based our simulation settings on natural disease progression in the ARSACS population of the ARCA registry assuming a disease modifying treatment effect on disease progression. Even though there are currently no disease-modifying treatments for most ARCAs, several clinical trials are ongoing for molecular therapies or gene therapies. For example, FDA just approved the use of levacetylleucine for Niemann-Pick disease type C [10] (NPC). It here followed a clinical trial protocol [23, 24] that will evaluate the efficacy of the drug also– in addition to NPC -on two other ultra-rare neurodegenerative diseases, including Ataxia Telangiectasia, an ARCA with fast progression [25]. They evaluated the efficacy of the compound for Niemann-Pick disease type C with 60 patients, with a crossover design including two 12-weeks periods using the SARA score as the primary endpoint. The authors were able to show evidence of efficacy, however, they also emphasized that the proposed

design could only demonstrate the symptomatic effect of the treatment and that they would need a larger sample size and a longer trial to show an effect on disease progression. In their protocol, they included a single-arm open label extension where they would monitor the progression for two years under treatment to investigate the effect on the disease progression. This difference of assumption on treatment effect (symptomatic versus disease-modifying) can explain why they could show a treatment effect with a crossover trial while, in our simulations, the crossover trial could not reach such levels of power, even with a duration of two years. The trial aiming to evaluate the efficacy of the compound on Ataxia Telangiectasia is a single arm trial [26], where patients are monitored 6 weeks with treatment and also for a 6-week post-treatment washout period. There are currently 39 patients enrolled (patients of 6 years of age and older). The primary outcome measured is the Clinical Impression of Change in Severity (CI-CS) (7-point Likert scale, from −3 = significantly worse to +3 = significantly
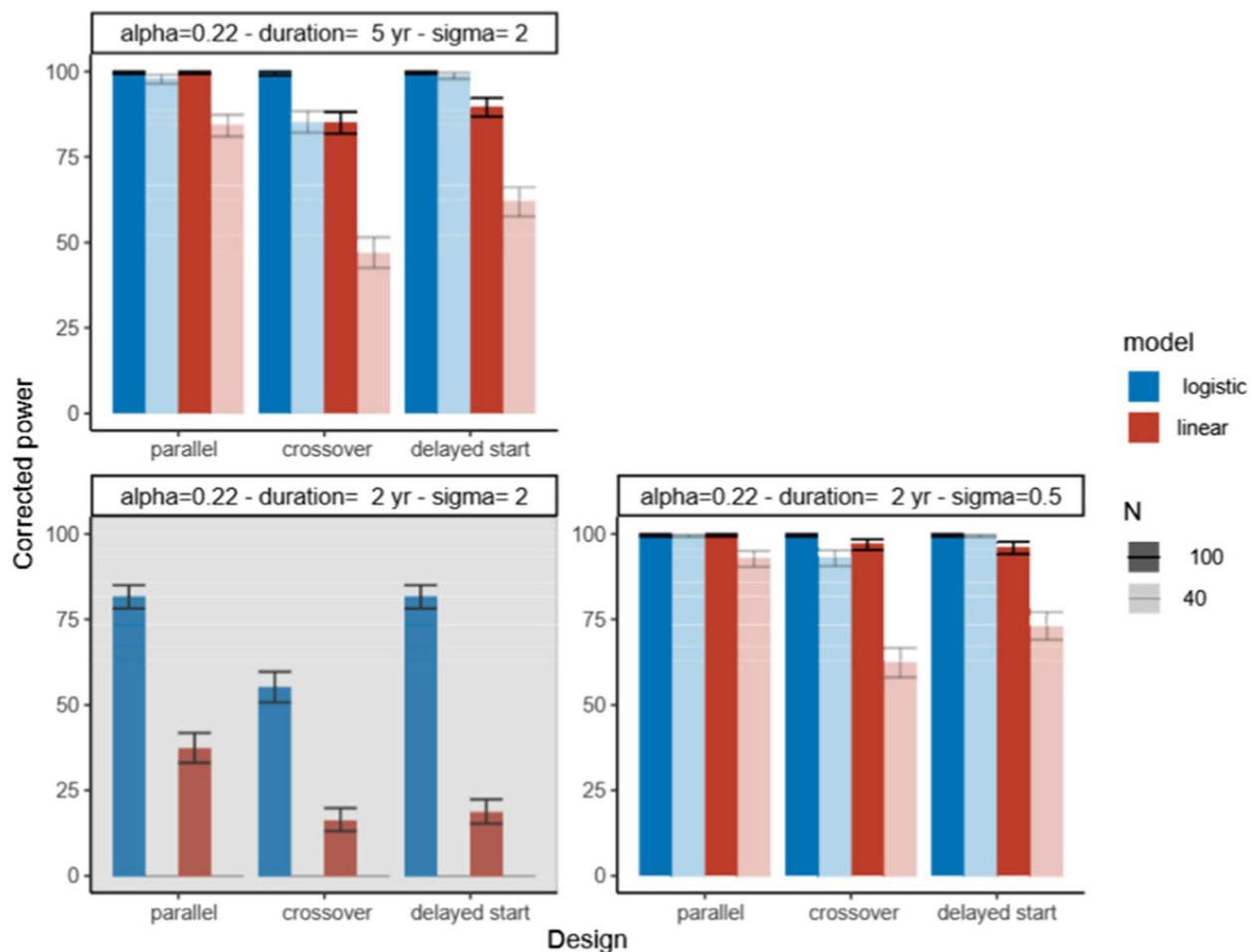
Fig. 9 Corrected power for the fast progression reference and the scenarios with duration = 5 years/σ = 2 and duration = 2 years/σ = 0.5. The colours of the bars correspond to the model used for estimation. The grey background (lower left panel) highlights the reference scenario (fast progression). Darker and lighter shades represent N = 100 and N = 40 respectively

improved) and the SARA score is measured as a secondary outcome. Ataxia Telangiectasia could be compared to our fast progression reference. Again, the trial duration is much shorter but the assumption on the magnitude of treatment effect is different. Bruegermann et al. [27] monitor the evolution of the SARA score on 6 patients with Ataxia Telangiectasia with the same compound. They found that, after one month of treatment, the SARA score is significantly lower (by 4 points on average), and that the SARA score goes back up after patients stop the treatment, suggesting the effect could be symptomatic. However, this trial design confirms that it would be feasible (if these effect sizes can indeed be independently confirmed) to enroll 40 patients in the fast-progression case. In addition to molecular therapies, clinical trials investigating the efficacy of gene therapy are also being conducted in ARCAs. In fact, the three ongoing gene therapy clinical trials in Friedrich's Ataxia [28–30] will follow patients for 5 years, with a disease progression in this genetic diagnostic similar to that of ARSACS [14],

but with much lower sample sizes, as those are phase 1 trials.

The parameters we used in the slow progression scenario correspond to the estimates found when modelling the change in SARA score in the ARSACS patients of the ARCA registry [7], where we found a high variability of the SARA score (σ = 2) in comparison to the yearly rate of disease progression. The implication of the poor signal/noise ratio as we saw in our simulations is the longer trial duration needed to discriminate natural progression from slower progression under treatment. Reducing the variability in the SARA score would open the possibility for shorter trials, as shown by the simulations performed with σ = 0.5. Grobe-Einsler et al. [31], evaluated the property of repeated measures of the score. They selected 5 subitems of the score which can be videotaped by the patient themselves without requiring an on-site examiner (excluding the sitting and two fine motor movement subitems), and evaluated the score on 12 patients with ataxia twice a day for 14 days. They notably highlighted

that there was no statistically significant training effect over the two-week period and that there was a four-fold reduction of variance of residual error by averaging all SARA assessments. This could confirm that the high residual variability found in our model is inherent to the SARA score and that repeating measures could improve the assessment of an individual's SARA score, even though this could be difficult to conduct in practice. In our simulation framework, we tested scenarios with a lower magnitude of residual error. We could assume that such a scenario would be feasible by either reporting an average SARA score over several measurements or increasing the visit frequency. Additionally, in our framework, for simulation and estimation the SARA score (which ranges from 0 to 40 points) was treated as continuous. We could also expect a small drop in power in all scenarios if the simulated score was discretized before the estimation. Alternatively, another modelling approach could be applied, with an Item Response Theory (IRT) model for example [14, 32], which would keep the discrete nature of the data and which would leverage information from each sub item of the SARA score instead of the total score.

In the simulation framework, we chose the SARA score as the primary endpoint to assess treatment efficacy. SARA score is the currently most widely used outcome to assess disease severity in ataxia patients. We chose the SARA score because it is included in most clinical trials, at least as a secondary endpoint or used in the inclusion criterion. It is a composite score comprised of 8 subitems evaluating gait, stance, sitting, speech, and 4 other items for fine motor movements. It was shown in Weyer al. [33] to be a reliable and valid measure is disease severity in patients with ataxia, but it was weakly correlated to disease duration (time since onset of symptoms). Furthermore, the FDA is also investigating a modified version of the SARA score, called the modified functional Scale for Assessment and Rating of Ataxia (f-SARA). In fact, Potashman et al. [34] discuss that the score was modified to only include the gait, stance, speech and sitting items, because, in the context of a clinical trial that would last one year, the other items were considered not sensitive enough to capture change in disease progression. Therefore, even though, in patient registries, the SARA score would be more meaningful to capture long term disease progression- and also upper limb functioning, The f-SARA score could be more relevant in the context of a clinical trial with a shorter duration, where the score might be more sensitive to change. However, our recent IRT models of the SARA score [14, 32] show it would lose informational value. The relative performance of the f-SARA score compared to the SARA score could be investigated in a future study. Finally, for ARCAs, composite clinical scores are being investigated because there

are currently no validated biomarkers that can be applied to all genotypes. However, other outcomes are being investigated, such as quantitative motor assessment, called digital biomarkers [35]. The goal is to quantify variability and stability of patient movement using sensors. They are being developed and being validated as a quantitative and continuous metrics that could be used as an outcome in clinical trials [36]. Fluid biomarkers are also being investigated, such as the Neurofilament Light chain (Nfl), a biomarker of neurodegeneration. In fact, Donath et al. [37] showed that Nfl levels were significantly higher in Ataxia Telangiectasia patients than healthy individuals. It was also shown in Li et al. [38] that, for patients with Spinocerebellar ataxia type 3, serum levels of Nfl were significantly correlated with disease severity (with both the ICARS and SARA scores). This biomarker is also included as a secondary outcome in a clinical trial [39] that evaluates the effect of a compound on patients with Ataxia Telangiectasia. Given the fact that, in our simulation framework, we assume that the SARA score is continuous, our modelling approach would be compatible with such continuous biomarkers.

In our work, the simulation framework for clinical trial designs was built upon a previously built non-linear mixed effect model [7], and several assumptions were made. The four-parameter logistic model was built using data from the ARCA registry [15], a multicentric registry of patients with Autosomal Recessive Cerebellar Ataxia. Then, since there is currently no disease-modifying drug approved for most ARCAs, we hypothesised that the treatment would reduce the α parameter, which implies that the treatment would have an effect on both the disease progression rate and the inflection point of the logistic curve. We could have implemented treatment effect differently, for example as a change in β, which controls the inflexion point, making patients progressing later, or in γ, assuming that the treatment would decrease the maximum score reachable by a patient, or a combination of both. Also, as discussed by Bermova-Ertl et al. [10], it is possible that a disease modifying treatment could also have a symptomatic effect, meaning that, for the patients, the SARA score could also decrease temporarily. Then, we also made an assumption on the inclusion criterion of the trials. The range of 0 to 30 years since onset of the disease was chosen because, in the slow progression case, it would translate to a range of 0–20 points of SARA score and, according to Benatar et al. [40], patients with a neurodegenerative disease would benefit from a clinical trial for a disease modifying drug when they are at most at a mild stage of the disease. Even though recruiting patients during the later stages of the range (20–30 years) would yield higher power [7, 14], an inclusion criterion based on an heterogeneous time since onset at inclusion was chosen because it would be the most realistic

possibility given the rare nature of the disease, which was confirmed by many of the ongoing clinical trials presented above, some of which included patients starting at 6 years of age. However, since this range was chosen for the slow progression case, it might not be completely comparable for the fast progression case (on average, patients would reach a SARA score of 20 points 15 years after the onset of symptoms). An important assumption in model-based analyses is that the model is well specified, meaning, in our case, that the logistic model is the simulation model describing the evolution of the SARA score. In our simulation framework, the logistic model was therefore advantaged compared the linear and sparse linear models, even though the parameters of the logistic model were re-estimated. While a four-parameter logistic model is a flexible and generic model, other, more robust, approaches could have been used to handle model misspecification, such as model averaging [3, 41, 42]. Furthermore, a sensitivity analysis was performed in Hamdan et al. [14] Data was generated using an Item Response Theory model (where the data is assumed to be discrete) (using parameters of the ARSACS genotype), and analysed with several models, including the logistic model presented in this manuscript. In that work, one of the scenarios presented is identical to our slow progression reference scenario (beside the simulation model). The results where that, with the logistic model, the type 1 error was slightly inflated (6–8%) and there was a loss in power (62% instead of 85%). Finally, to identify a treatment effect, we used the likelihood ratio test, which relies on an asymptotic assumption. The LRT was chosen over other asymptotic tests such as the Wald test because of its practicality and better numerical stability: only the likelihood is required instead of the Fisher Information Matrix (which is derived from the likelihood). Also, the Wald test assumes a symmetry of the uncertainty, which is not necessary for the LRT [43]. In non-linear mixed effect models, the asymptotic assumption translates to having sufficient patients and observations per patient. In our simulations, we considered that this condition was met with 40 and 100 patients, with 6–11 observations per patients. Such approaches could still be used in small samples, by correcting for the type 1 error inflation using randomisation tests [44]. Alternatively, Bayesian methods could be used, for example by using external control using Bayesian borrowing [45].

In this work, we primarily focused on the simulation framework for clinical trial designs, but in the event of the analysis of a real data set, additional steps would be required to handle model misspecification. For example, other models could be tested (other forms of logistic models, exponential model, Gompertz models, IRT models) and selected according to their BIC or goodness of fits. If the performance of several models is comparable,

model averaging could be implemented as in [41, 42]. In addition, since, in our logistic model, the γ parameter was fixed, a sensitivity analysis could be performed by changing the value of that parameter (as its value could be specific to a genotype of ARCA, and not generalisable to the entire population).

Conclusion

In this work, we proposed a simulation framework to compare clinical trial designs and settings in the context of rare neurological diseases, using as showcase basis for the simulations the disease group of ARCAs, characterised by small sample sizes (less than 100), patient heterogeneity (in terms of disease severity at inclusion), use of real-world data, lack of curative/efficient treatments. We studied the influence of using longitudinal models versus more standard statistical analyses, the influence of disease progression rate, trial duration and magnitude of residual error on the type 1 error and power on a clinical trial that would quantify a disease-modifying treatment effect. In our settings the parallel performed best. The delayed start design had similar performance with the advantage that all patients are treated in this design. In our framework, the crossover design had lower power, mainly due to the slow disease progression coupled with high residual error, requiring to observe disease progression for a longer time (at least in a disease-modifying treatment setting, as tested here). This work showed the complex interaction between trial settings and power. In a practical situation, different approaches could be used to predict power, such as simulations using the design of the planned study as we did in this work. Such a framework could be implemented in a simulation platform to assess the suitability of a given of trial settings for future trials. Alternatively, we could use optimal design approaches based on the Fisher Information Matrix to evaluate the power of a design, which are implemented in different softwares [46–48]. Reducing the sample size to match disease rarity would require smaller residual variability in the primary outcome, here the SARA score, to better identify disease progression, which would need to be achieved by less noisy endpoints or more frequent assessments.

Abbreviations

ARCA	Autosomal Recessive Cerebellar Ataxia
ARSACS	Autosomal Recessive Spastic Ataxia of Charlevoix Saguenay
CI-CS	Clinical Impression of Change in Severity
DE	Drug Effect
FDA	Food and Drug Administration
ICARS	International Cooperative Ataxia Rating Scale
IRT	Item Response Theory
LRT	Likelihood Ratio Test
NLMEM	Non-Linear Mixed Effect Model
Nfl	Neurofilament Light chain
NPC	Niemann Pick disease type C
PsN	Pearl speaks Nonmem

SARA   Scale for the assessment and Rating of Ataxia
TRT   Treatment
TSO   Time Since Onset

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s12874-025-02626-x.

Supplementary Material 1.

Data availability
For this study, we used a previously published model to simulate data, so no personal data was collected and/or processed. The code to reproduce the simulation study is available at the following link: https://doi.org/10.5281/zenodo.14755801.

Declarations

Ethics approval and consent to participate
For this study, we used a previously published model to simulate data, so no personal data was collected and/or processed.

Consent for publication
Not applicable.

Competing interests
Dr. Synofzik has received consultancy honoraria from Ionis, UCB, Prevail, Orphazyme, Servier, Reata, Biogen, GenOrph, AviadoBio, Biohaven, Zevra, Solaxa, and Lilly, all unrelated to the present manuscript. Dr Emmanuelle Comets has received consultancy honoraria from Sanofi, unrelated to the present manuscript. Drs Hooker and Karlsson have received consultancy fees from and own stock in Pharmetheus, all unrelated to this manuscript. Dr. Mentré has received consultancy fees from Pharmetheus and Ipsen, all unrelated to this manuscript. All other authors declared no competing interests in this work.

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