Using a Decision-Theoretic Approach to Optimize Design Characteristics in Rare Disease Trials

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Abstract

Typically, the size of a clinical trial is determined on the basis of statistical error rates (i.e. α and β). An alternative approach, which has received considerable attention in the literature [7, 11], is a decision-theoretic approach. Such an approach may be particularly useful in the context of rare-disease trials, where the available patient population is limited. In addition, it offers the benefit of explicitly addressing the consequences of different design options in terms of expected health benefits for the population, as well as trial costs. In this paper, it will be illustrated how a decision theoretic perspective can be used to optimize a trial design, with a specific focus on an Amyotrophic Lateral Sclerosis (ALS) population. Within this trial, survival between two treatments (E and C) will be compared. The primary focus is maximizing the expected overall life expectancy. The parameters to be optimized are t_1 and t_2, which represent the start of trial recruitment and the end of the trial, and in turn determine the size and duration of the trial. In addition, the (monetary)costs and expected power will be evaluated. Results will provide researchers with a more elaborate perspective on the consequences of different trial design options.

1 Introduction

Considerations concerning clinical trial design characteristics, such as sample size and follow-up duration, are of vital importance in the planning of a clinical trial. In the traditional frequentist approach, sample size determination is based upon statistical error rates. Determining sample size can be challenging in the case of a rare disease, when there are clear limitations to the maximum sample size that can be obtained. In the United States, a rare disease is a disorder or condition that affects less than 200,000 persons. In Europe a disease is defined as rare if the prevalence is not more than 5 in 10,000. Both the Food Drug Administration (FDA) and European Medicines Agency (EMA) state that less commonly seen methodological designs may be acceptable in small population conditions if they might improve the interpretability of the results in the study[4, 6]. Other authors advise that trialists look systematically at alternative design options when setting up a clinical trial for a rare disease [8].

Various alternative approaches have been proposed. One approach is the decision theoretic approach [11]. Decision theory is an analytical technique by which the problem of decision-making under uncertainty may be formalized. In this approach, the consequences of different possible decision options are explicitly modelled. In the setting of a clinical trial, we may wish to decide between a number of possible design options [7].

One example of a design option is sample size, another is follow-up duration. Suppose that the consequences associated with each action (choice of sample size and follow-up duration) can be expressed by some utility (some loss or gain). This utility can be described by a *utility function*. The consequences may well depend on the true unknown state of nature, the 'real' effect size. The sample size and follow-up duration that are chosen for the clinical study are those that maximize the *utility*, and thus the expected gain for the total population [see e.g. 7, 11]. The concept *gain* can be defined very broadly from, for example, the patient, sponsor, or society perspective – or various perspectives can be combined. The *gain* will thus depend on which perspective is chosen [11]. The utility function should express the values of the consequences, for example in terms of life expectancy or (monetary) costs of possible actions, from the perspective of the decision-maker.

Various authors explored the field of decision-theory and formulated utility functions incorporating various perspectives [see e.g. 5, 12, 17] For a recent overview of decision theoretic approaches for small trials, see [7]. This paper will focus on the decision-theoretic approach in the context of survival data, using data from Amyotrophic Lateral Sclerosis (ALS) trials as a motivating example. Results will provide researchers with a more elaborate perspective on the consequences of different trial design options.

1.1 Motivating Example

An example of a rare disease is Amyotrophic Lateral Sclerosis (ALS). ALS is one of the most severe and invalidating diseases of the nervous system [16]. Each year, around 15.000 people are diagnosed with ALS all over Europe (2.2 per 100,000 person-years) [9], and approximately 6.000 people are diagnosed in the U.S.A [2]. The average survival time is only three years, making the patient population clearly delimited. Up until now, the specific cause remains unknown and except for treatment with *Riluzole* which extends survival with a few months, no effective treatments exist [3, 10]. Most studies concerning ALS investigate the survival time, and since the current average lifespan is short, gain in terms of survival would benefit patients the most.

2 Methods

We are going to apply the decision theoretic framework to a specific setting and formulate three *utility* functions, representing different perspectives. The first function covers the perspective of life expectancy for the population (section 2.4), the second will give insight in the costs (monetary) of a trial (section 2.5) and finally the power will be evaluated (section 2.6). The goal is to use these functions to optimize the design characteristics sample size and follow-up duration.

2.1 Setting & Notation

Suppose we want to conduct a clinical trial, with the aim of demonstrating superiority of experimental treatment (E) over the standard of care (C) in terms of survival. We want to show superiority by means of a logrank test, with one-sided $\alpha = .025$. The population of interest is defined as consisting of all newly diagnosed patients from $t_0 = 0$ until some future time point t^*. t is measured in years. Let N denote the size of this population.

Trial recruitment starts at $t_0 = 0$ and stops at t_1, and the trial follow-up stops at t_2 for all subjects ($t_0 < t_1 \leq t_2 \leq t^*$), so that the follow-up duration will be shorter for subjects included at a later point in time (see figure 1). t_i' represents the moment in time of a possible treatment switch for an individual, either from $E \to C$, or from $C \to E$.

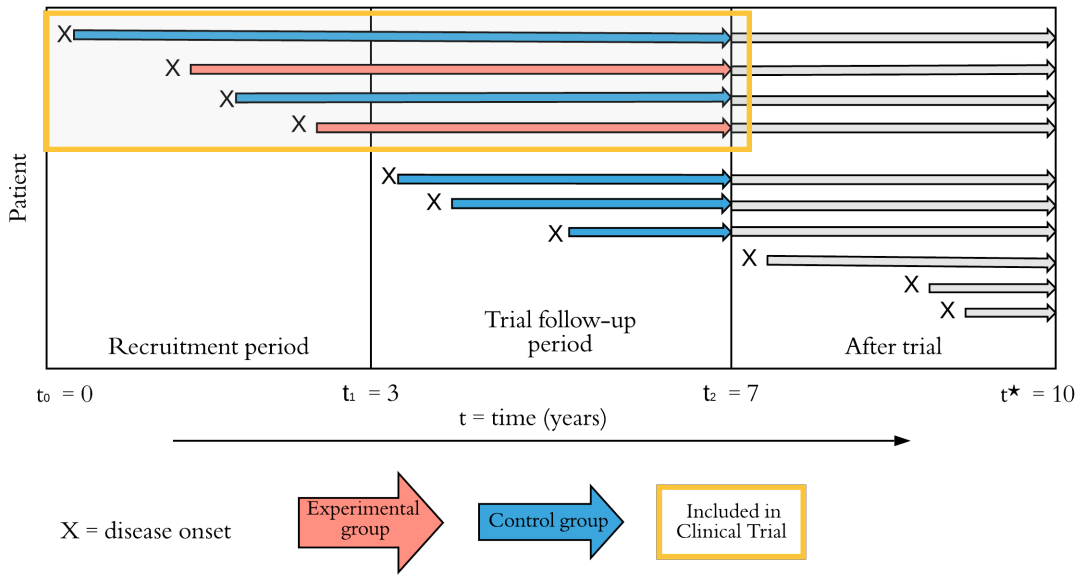

Figure 1: Schematic representation of a hypothetical clinical trial.

It is assumed that each new diagnosed patient will participate in the trial, and thus the set of patients entering the trial is a representative of the disease population. Further, we assume equal allocation, constant hazard rates within the groups for the control and experimental treatment, and a constant onset rate of new diagnoses.

2.2 Subgroups

In this setting, the total population can be divided into four subgroups (see figure 1), the first two groups consist of patients in the trial receiving either the standard treatment (C) or the experimental treatment (E). The third group consists of patients not in the trial, with disease onset between t_1 and t_2, which is the trial follow-up period. The last group consists of patients not within the trial with disease onset after t_2. The treatment these patients receive can either be E, C, or a combination of the two. The size of the subgroups is dependent on the begin- and endpoint of the trial, and the patient horizon. The following combinations of treatments are possible, depending on the outcome of the trial:

Subgroup	**Size**	**Superiority of E not demonstrated**	**Superiority of E demonstrated**
1	$n_1 = 0.5 * N * \frac{t_1}{t*}$	C	C $\rightarrow E$
2	$n_2 = 0.5 * N * \frac{t_1}{t*}$	E $\rightarrow C$	E
3	$n_3 = N * \frac{(t_2 - t_1)}{t*}$	C	C $\rightarrow E$
4	$n_4 = N * \frac{(t* - t_2)}{t*}$	C	E

Table 1. Possible combinations of control treatment and experimental treatment for subsets of the population.

The choice to introduce new treatment E into clinical practice is dependent on the outcome of the statistical test in respect of the clinical trial. Patients may switch from E to C when they were first assigned to the experimental treatment during the trial, but trial results did not show superiority and thus they switch back to C after the trial has finished. Patients may switch from C to E, when they were either in the control condition during the trial, or not taking part in the trial at all, and the outcome of the trial shows superiority of E, thus all patients switch to this new treatment in practice.

2.3 Expected overall life expectancy

The first *utility* function we are going to formulate concerns the relation between the life expectancy for the entire patient population and t_1 and t_2, for given values of λ_e and λ_c. We are going to search for the optimal combination of values of t_1 and t_2 that maximizes this *utility*.

For the subgroups of the population that do not undergo a treatment switch, the hazards (defined by λ_e and λ_c), are constant over time. The life expectancy turns out to be simply $\frac{1}{\lambda}$, so either $\frac{1}{\lambda_c}$ or $\frac{1}{\lambda_e}$ for the control or experimental treatment, respectively [13].

2.3.1 Survival function

In the case of a treatment switch at timepoint t'_i, the hazards are not constant over time, but can be considered stepwise constant (3.1 for detailed steps). The survival function for both scenario's: with either no treatment switch, or a treatment switch at t'_i, can be defined by,

$$S(t, t') = \begin{cases} \exp(-t \cdot \lambda_e) & \text{if } 0 \leq t < t'_i \\ \exp[-t'_i \cdot \lambda_e - (t - t'_i) \cdot \lambda_c] & \text{if } t'_i \geq t \end{cases} \tag{1}$$

Where t'_i represents the moment in time where an individual, i, undergoes a treatment switch.

2.3.2 Life Expectancy Individuals

In general, life expectancy is defined as follows [13]:

$$LE = \int_0^\infty S(t, t'_i)dt \tag{2}$$

If we want to obtain a definition for the survival function in the case of a treatment switch from E $\rightarrow$ C, we apply the definition given above (2), finally leading to (see 3.2),

$$LE = \frac{1 - exp(-t'_i \cdot \lambda_e)}{\lambda_e} + \frac{exp(-t'_i \cdot \lambda_e)}{\lambda_c}. \tag{3}$$

In the case of a treatment switch from C $\rightarrow$ E, the hazards can simply be reversed. We have now defined the life expectancy for individuals receiving only either C or E, and life expectancy in the situation where individuals undergo a treatment switch.

2.3.3 Life Expectancy Subgroup

In 2.3.2 we have determined the life expectancy for individuals. Now, we want to determine the life expectancy for each of the subgroups of the population. We assume disease diagnosis times are constant over time, and can be described by a uniform distribution. The overal life expectancy for subgroups of the population that undergo a treatment switch can be calculated with (see 3.3),

$$\frac{\frac{exp(t_1 \cdot \lambda_e - 1) + exp(-t_2 \cdot \lambda_e(\lambda_e - \lambda_c))}{(t_1 \cdot \lambda_c)} + \lambda_e}{\lambda_e^2}. \tag{4}$$

The function specified above enables us to calculate the overall life expectancy by summing the subgroup-specific life expectancies (table 2).

Subgroup	Outcome of trial: E treatment not superior	Outcome of trial: E treatment superior
1	$n_1 \cdot \frac{1}{\lambda_c}$	$n_1 \cdot \frac{\frac{exp(t_1 \cdot \lambda_c - 1) + exp(-t_2 \cdot \lambda_c(\lambda_c - \lambda_e))}{(t_1 \cdot \lambda_e)} + \lambda_c}{\lambda_c^2}$
2	$n_2 \cdot \frac{\frac{exp(t_1 \cdot \lambda_e - 1) + exp(-t_2 \cdot \lambda_e(\lambda_e - \lambda_c))}{(t_1 \cdot \lambda_c)} + \lambda_e}{\lambda_e^2}$	$n_2 \cdot \frac{1}{\lambda_e}$
3	$n_3 \cdot \frac{1}{\lambda_c}$	$n_3 \cdot \frac{\frac{exp(t_1 \cdot \lambda_c - 1) + exp(-t_2 \cdot \lambda_c(\lambda_c - \lambda_e))}{(t_1 \cdot \lambda_e)} + \lambda_c}{\lambda_c^2}$
4	$n_4 \cdot \frac{1}{\lambda_c}$	$n_4 \cdot \frac{1}{\lambda_e}$
Sum	OLE_c	OLE_e

Table 2. Calculations for life expectancy for the entire population per trial outcome. OLE_c = Overall Life Expectancy, E treatment not superior. OLE_e = Overall Life Expectancy, E treatment superior.

2.3.4 Power logrank test

We are in the setting of survival analysis and want to evaluate experimental treatment E over control treatment C by means of a logrank test. In order to do so, we need to evaluate the power of the logrank test. The test statistic of the logrank test is $\sim N(0,1)$ under h_0. The logrank test statistic T has the following distribution under h_a[14],

$$T \overset{a}{\sim} N(\beta\sqrt{(}\theta(1-\theta)D), 1) \tag{5}$$

where β is the log hazard ratio, θ is the allocation probability to the treatment condition, and D is the total expected number of deaths under h_a from both groups. To derive the expected number of deaths (D), we integrate over the uniform distribution and $(1 - S(t, t'))$, and subsequently integrate out t, leading to the following results (see 3.4):

$$D = n * (\frac{exp - ((t_2 - t_1) \cdot \lambda) - exp(-t_2 \cdot \lambda)}{((t_2 - t_1) \cdot \lambda) - (t_2 \cdot \lambda)} + 1). \tag{6}$$

When we know D, we are able to calculate the power using the critical value (one sided $\alpha = .025$). See 3.6 for implementation in R.

2.4 Utility function

We have now determined the power and can give weight to both of the scenario's described above (accept or reject new experimental treatment E). Thus, we first calculate the overal life expectancy for scenario where we accept E, and subsequently for the scenario where we reject E. We can then easily combine this with the power to find the *Expected Utility*:

$$Expected\ utility = power * OLE_e + ((1 - power) * OLE_c), \tag{7}$$

where OLE_e stands for the overal life expectancy in the experimental group, and OLE_c for the overal life expectancy in the control group.

The utility function describing the expected overal life expectancy implemented in R can be found in section 3.6. Next, we will include realistic estimates of hazards for ALS and using

these as a baseline for the control group, and start varying the hazards (λ_e) for the experimental group. Subsequently, the optimal combination of values for t_1 and t_2 can be investigated.

2.5 Cost function

Next to the utility function displaying the *'expected overall life expectancy'* we will provide researchers with a function giving insight into the (monetary) costs of a clinical trial. The *costs* function will give insight into costs and gains within the trial. Costs will be evaluated separately for the control (C) and experimental (E) group.

Roughly, the function will have a few parameters covering both fixed and variable costs. The first parameter will be the fixed costs for starting a new clinical trial. The next parameter will represent fixed costs for including one extra patient into the trial. The next parameter will represent variable costs per patient, per year. Possibly other factors will be included as well. The purpose of this function is to illustrate how costs develop in a clinical trial, when including less or more patients.

2.6 Power function

Still an important aspect in the design of a clinical trial is the power. We have already derived the power function as part of the utility function (see 3.5 and 3.6). This function of power is informative by itself already, because it gives insight into the probability of rejecting h_0 given h_0 is false, for combinations of values of t_1 and t_2.

2.7 Results

The results of these three functions can then be displayed in the form of a 3D plot, where the x- and y-axis will represent a range of values for t_1 and t_2, and the z-axis will display the corresponding *expected utility*. By graphically displaying the results of design choices from different perspectives, researchers get insight in consequences of these decisions in an accessible way.

2.8 Priors

Up until this point, we have assumed fixed values for the hazards. Next, we will incorporate *prior distributions* for the hazards, which cover a range of values. This approach can be useful when previous studies of the treatment of interest exist [11]. Priors can for example be based on historic data, or experts' opinion [1]. Since hazards are always positive, a gamma distribution is an appropriate distribution which can represent the beliefs we have about λ_e and λ_c, based on historic data (ALS registry data and [15]).

2.9 Extensions

The setting described in this paper is a simplification of the reality. To better approach the complexity of reality, we will look into several possible extentions. First, we are going to look into into more complex designs, where we will incorporate the possibility to change the allocation ratio (which is assumed to be 1:1).

Second, we want to look into more realistic assumptions. It is known that increasing hazard rates are a better description of reality than constant hazard rates [15]. The next step would be to incorporate a Weibull distribution (which has an extra parameter which takes into account

increasing hazards) instead of the exponential distribution, which only accounts for constant hazards. Further, it would be more realistic to have an extra (fifth) group of patients who do not want to be included in the trial, instead of assuming all patients will participate in the trial.

Third, possible extensions of the described perspectives are possible. For example, we can elaborate the costs perspective. Instead of focusing on costs and gains **within** the trial, also costs **outside** the trial can be evaluated, taking a broader, societal perspective.

3 Appendix

3.1 Derivation survival function

The hazard function in the case of a treatment switch from E $\rightarrow$ C is,

$$\lambda_{e\rightarrow c}(t) = \begin{cases} \lambda_e & \text{if } 0 \leq t_i' \\ \lambda_c & \text{if } t_i' \geq t \end{cases} \tag{8}$$

The survival function thus now becomes,

$$S(t,t') = \begin{cases} \exp(-t \cdot \lambda_e) & \text{if } 0 \leq t < t_i' \\ \exp - \int_0^t \lambda(x)dx & \text{if } t_i' \geq t \end{cases}$$

The integral can be rewritten,

$$\int_0^t \lambda(x)dx = \int_0^{t_i'} \lambda_e dx + \int_{t_i'}^t \lambda_c dx \tag{10}$$

Solving this yields,

$$t_i' \cdot \lambda_e + (t - t_i') \cdot \lambda_c \tag{11}$$

The survival function, in the case of a treatment switch from E to C, can thus be defined as,

$$S(t,t') = \begin{cases} \exp(-t \cdot \lambda_e) & \text{if } 0 \leq t < t_i' \\ \exp[-t_i' \cdot \lambda_e - (t - t_i') \cdot \lambda_c] & \text{if } t_i' \geq t \end{cases} \tag{12}$$

where t_i' represents the moment in time where an individual undergoes a treatment switch.

3.2 Derivation life expectancy with treatment switch (E $\rightarrow$ C) for individuals

Life expectancy is defined as follows:

$$LE = \int_0^\infty S(t, t_i')dt \tag{13}$$

Using the definition the survival function obtained above, we obtain:

$$\int_0^{t_i'} exp(-t \cdot \lambda_e)dt + \int_{t_i'}^\infty exp[-t_i' \cdot \lambda_e - (t - t_i') \cdot \lambda_c]dt \tag{14}$$

Integration yields,

$$-\frac{exp - \lambda_e \cdot t}{\lambda_e}\Big|_0^{t_i'} + -\frac{exp - t'(\lambda_c - \lambda_e) - \lambda_c \cdot t}{\lambda_c}\Big|_{t_i'}^\infty \tag{15}$$

Solving this gives us,

$$\frac{1 - exp(-t_i' \cdot \lambda_e)}{\lambda_e} + \frac{exp(-t_i' \cdot \lambda_e)}{\lambda_c}. \tag{16}$$

.

3.3 Derivation life expectancy for subgroups with treatment switch

The uniform distribution can be described by,

$$P(x) = \begin{cases} 0 & \text{for } x < a \\ \frac{1}{b-a} & \text{for } a \leq x \leq b \\ 0 & \text{for } x > b \end{cases} \tag{17}$$

Where in this situation b represents the endpoint of the trial (t_2), and a represents the starting point of the trial ($t_2 - t_1$).

We can calculate the overal life expectancy for the subsets of the population that undergo a treatment from E $\rightarrow$ C by,

$$\int_{(t_2-t_1)}^{t_2} \frac{\frac{exp(-t_i' \cdot \lambda_e)}{\lambda_c} + \frac{1-exp(-t_i' \cdot \lambda_e)}{\lambda_e}}{t_2 - (t_2 - t_1)} dt \tag{18}$$

Integration with respect to t yields,

$$\frac{\frac{exp(t_1 \cdot \lambda_e - 1) + exp(-t_2 \cdot \lambda_e(\lambda_e - \lambda_c))}{(t_1 \cdot \lambda_c)} + \lambda_e}{\lambda_e^2} \tag{19}$$

The hazards can simply be reversed in the scenario of a treatment switch from C $\rightarrow$ E,

$$\frac{\frac{exp(t_1 \cdot \lambda_c - 1) + exp(-t_2 \cdot \lambda_c(\lambda_c - \lambda_e))}{(t_1 \cdot \lambda_e)} + \lambda_c}{\lambda_c^2}. \tag{20}$$

3.4 Derivation expected number of events

To obtain the expected number of events we solve the following integral,

$$\int_{(t_2-t_1)}^{t_2} \frac{1 - exp(-\lambda x)}{t_2 - (t_2 - t_1)} dx \tag{21}$$

Integrating this yields the following indefinite integral,

$$\frac{\frac{exp - \lambda \cdot x}{\lambda} + x}{t_2 - (t_2 - t_1)} \Big|_{t_2 - t_1}^{t_2} \tag{22}$$

Filling in the values of t leads to the following result,

$$\frac{\frac{exp - \lambda \cdot t_2}{\lambda} + t_2}{t_2 - (t_2 - t_1)} - \frac{\frac{exp - \lambda \cdot (t_2 - t_1)}{\lambda} + (t_2 - t_1)}{t_2 - (t_2 - t_1)}. \tag{23}$$

Which can be rewritten as,

$$\frac{\frac{exp - \lambda \cdot t_2 + \lambda \cdot t_2}{\lambda}}{t_2 - (t_2 - t_1)} - \frac{\frac{exp - \lambda \cdot (t_2 - t_1) + \lambda \cdot (t_2 - t_1)}{\lambda}}{t_2 - (t_2 - t_1)} \tag{24}$$

This can be solved to obtain the definitive integral,

$$\frac{exp - ((t_2 - t_1) \cdot \lambda) - exp(-t_2 \cdot \lambda)}{((t_2 - t_1) \cdot \lambda) - (t_2 \cdot \lambda)} + 1 \tag{25}$$

To finally get to the expected number of events, we multiply by n,

$$D = n * (\frac{exp - ((t_2 - t_1) \cdot \lambda) - exp(-t_2 \cdot \lambda)}{((t_2 - t_1) \cdot \lambda) - (t_2 \cdot \lambda)} + 1). \tag{26}$$

3.5 Power Logrank test

$$H_\alpha = \frac{\lambda_e(t)}{\lambda_c(t)} = e^\beta \tag{27}$$

$$\beta = log\frac{\lambda_e}{\lambda_c} \tag{28}$$

$$T \overset{a}{\sim} N(\beta\sqrt{(}\theta(1-\theta)D), 1) \tag{29}$$

where β is the log hazard ratio, θ is the allocation probability to the treatment condition, and D is the total expected number of deaths under h_a from both groups. With the assumption of allocation 1:1, this can be simplified to:

$$T \overset{a}{\sim} N(\beta\sqrt{(}\frac{1}{4} \cdot D), 1). \tag{30}$$

3.6 Power calculations in R

```
# Calculating the expected number of events for E and C.
D.E <- n2*(1+((exp(-1*(t2-t1)*hE) - exp(-1*t2*hE))/((t2-t1)*hE - t2*hE)))
D.C <- n1*(1+((exp(-1*(t2-t1)*hC) - exp(-1*t2*hC))/((t2-t1)*hC - t2*hC)))

# Calculating the total number of expected events
D <- D.E + D.C

# The proportion of people in the experimental treatment (allocation)
PropE <- .5

# Distribution under the alternative hypothesis
muHa <- log(hE/hC) * sqrt(PropE * (1-PropE) * D)

# Critical value
Cr <- qnorm(0.025, 0, 1)

# Calculate power by taking the area left of the critical value
pwr <- pnorm(Cr, muHa, 1)
```

3.7 Overal life expectancy integrated in R

```
#########################################################################
# Author: Naomi Smorenburg
# Utility function maximizing the overall life expectancy for the
entire population for a combination of values for t1 and t2.
#########################################################################

# OLE = overall life expectancy

OLE <- function(N, hE, hC, t1, t2, t_star) {

  ### Function input ---

  # N = patient horizon
  # hE = hazard rate experimental treatment
  # hC = hazard rate control treatment
  # t1 = starting point of trial (in years)
  # t2 = endpoint of trial (in years)
  # t_star = time until N new onset

  ### Computations ---

  # 1. Calculate the sample size of the different groups
  n1 <- 0.5*N*(t1/t_star)
  n2 <- 0.5*N*(t1/t_star)
  n3 <- N*((t2-t1)/t_star)
  n4 <- N*((t_star-t2)/t_star)

  # 2. Calculating the average life expectancy when E is not superior
  # group only receives C
  C.LE1 <- 1/hC

   # group receives E first, after t' C
  C.LE2 <- (1/hE^2) * (hE + (((exp(t1*hE)-1)*exp(-t2*hE)*(hE-hC))/(t1*hC)))

 # group only receives C
  C.LE3 <- 1/hC

  # group only receives C
  C.LE4 <- 1/hC

  # 3. Calculating the average life expectancy when E is superior
  E.LE1 <- (1/hC^2)*(hC + (((exp(t1*hC)-1)*exp(-t2*hC)*(hC-hE))/(t1*hE)))
  E.LE2 <- 1/hE
  E.LE3 <- (1/hC^2)*(hC + (((exp(t1*hC)-1)*exp(-t2*hC)*(hC-hE))/(t1*hE)))
  E.LE4 <- 1/hE
```

```
  # 4. Calculating the overall life expectancy for the entire population N,
  # for situation E is superior and E is not superior

  #### By multiplying group size with LE for individuals
  C.OLE <- (n1 * C.LE1) + (n2 * C.LE2) + (n3 * C.LE3) + (n4 * C.LE4)
  E.OLE <- (n1 * E.LE1) + (n2 * E.LE2) + (n3 * E.LE3) + (n4 * E.LE4)

  # 5. Calculating the power

  ### First calculate the expected number of events for each group
  D.E <- n2*(1 + ((exp(-1*(t2-t1)*hE)-exp(-1*t2*hE))/((t2-t1)*hE - t2*hE)))
  D.C <- n1*(1 + ((exp(-1*(t2-t1)*hC)-exp(-1*t2*hC))/((t2-t1)*hC - t2*hC)))

  ### Calculate the total expected number of events
  D <- D.E + D.C

  ### PropE = proportion in E group
  PropE <- 0.5

  ### Calculate the mean under the alternative hypothesis
  ### Log-rank test statistic T has distribution
  muHa <- log(hE/hC) * sqrt(PropE * (1-PropE) * D)

  ### Determine the critical value for one sided alpha of 0.05.
  Cr <- qnorm(0.025, 0, 1)

  ### Determine the power by taking the area left of the critical value
  pwr <- pnorm(Cr, muHa, 1)

  # 6. Weigh the two possible outcomes by the power
  U <- (pwr*E.OLE) + ((1-pwr)*C.OLE)


  ### Output ----

  # 7. Take the results and put in a list
  result <- list(
    'Overall life expectancy E not superior' = C.OLE,
    'Overall life expectancy E superior' = E.OLE,
    'Utility' = U
  )

  # 6. Return a list with the results
  return(result)

  # End of function
}
```

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