Sample Size considerations for the KIPRUN study

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# *Summary & assumptions*

For the planned study, a total of **250** patients with a possible infection must be observed given the below assumptions.

For the proposed randomized clinical study, the sample size considerations are given with the following suppositions:

* 2 arms (arm A, B)
* binary outcome variable (ie. rates between groups)
* aim: to show statistical significant difference between the two arms
* arm A is hypothecized to be 30%
* arm B is hypothecized to be 15%
* Power of 80%
* Type I error rate of 5% (2-sided, equal to 2.5% one-sided)
* 1 interim analysis (at 50% of cases, but this is flexible), 1 final analysis
* Hwang, Shi & DeCani alpha spending function, gamma = -2
* 1:1 randomization

## R outputs

*Design parameters and output of group sequential design*

*User defined parameters*

* Type of design: Hwang, Shi & DeCani alpha spending
* Information rates: 0.500, 1.000
* Parameter for alpha spending function: -2

*Derived from user defined parameters*

* Maximum number of stages: 2
* Stages: 1, 2
* Futility bounds (non-binding): -Inf

*Default parameters*

* Significance level: 0.0250
* Type II error rate: 0.2000
* Binding futility: FALSE
* Test: one-sided
* Tolerance: 1e-08
* Type of beta spending: none

*Output*

* *Cumulative alpha spending*: 0.006724, 0.025000
* *Critical values*: 2.472, 2.025
* *Stage levels (one-sided)*: 0.006724, 0.021451 *Group sequential design characteristics*
* *Number of subjects fixed*: 7.8489
* *Shift*: 8.0900
* *Inflation factor*: 1.0307
* *Informations*: 4.045, 8.090
* *Power*: 0.3226, 0.8000
* *Rejection probabilities under H1*: 0.3226, 0.4774
* *Futility probabilities under H1*: 0
* *Ratio expected vs fixed sample size under H1*: 0.8645
* *Ratio expected vs fixed sample size under a value between H0 and H1*: 0.9940
* *Ratio expected vs fixed sample size under H0*: 1.0273 *Design plan parameters and output for rates*

*Design parameters*

* Information rates: 0.500, 1.000
* Critical values: 2.472, 2.025
* Futility bounds (non-binding): -Inf
* Cumulative alpha spending: 0.006724, 0.025000
* Local one-sided significance levels: 0.006724, 0.021451
* Significance level: 0.0250
* Type II error rate: 0.2000
* Test: one-sided

*User defined parameters*

* Assumed treatment rate: 0.300
* Assumed control rate: 0.150

*Default parameters*

* Risk ratio: FALSE
* Theta H0: 0
* Normal approximation: TRUE
* Treatment groups: 2
* Planned allocation ratio: 1

*Sample size and output*

* Direction upper: TRUE
* Maximum number of subjects: 248.3
* Maximum number of subjects (1): 124.2
* Maximum number of subjects (2): 124.2
* Number of subjects [1]: 124.2
* Number of subjects [2]: 248.3
* Reject per stage [1]: 0.3226
* Reject per stage [2]: 0.4774
* Early stop: 0.3226
* Expected number of subjects under H0: 247.5
* Expected number of subjects under H0/H1: 239.5
* Expected number of subjects under H1: 208.3
* Critical values (treatment effect scale) [1]: 0.191
* Critical values (treatment effect scale) [2]: 0.103

*Legend*

* (i): values of treatment arm i
* [k]: values at stage k

*Sample size calculation for a binary endpoint*

Sequential analysis with a maximum of 2 looks (group sequential design), one-sided overall significance level 2.5%, power 80%. The results were calculated for a two-sample test for rates (normal approximation), H0: pi(1) - pi(2) = 0, H1: pi(1) = 0.3, control rate pi(2) = 0.15.

| Stage | 1 | 2 |
| --- | --- | --- |
| Planned information rate | 50% | 100% |
| Cumulative alpha spent | 0.0067 | 0.0250 |
| Stage levels (one-sided) | 0.0067 | 0.0215 |
| Efficacy boundary (z-value scale) | 2.472 | 2.025 |
| Efficacy boundary (t) | 0.191 | 0.103 |
| Cumulative power | 0.3226 | 0.8000 |
| Number of subjects | 124.2 | 248.3 |
| Expected number of subjects under H1 |  | 208.3 |
| Exit probability for efficacy (under H0) | 0.0067 |  |
| Exit probability for efficacy (under H1) | 0.3226 |  |

Legend:

* (t): treatment effect scale Design plan parameters and output for rates

*Design parameters*

* Information rates: 0.500, 1.000
* Critical values: 2.472, 2.025
* Futility bounds (non-binding): -Inf
* Cumulative alpha spending: 0.006724, 0.025000
* Local one-sided significance levels: 0.006724, 0.021451
* Significance level: 0.0250
* Type II error rate: 0.2000
* Test: one-sided

*User defined parameters*

* Assumed treatment rate: 0.300
* Assumed control rate: 0.150

*Default parameters*

* Risk ratio: FALSE
* Theta H0: 0
* Normal approximation: TRUE
* Treatment groups: 2
* Planned allocation ratio: 1

*Sample size and output*

* Direction upper: TRUE
* Maximum number of subjects: 248.3
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*Legend*

* (i): values of treatment arm i
* [k]: values at stage k

# Remarks

### Information regarding the document’s compilation

Analyses were conducted using the R Statistical language (version 4.4.1; R Core Team, 2024) on Windows 11 x64 (build 26100), using the packages caret (version 6.0.94; Kuhn, Max, 2008), randomForest (version 4.7.1.2; Liaw A, Wiener M, 2002), pROC (version 1.18.5; Robin X et al., 2011), lattice (version 0.22.6; Sarkar D, 2008), rpart (version 4.1.23; Therneau T, Atkinson B, 2023), rpact (version 4.1.0; Wassmer G, Pahlke F, 2024), ggplot2 (version 3.5.1; Wickham H, 2016) and dplyr (version 1.1.4; Wickham H et al., 2023).

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### Time of compilation

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