Case studies with CompAREdesign

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Introduction

This vignette presents two examples of application of the R package CompAREdesign for the design of clinical trials with composite endpoints:

- First example: **time-to-event** endpoints
- Second example: **binary** endpoints

Time-to-event endpoint: ZODIAC TRIAL

This example is based on the data from the ZODIAC trial [1].

Input Parameters

First of all, the information for the components of the composite endpoint should be defined.

```
## Probabilities of observing the event in control arm during follow-up
p0_e1 <- 0.59    # Death
p0_e2 <- 0.74    # Disease Progression

## Effect size (Cause specific hazard ratios) for each endpoint
HR_e1 <- 0.91    # Death
HR_e2 <- 0.77    # Disease Progression

## Hazard rates over time
beta_e1 <- 2     # Death --> Increasing risk over time
beta_e2 <- 1     # Disease Progression --> Constant risk over time

## Correlation
rho      <- 0.1       # Correlation between components
rho_type <- 'Spearman' # Type of correlation measure
copula   <- 'Frank'    # Copula used to get the joint distribution

## Additional parameter
case  <- 3  # 1: No deaths;                    2: Death is the secondary event;
            # 3: Death is the primary event; 4: Both events are death by different causes
```

ARE: Asymptotic Relatively Efficiency

As the ARE is greater than 1, the design using the composite endpoint as the primary endpoint is more efficient from the statistical point of view.

```
ARE_tte(p0_e1   = p0_e1   , p0_e2   = p0_e2,
        HR_e1   = HR_e1   , HR_e2   = HR_e2,
        beta_e1 = beta_e1 , beta_e2 = beta_e2,
```

```
          rho      = rho      , rho_type = rho_type,
          copula   = copula    , case      = case)
```

```
## [1] 8.791
```

Effect size of the Composite Endpoint

Several summary measures of the treatment effect are provided.

```
effectsize_tte(p0_e1   = p0_e1    , p0_e2     = p0_e2,
               HR_e1   = HR_e1    , HR_e2     = HR_e2,
               beta_e1 = beta_e1  , beta_e2   = beta_e2,
               rho     = rho      , rho_type  = rho_type,
               copula  = copula   , case      = case)
```

```
##  Effect measure Effect value | Group measure Reference Treated
##  -------------- ------------ | ------------- --------- -------
##  gAHR            0.8015       |
##  AHR             0.8016       |
##  RMST ratio      1.1633       | RMST          0.3918    0.4558
##  Median ratio    1.2321       | Median        0.3212    0.3958
##                               | Prob. E1      0.5900    0.5557
##                               | Prob. E2      0.7400    0.7125
##                               | Prob. CE      0.9300    0.8847
```

Sample size

The required number of patients for the design of the trial using the composite endpoint as the primary endpoint is **1118**.

```
samplesize_tte(p0_e1   = p0_e1    , p0_e2     = p0_e2,
               HR_e1   = HR_e1    , HR_e2     = HR_e2,
               beta_e1 = beta_e1  , beta_e2   = beta_e2,
               rho     = rho      , rho_type  = rho_type,
               copula  = copula   , case      = case,
               alpha   = 0.025    , power     = 0.90,
               ss_formula = 'schoenfeld')
```

```
##  Endpoint            Total sample size
##  --------            -----------------
##  Endpoint 1          9744
##  Endpoint 2          1002
##  Composite endpoint  1118
```

Influence of hazards rates over time on the effect size

The influence of the behaviour of the hazard rates over time on the treatment effect can be studied by the function effectsize_tte.

```
## Hazard rates over time Case 1
beta_e1 <- 1    # Death --> constant over time
beta_e2 <- 2    # Disease Progression --> increase over time
effectsize_tte(p0_e1   = p0_e1    , p0_e2     = p0_e2,
               HR_e1   = HR_e1    , HR_e2     = HR_e2,
               beta_e1 = beta_e1  , beta_e2   = beta_e2,
               rho     = rho      , rho_type  = rho_type,
               copula  = copula   , case      = case)
```

```
##  Effect measure Effect value | Group measure Reference Treated
##  -------------- ------------ | ------------- --------- -------
##  gAHR             0.8046     |
##  AHR              0.8046     |
##  RMST ratio       1.1310     | RMST             0.3070    0.3472
##  Median ratio     1.1310     | Median           0.2820    0.3190
##                              | Prob. E1         0.5900    0.5557
##                              | Prob. E2         0.7400    0.7381
##                              | Prob. CE         0.9986    0.9943
```

```r
## Hazard rates over time Case 2
beta_e1 <- 1    # Death --> constant over time
beta_e2 <- 1    # Disease Progression --> constant over time
effectsize_tte(p0_e1   = p0_e1   , p0_e2    = p0_e2,
               HR_e1   = HR_e1   , HR_e2    = HR_e2,
               beta_e1 = beta_e1 , beta_e2  = beta_e2,
               rho     = rho     , rho_type = rho_type,
               copula  = copula  , case     = case)
```

```
##  Effect measure Effect value | Group measure Reference Treated
##  -------------- ------------ | ------------- --------- -------
##  gAHR             0.8039     |
##  AHR              0.8039     |
##  RMST ratio       1.2055     | RMST             0.2804    0.3380
##  Median ratio     1.2454     | Median           0.1990    0.2478
##                              | Prob. E1         0.5900    0.5557
##                              | Prob. E2         0.7400    0.7332
##                              | Prob. CE         0.9676    0.9360
```

Binary endpoint: TUXEDO TRIAL

This example is based on the data from the TUXEDO trial [2].

Input Parameters

First of all, the information for the components of the composite endpoint should be defined.

```r
## Probabilities of observing the event in control arm at the end of follow-up
p0_e1 <- 0.059    # Ischemia-driven target-lesion revascularization
p0_e2 <- 0.032    # Cardiac death or target-vessel MI

## Effect size (absolute reduction) for each endpoint
AR_e1 <- -0.0196  # Ischemia-driven target-lesion revascularization
AR_e2 <- -0.0098  # Cardiac death or target-vessel MI

## Correlation
rho   <- 0.4
```

ARE: Asymptotic Relatively Efficiency

As the ARE is greater than 1, we can state that the design using the composite endpoint is more efficient.

```r
ARE_cbe(p0_e1   = p0_e1   , p0_e2   = p0_e2,
        eff_e1  = AR_e1   , eff_e2  = AR_e2,
        effm_e1 = "diff"  , effm_e2 = "diff", effm_ce = "or",
        rho     = rho)
```

```
## [1] 1.139515
```

Effect size of the Composite Endpoint

We can obtain the expected treatment effect based on the odds ratio (OR).

```
effectsize_cbe(p0_e1   = p0_e1  , p0_e2   = p0_e2,
               eff_e1  = AR_e1  , eff_e2  = AR_e2,
               effm_e1 = "diff" , effm_e2 = "diff", effm_ce = "or",
               rho     = rho)
```

```
##   Effect E1 Effect E2 Effect CE
## 1 0.6541709 0.6867969  0.662605
```

Sample size

The required sample size for the design usign the composite endpoint is **2644**.

```
samplesize_cbe(p0_e1   = p0_e1  , p0_e2   = p0_e2,
               eff_e1  = AR_e1  , eff_e2  = AR_e2,
               effm_e1 = "diff" , effm_e2 = "diff", effm_ce = "or",
               rho     = rho,
               alpha   = 0.05, beta = 0.2)
```

```
## [1] 2643.829
```

References

1. Herbst RS, Sun Y, Eberhardt WEE, Germonpré P, Saijo N, Zhou C et al. Vandetanib plus docetaxel versus docetaxel as second-line treatment for patients with advanced non-small-cell lung cancer (ZODIAC): a double-blind, randomised, phase 3 trial. Lancet Oncol. 2010;11(7):619–26.

2. Kaul U, Bangalore S, Seth A, Priyadarshini A, Rajpal KA, Tejas MP et al. Paclitaxel-Eluting versus EverolimusEluting Coronary Stents in Diabetes. N Engl J Med. 2015;373(18):1709-19.