Package ‘adaptr’

June 17, 2022

Title Adaptive Trial Simulator

Version 1.1.0

Date 2022-06-16

Description Package that simulates adaptive clinical trials using adaptive stopping, adaptive arm dropping, and/or adaptive randomisation. Developed as part of the INCEPT (Intensive Care Platform Trial) project (<https://incept.dk/>), which is primarily supported by a grant from Sygeforsikringen "danmark" (<https://www.sygeforsikring.dk/>).

License GPL (>= 3)

Imports stats, parallel, utils

Encoding UTF-8

NeedsCompilation no


BugReports https://github.com/INCEPTdk/adaptr/issues/

RoxygenNote 7.2.0

Suggests covr, ggplot2, rmarkdown, knitr, testthat, vdiffr

VignetteBuilder knitr

Config/testthat/edition 3

Author Anders Granholm [aut, cre] (<https://orcid.org/0000-0001-5799-7655>), Benjamin Skov Kaas-Hansen [aut] (<https://orcid.org/0000-0003-1023-0371>), Aksel Karl Georg Jensen [ctb] (<https://orcid.org/0000-0002-1459-0465>), Theis Lange [ctb] (<https://orcid.org/0000-0001-6807-8347>)

Maintainer Anders Granholm <andersgran@gmail.com>

Repository CRAN

Date/Publication 2022-06-17 08:20:18 UTC
The `adaptr` package simulates adaptive (multi-arm) trials using adaptive stopping, adaptive arm dropping and/or response-adaptive randomisation. The package is developed as part of the INCEPT (Intensive Care Platform Trial) project, funded primarily by a grant from Sygeforsikringen "danmark".

The `adaptr` package contains the following primary functions:

1. `setup_trial()` is the general function that sets up a trial specification. The simpler, special-case functions `setup_trial_binom()` and `setup_trial_norm()` may be used for easier specification of trial designs using binary, binomially distributed or continuous, normally distributed outcomes, respectively, with some limitations in flexibility.

2. The `run_trial()` and `run_trials()` functions are used to conduct single or multiple simulations, respectively, according to a trial specification setup as described in #1.

3. The `extract_results()` and `summary()` functions are used to extract or summarise the results of multiple trial simulations.

4. The `plot_status()` and `plot_history()` functions are used to plot the overall trial/arm statuses for multiple simulated trials or the history of trial metrics over time for single/multiple simulated trials, respectively.

For further information see the function documentation or the `Overview` vignette (vignette("Overview", package = "adaptr")) for an example of how the functions work in combination. For further examples and guidance on setting up trial specifications, see `setup_trial` documentation, the `Basic examples` vignette (vignette("Basic-examples", package = "adaptr")) and the `Advanced example` vignette (vignette("Advanced-example", package = "adaptr")).

If using the package, please consider citing it using `citation(package = "adaptr")`. 
extract_results

References


Website/manual
GitHub repository

See Also

setup_trial(), setup_trial_binom(), setup_trial_norm(), run_trial(), run_trials(), extract_results(), summary(), print(), plot_status() and plot_history().

extract_results

Extract simulation results

Description

This function extracts relevant information from multiple simulations of the same trial specification in a tidy data.frame (1 simulation per row). See also the summary() function.

Usage

extract_results(
  object,
  select_strategy = "control if available",
  select_last_arm = FALSE,
  select_preferences = NULL,
  te_comp = NULL,
  raw_ests = FALSE
)

Arguments

object trial_results object, output from the run_trials() function.
select_strategy single character string. For trials not stopped due to superiority (or with only 1 arm remaining, if select_last_arm is set to TRUE in trial designs with a common control arm; see below), this parameter specifies which arm will be considered selected when calculating trial design performance metrics (described below; this corresponds to the consequence of an inconclusive trial, i.e., which arm would then be used in practice). The following options are available and must be written exactly as below (case sensitive, cannot be abbreviated):
  • "control if available" (default): selects the first control arm for trials with a common control arm if this arm is active at end-of-trial, otherwise no arm will be selected. For trial designs without a common control, no arm will be selected.
• "none": selects no arm in trials not ending with superiority.
• "control": similar to "control if available", but will throw an error for trial designs without a common control arm.
• "final control": selects the final control arm regardless of whether the trial was stopped for practical equivalence, futility, or at the maximum sample size; this strategy can only be specified for trial designs with a common control arm.
• "control or best": selects the first control arm if still active at end-of-trial, otherwise selects the best remaining arm (defined as the remaining arm with the highest probability of being the best in the final analysis). Only works for trial designs with a common control arm.
• "best": selects the best remaining arm (as described under "control or best").
• "list or best": selects the first remaining arm from a specified list (specified using select_preferences, technically a character vector). If none of these arms are still active at end-of-trial, the best remaining arm will be selected (as described above).
• "list": as specified above, but if no arms on the provided list remain active at end-of-trial, no arm is selected.

select_last_arm
single logical, defaults to FALSE. If TRUE, the only remaining active arm (the last control) will be selected in trials with a common control arm ending with equivalence or futility, before considering the options specified in select_strategy. Must be FALSE for trial designs without a common control arm.

select_preferences
character vector specifying a number of arms used for selection if one of the "list or best" or "list" options are specified for select_strategy. Can only contain valid arms available in the trial.

te_comp
character string, treatment-effect comparator. Can be either NULL (the default) in which case the first control arm is used for trial designs with a common control arm, or a single trial arm. Will be used when calculating sq_err_te (the squared error of the treatment effect comparing the selected arm to the comparator arm, as described below).

raw_ests
single logical. If FALSE (default), the posterior estimates (post_est, see setup_trial() and run_trial()) will be used to calculate sq_err (the squared error of the estimated compared to the specified effect in the selected arm) and sq_err_te (the squared error of the treatment effect comparing the selected arm to the comparator arm, as described for te_comp and below). If TRUE, the raw estimates (raw_est, see setup_trial() and run_trial()) will be used instead of the posterior estimates.

Value
A data.frame containing the following columns:

• sim: the simulation number (from 1 to the number of simulations).
find_beta_params

- final_n: the final sample size in each simulation.
- sum_ys: the sum of the total counts in all arms, e.g., the total number of events in trials with a binary outcome (setup_trial_binom()) or the sum of the arm totals in trials with a continuous outcome (setup_trial_norm()).
- ratio_ys: calculated as sum_ys/final_n.
- final_status: the final trial status for each simulation, either "superiority", "equivalence", "futility", or "max", as described in run_trial().
- superior_arm: the final superior arm in simulations stopped for superiority, will be NA in simulations not stopped for superiority.
- selected_arm: the final selected arm (as described above), will correspond to the superior_arm in simulations stopped for superiority and be NA if no arm is selected. See select_strategy above.
- sq_err: the squared error of the estimate in the selected arm, calculated as \((\text{estimated effect} - \text{true effect})^2\) for the selected arms.
- sq_err_te: the squared error of the treatment effect comparing the selected arm to the comparator arm (as specified in te_comp). Calculated as:
  \[ ((\text{estimated effect in the selected arm} - \text{estimated effect in the comparator arm}) - (\text{true effect in the selected arm} - \text{true effect in the comparator arm}))^2 \]
  Will be NA for simulations without a selected arm or with no comparator specified (see te_comp above).

Examples

```r
# Setup a trial specification
binom_trial <- setup_trial_binom(arms = c("A", "B", "C", "D"),
                   control = "A",
                   true_ys = c(0.20, 0.18, 0.22, 0.24),
                   data_looks = 1:20 * 100)

# Run 10 simulations with a specified random base seed
res <- run_trials(binom_trial, n_rep = 10, base_seed = 12345)

# Extract results and Select the control arm if available
# in simulations not ending with superiority
extract_results(res, select_strategy = "control")
```

find_beta_params

Find beta distribution parameters from thresholds

Description

Helper function to find a beta distribution with parameters corresponding to the fewest possible patients with events/non-events and a specified event proportion. Used in the Advanced example vignette (vignette("Advanced-example", "adaptr")) to derive beta prior distributions for use in beta-binomial conjugate models, based on a belief that the true event probability lies within a specified percentile-based interval (defaults to 95%). May similarly be used by users to derive other beta priors.
Usage

```r
find_beta_params(
  theta = NULL,
  boundary_target = NULL,
  boundary = "lower",
  interval_width = 0.95,
  n_dec = 0,
  max_n = 10000
)
```

Arguments

- **theta**
single numeric > 0 and < 1, expected true event probability.

- **boundary_target**
single numeric > 0 and < 1, target lower or upper boundary of the interval.

- **boundary**
single character string, either "lower" (default) or "upper", used to select which boundary to use when finding appropriate parameters for the beta distribution.

- **interval_width**
width of the credible interval whose lower/upper boundary should be used (see `boundary_target`); must be > 0 and < 1; defaults to 0.95.

- **n_dec**
single non-negative integer; the returned parameters are rounded to this number of decimals. Defaults to 0, in which case the parameters will correspond to whole number of patients.

- **max_n**
single integer > 0 (default 10000), the maximum total sum of the parameters, corresponding to the maximum total number of patients that will be considered by the function when finding the optimal parameter values. Corresponds to the maximum number of patients contributing information to a beta prior; more than the default number of patients are unlikely to be used in a beta prior.

Value

A single-row `data.frame` with five columns: the two shape parameters of the beta distribution (alpha, beta), rounded according to `n_dec`, and the actual lower and upper boundaries of the interval and the median (with appropriate names, e.g. `p2.5`, `p50`, and `p97.5` for a 95% interval), when using those rounded values.

---

**plot_history**

*Plot trial metric history*

Description

Plots the history of relevant metrics over the progress of single or multiple simulations. Simulated trials only contribute until the time they are stopped, i.e., if some trials are stopped earlier than others, they will not contribute to the summary statistics at later adaptive looks. Data from individual arms in a trial contribute until the complete trial is stopped.

These history plots require non-sparse results (sparse set to FALSE; see `run_trial()` and `run_trials()`) and the ggplot2 package installed.
Usage

plot_history(object, x_value = "look", y_value = "prob", line = NULL, ...)

## S3 method for class 'trial_result'
plot_history(object, x_value = "look", y_value = "prob", line = NULL, ...)

## S3 method for class 'trial_results'
plot_history(
  object,
  x_value = "look",
  y_value = "prob",
  line = NULL,
  ribbon = list(width = 0.5, alpha = 0.2),
  ...
)

Arguments

object trial_results object, output from the run_trials() function.
x_value single character string, determining whether the number of adaptive analysis
looks ("look", default) or the total cumulated number of patients allocated
("total n") are plotted on the x-axis.
y_value single character string, determining which values are plotted on the y-axis. The
following options are available: allocation probabilities ("prob", default), the
total number of patients allocated to each arm ("n"), the percentage of patients
allocated to each arm of the total number of patients randomised ("pct"), the
sum of all outcomes in each arm ("sum ys"), the ratio of outcomes ("ratio ys",
the sum of outcomes in each arm divided by the number of patients allocated to
that arm).
line list styling the lines as per ggplot2 conventions (e.g., linetype, size).
... additional arguments, not used.
ribbon list, as line but only appropriate for trial_results objects (i.e., when multi-
ple simulations are run). Also allows to specify the width of the interval: must
be between 0 and 1, with 0.5 (default) showing the inter-quartile ranges.

Value

A ggplot2 plot object.

See Also

plot_status().

Examples

#### Only run examples if ggplot2 is installed ####
if (requireNamespace("ggplot2", quietly = TRUE)){


# Setup a trial specification
binom_trial <- setup_trial_binom(arms = c("A", "B", "C", "D"),
control = "A",
true_ys = c(0.20, 0.18, 0.22, 0.24),
data_looks = 1:20 * 100)

# Run a single simulation with a fixed random seed
res <- run_trial(binom_trial, seed = 12345)

# Plot total allocations to each arm according to overall total allocations
plot_history(res, x_value = "total n", y_value = "n")

# Run multiple simulation with a fixed random base seed
# Notice that sparse = FALSE is required
res_mult <- run_trials(binom_trial, n_rep = 15, base_seed = 12345, sparse = FALSE)

# Plot allocation probabilities at each look
plot_history(res_mult, x_value = "look", y_value = "prob")

# Other y_value options are available but not shown in these examples
# Do not return/print last plot in documentation
invisible(NULL)

---

**plot_status**

**Plot statuses**

### Description

Plots the statuses over time of multiple simulated trials (overall or for a specific arm). Requires the ggplot2 package installed.

### Usage

plot_status(object, x_value = "look", arm = NULL, area = list(alpha = 0.5))

## S3 method for class 'trial_results'

plot_status(object, x_value = "look", arm = NULL, area = list(alpha = 0.5))

### Arguments

- **object**
  - trial_results object, output from the run_trials() function.
x_value

single character string, determining whether the number of adaptive analysis
looks ("look", default) or the total cumulated number of patients allocated
("total n") are plotted on the x-axis.

arm

single character string or NULL (default); can be set to a valid trial arm. If NULL,
the overall trial statuses are plotted, otherwise the statuses for a single, specific
trial arm are plotted.

area

list of styling settings for the area as per ggplot2 conventions (e.g., alpha,
size). The default (list(alpha = 0.5)) sets the transparency to 50% so over-
lain shaded areas are visible.

Value

A ggplot2 plot object.

See Also

plot_history().

Examples

### Only run examples if ggplot2 is installed ###
if (requireNamespace("ggplot2", quietly = TRUE)){

  # Setup a trial specification
  binom_trial <- setup_trial_binom(arms = c("A", "B", "C", "D"),
                                 control = "A",
                                 true_ys = c(0.20, 0.18, 0.22, 0.24),
                                 data_looks = 1:20 * 100)

  # Run multiple simulation with a fixed random base seed
  res_mult <- run_trials(binom_trial, n_rep = 25, base_seed = 12345)

  # Plot trial statuses at each look according to total allocations
  plot_status(res_mult, x_value = "total n")

  # Do not return/print last plot in documentation
  invisible(NULL)
}

print

Print methods for adaptive trial objects

Description

Prints contents of the first input x in a human-friendly way, see Details for more information.
Usage

```r
## S3 method for class 'trial_spec'
print(x, prob_digits = 3, ...)

## S3 method for class 'trial_result'
print(x, prob_digits = 3, ...)

## S3 method for class 'trial_results'
print(
  x,
  select_strategy = "control if available",
  select_last_arm = FALSE,
  select_preferences = NULL,
  te_comp = NULL,
  raw_ests = FALSE,
  restrict = NULL,
  digits = 1,
  ...)

## S3 method for class 'trial_results_summary'
print(x, digits = 1, ...)
```

Arguments

- `x` object to print, see Details below.
- `prob_digits` single integer, the number of digits used when printing probabilities, allocation probabilities and softening powers.
- `...` additional arguments, not used.
- `select_strategy` single character string. For trials not stopped due to superiority (or with only 1 arm remaining, if select_last_arm is set to TRUE in trial designs with a common control arm; see below), this parameter specifies which arm will be considered selected when calculating trial design performance metrics (described below; this corresponds to the consequence of an inconclusive trial, i.e., which arm would then be used in practice). The following options are available and must be written exactly as below (case sensitive, cannot be abbreviated):
  - "control if available" (default): selects the first control arm for trials with a common control arm if this arm is active at end-of-trial, otherwise no arm will be selected. For trial designs without a common control, no arm will be selected.
  - "none": selects no arm in trials not ending with superiority.
  - "control": similar to "control if available", but will throw an error for trial designs without a common control arm.
  - "final control": selects the final control arm regardless of whether the trial was stopped for practical equivalence, futility, or at the maximum sam-
ple size; this strategy can only be specified for trial designs with a common control arm.

- "control or best": selects the first control arm if still active at end-of-trial, otherwise selects the best remaining arm (defined as the remaining arm with the highest probability of being the best in the final analysis). Only works for trial designs with a common control arm.

- "best": selects the best remaining arm (as described under "control or best").

- "list or best": selects the first remaining arm from a specified list (specified using select_preferences, technically a character vector). If none of these arms are active at end-of-trial, the best remaining arm will be selected (as described above).

- "list": as specified above, but if no arms on the provided list remain active at end-of-trial, no arm is selected.

**select_last_arm**

single logical, defaults to FALSE. If TRUE, the only remaining active arm (the last control) will be selected in trials with a common control arm ending with equivalence or futility, before considering the options specified in select_strategy. Must be FALSE for trial designs without a common control arm.

**select_preferences**

character vector specifying a number of arms used for selection if one of the "list or best" or "list" options are specified for select_strategy. Can only contain valid arms available in the trial.

**te_comp**

character string, treatment-effect comparator. Can be either NULL (the default) in which case the first control arm is used for trial designs with a common control arm, or a single trial arm. Will be used when calculating sq_err_te (the squared error of the treatment effect comparing the selected arm to the comparator arm, as described below).

**raw_est**

single logical. If FALSE (default), the posterior estimates (post_est, see setup_trial() and run_trial()) will be used to calculate sq_err (the squared error of the estimated compared to the specified effect in the selected arm) and sq_err_te (the squared error of the treatment effect comparing the selected arm to the comparator arm, as described for te_comp and below). If TRUE, the raw estimates (raw_est, see setup_trial() and run_trial()) will be used instead of the posterior estimates.

**restrict**

single character string or NULL. If NULL (default), results are summarised for all simulations; if "superior", results are summarised for simulations ending with superiority only; if "selected", results are summarised for simulations ending with a selected arm (according to the specified arm selection strategy for simulations not ending with superiority). Some summary measures (e.g., prob_conclusive) can only be calculated across all simulations and several are calculated regardless of restrict settings, but have substantially different interpretations if restricted.

**digits**

single integer, number of digits to print for probabilities and some other summary values (with 2 extra digits added for outcome rates).
Details

The behaviour depends on the class of x:

- **trial_spec**: prints a trial specification setup by `setup_trial()`, `setup_trial_binom()` or `setup_trial_norm()`.

- **trial_result**: prints the results of a single trial simulated by `run_trial()`. More details are saved in the `trial_result` object and thus printed if the `sparse` argument in `run_trial()` or `run_trials()` is set to FALSE; if TRUE, fewer details are printed, but the omitted details are available by printing the `trial_spec` object created by `setup_trial()`, `setup_trial_binom()` or `setup_trial_norm()`.

- **trial_results**: prints the results of multiple simulations generated using `run_trials()`. Further documentation on how multiple trials are summarised before printing can be found in the `summary()` function documentation.

- **trial_results_summary**: print method for summary of multiple simulations of the same trial specification, generated by using the `summary()` function on an object generated by `run_trials()`.

Value

Invisibly returns x.

Methods (by class)

- **trial_spec**: Trial specification
- **trial_result**: Single trial result
- **trial_results**: Multiple trial results
- **trial_results_summary**: Summary of multiple trial results

---

**run_trial**

*Simulate a single trial*

**Description**

This function conducts a single trial simulation using a trial specification as specified by `setup_trial()`, `setup_trial_binom()` or `setup_trial_norm()`. During simulation, the function randomises "patients", randomly generates outcomes, calculates the probabilities that each arm is the best (and better than the control, if any). This is followed by checking inferiority, superiority, equivalence and/or futility as desired; dropping arms, and re-adjusting allocation probabilities according to the criteria specified in the trial specification. If there is no common control arm, the trial simulation will be stopped at the maximum sample size, when 1 arm is superior to the others, or when all arms are considered equivalent (if equivalence testing is specified).

If a common control arm is specified, all other arms will be compared to that, and if 1 comparison crosses the superiority threshold, that arm will become the new control and the old control will be
run_trial

considered inferior. If multiple non-control arms cross the superiority threshold in the same analysis, the one with the highest probability of being the overall best will become the new control. Equivalence/futility will also be checked in trial designs with common controls if specified, and equivalent or futile arms will be dropped. The trial simulation will be stopped when only 1 arm is left, when the final arms are all equivalent, or when the maximum sample size has been reached.

Usage

run_trial(trial_spec, seed = NULL, sparse = FALSE)

Arguments

trial_spec trial_spec object, generated and validated by the setup_trial(), setup_trial_binom() or setup_trial_norm() function.

seed single integer or NULL (default), if a value is provided, this value will be used as the random seed when running (the global random seed will be restored after the function has run, so it is not affected).

sparse single logical; if FALSE (default) everything listed below is included in the returned object. If TRUE, only a limited amount of data is included in the returned object. This can be practical when running many simulations and saving the results using the run_trials() function (which relies on this function), as the output file will thus be substantially smaller. However, printing of individual trial results will be substantially less detailed for sparse results and non-sparse results are required by plot_history().

Value

A trial_result object containing everything listed below if sparse (as described above) is FALSE. Otherwise only final_status, final_n, trial_res, seed and sparse are included.

- final_status: either "superiority", "equivalence", "futility", or "max".
- final_n: the total number of patients randomised.
- max_n: the pre-specified maximum sample size.
- looks: numeric vector, the total number of patients at each conducted adaptive analysis.
- planned_looks: numeric vector, the cumulated number of patients planned to be randomised at each adaptive analysis, even those not conducted if the simulation is stopped before the maximum sample size.
- start_control: character, initial common control arm (if specified).
- final_control: character, final common control arm (if relevant).
- control_prob_fixed: fixed common control arm probabilities (if specified; see setup_trial()).
- inferiority, superiority, equivalence_prob, equivalence_diff, equivalence_only_first, futility_prob, futility_diff, futility_only_first, highest_is_best, and soften_power: as specified in setup_trial().
- best_arm: the best arm(s), as described in setup_trial().
• trial_res: a data.frame containing most of the information specified for each arm in setup_trial() including true_ys (true outcomes as specified in setup_trial()) and for each arm the sum of the outcomes (sum_ys; i.e., the total number of events for binary outcomes or the totals of continuous outcomes) and patients randomised (ns), summary statistics for the raw outcome data (raw_est, calculated as specified in setup_trial(), defaults to mean values, i.e., event rates for binary outcomes or means for continuous outcomes) and posterior estimates (post_est, post_err, lo_cri, and hi_cri, as specified in setup_trial()), final_status of each arm ("inferior", "superior", "equivalence", "futile", "active", or "control" (currently active control arm, including if the current control when stopped for equivalence)), status_look (specifying the cumulated number of patients randomised when an adaptive analysis changed the final_status to "superior", "inferior", "equivalence", or "futile"), status_probs, the probability that each treatment was the best/better than the common control arm (if any)/equivalent to the common control arm (if any and stopped for equivalence); NA if the control arm was stopped due to the last remaining other arm(s) being stopped for equivalence)/futile if stopped for futility at the last analysis it was included in, final_alloc, the final allocation probability for each arm the last time patients were randomised to it, including for arms stopped at the maximum sample size, and probs_best_last, the probabilities of each remaining arm being the overall best in the last conducted analysis (NA for previously dropped arms).

• all_looks: a list of lists containing one list per conducted trial look (adaptive analysis). These lists contain the variables arms, old_status (status before the analysis of the current round was conducted), new_status (as specified above, status after current analysis has been conducted), sum_ys (as described above), ns (as described above), old_alloc (the allocation probability used during this look), probs_best (the probabilities of each arm being the best in the current adaptive analysis), new_alloc (the allocation probabilities after updating these in the current adaptive analysis; NA for all arms when the trial is stopped and no further analyses will be conducted), probs_better_first (if a common control is provided, specifying the probabilities that each arm was better than the control in the first analysis conducted during that look), probs_better (as probs_better_first, but updated if another arm becomes the new control), probs_equivalence_first and probs_equivalence (as for probs_better/probs_better_first, but for equivalence if equivalence is assessed). The last variables are NA if the arm was not active in the applicable adaptive analysis or if they would not be included during the next adaptive analysis.

• allocs: a character vector containing the allocations of all patients in the order of randomization.

• ys: a numeric vector containing the outcomes of all patients in the order of randomization (0 or 1 for binary outcomes).

• seed: the random seed used, if specified.

• description, add_info, cri_width, n_draws, robust: as specified in setup_trial(), setup_trial_binom() or setup_trial_norm().

• sparse: single logical, corresponding to the sparse input.

Examples

# Setup a trial specification
binom_trial <- setup_trial_binom(arms = c("A", "B", "C", "D"),
true_ys = c(0.20, 0.18, 0.22, 0.24),
...
```r
# Run trial with a specified random seed
res <- run_trial(binom_trial, seed = 12345)

# Print results with 3 decimals
print(res, digits = 3)
```

### Description

This function conducts multiple simulations using a trial specification as specified by `setup_trial()`, `setup_trial_binom()` or `setup_trial_norm()`. This function essentially manages random seeds and runs multiple simulation using `run_trial()` - additional details on individual simulations are provided in that function’s description. This function allows simulating trials in parallel using multiple cores, automatically saving and re-loading saved objects, and "growing" already saved simulation files (i.e., appending additional simulations to the same file).

### Usage

```r
run_trials(
  trial_spec,  # trial_spec object, generated and validated by the setup_trial(), setup_trial_binom() or setup_trial_norm() function.
  n_rep,       # single integer; the number of simulations to run.
  path = NULL, # single character; if specified (defaults to NULL), files will be written to and loaded from this path using the saveRDS() / readRDS() functions.
  overwrite = FALSE,
  grow = FALSE,
  cores = 1,
  base_seed = NULL,
  sparse = TRUE,
  progress = NULL,
  version = NULL,
  compress = TRUE,
  export = NULL,
  export_envir = parent.frame()
)
```

### Arguments

- **trial_spec**: trial_spec object, generated and validated by the `setup_trial()`, `setup_trial_binom()` or `setup_trial_norm()` function.
- **n_rep**: single integer; the number of simulations to run.
- **path**: single character; if specified (defaults to NULL), files will be written to and loaded from this path using the `saveRDS()` / `readRDS()` functions.
overwrite

single logical; defaults to FALSE, in which case previous simulations saved in the same path will be re-loaded (if the same trial specification was used). If TRUE, the previous file is overwritten. If grow is TRUE, this argument must be set to FALSE.

grow

single logical; defaults to FALSE. If TRUE and a valid path to a valid previous file containing less simulations than n_rep, the additional number of simulations will be run (appropriately re-using the same base_seed, if specified) and appended to the same file.

cores

single integer; the number of cores to run the simulations on using the parallel library. Defaults to 1; may be increased to run multiple simulations in parallel.

parallel::detectCores() may be used to find the number of available cores.

base_seed

single integer; a random seed used as the basis for simulations; each simulation will set the random seed to a value based on this (+ the trial number), without affecting the global random seed after the function has been run.

sparse

single logical, as described in run_trial(); defaults to TRUE when running multiple simulations, in which case only the data necessary to summarise all simulations are saved for each simulation. If FALSE, more detailed data for each simulation is saved, allowing more detailed printing of individual trial results and plotting using plot_history() (plot_status() does not require non-sparse results).

progress

single numeric > 0 and <= 1 or NULL. If NULL (default), no progress is printed to the console. Otherwise, progress messages are printed to the control at intervals proportional to the value specified by progress.

Note: as printing is not possible from within clusters on multiple cores, the function conducts batches of simulations on multiple cores (if specified), with intermittent printing of statuses. Thus, all cores have to finish running their current assigned batches before the other cores may proceed with the next batch. If there is substantial differences in the simulation speeds across cores, using progress may thus increase total simulation times.

version

passed to saveRDS() when saving simulations, defaults to NULL (as in saveRDS()), which means that the current default version is used. Ignored if simulations are not saved.

compress

passed to saveRDS() when saving simulations, defaults to TRUE (as in saveRDS()), see saveRDS() for other options. Ignored if simulations are not saved.

export

character vector of names of objects to export to each parallel core if cores > 1; passed as the varlist argument to parallel::clusterExport(). Defaults to NULL (no objects exported), ignored if cores == 1. See Details below.

export_envir

environment where to look for the objects defined in export if cores > 1 and export is not NULL. Defaults to the environment from where run_trials() is called.

Details

Exporting objects when using multiple cores

If setup_trial() is used to define a trial specification with custom functions (in the fun_y_gen, fun_draws, and fun_raw_est arguments of setup_trial()) and run_trials() is run with cores
> 1, it is necessary to export additional functions or objects used by these functions and defined by
the user outside the function definitions provided. Similarly, functions from external packages
loaded using `library()` or `require()` must be exported or called prefixed with the namespace,
I.e., `package::function`. The export and export_envir arguments are used to export objects
calling the `parallel::clusterExport()`-function.

Value

A list of a special class "trial_results", which contains the trial_results (results from all
simulations), trial_spec (the trial specification), n_rep, base_seed, elapsed_time (the total
simulation run time) and sparse (as described above). These results may be extracted using the
extract_results() function and summarised using the summary() or print (print.trial_results())
functions; see function documentation for details on additional arguments used to select arms in
simulations not ending in superiority and other summary choices.

Examples

# Setup a trial specification
binom_trial <- setup_trial_binom(arms = c("A", "B", "C", "D"),
  true_ys = c(0.20, 0.18, 0.22, 0.24),
  data_looks = 1:20 * 100)

# Run 10 simulations with a specified random base seed
res <- run_trials(binom_trial, n_rep = 10, base_seed = 12345)

# See ?summary and ?print for details on summarising and printing
start_probs = NULL,
fixed_probs = NULL,
min_probs = rep(NA, length(arms)),
max_probs = rep(NA, length(arms)),
data_looks = NULL,
max_n = NULL,
look_after_every = NULL,
control = NULL,
control_prob_fixed = NULL,
inferiority = 0.01,
superiority = 0.99,
equivalence_prob = NULL,
equivalence_diff = NULL,
equivalence_only_first = NULL,
futility_prob = NULL,
futility_diff = NULL,
futility_only_first = NULL,
highest_is_best = FALSE,
soften_power = 1,
fun_raw_est = mean,
cri_width = 0.95,
n_draws = 5000,
robust = TRUE,
description = NULL,
add_info = NULL
)

Arguments

arms character vector with unique names for the trial arms.
true_ys numeric vector specifying true outcomes (e.g., event probabilities, mean values, etc.) for all trial arms.
fun_y_gen function, generates outcomes. See `setup_trial()` Details for information on how to specify this function.
Note: this function is called once during setup to validate the output structure.
fun_draws function, generates posterior draws. See `setup_trial()` Details for information on how to specify this function.
Note: this function is called up to three times during setup to validate the output structure.
start_probs numeric vector, allocation probabilities for each arm at the beginning of the trial. The default (NULL) is automatically changed to equal randomisation.
fixed_probs numeric vector, fixed allocation probabilities for each arm - must be either a numeric vector with NA for arms without fixed probabilities and values between 0 and 1 for the other arms or NULL (default), if adaptive randomisation is used for all arms or if one of the special settings ("sqrt-based", "sqrt-based start", "sqrt-based fixed", or "match") is specified for control_prob_fixed (described below).
min_probs numeric vector, lower threshold for adaptive allocation probabilities, lower probabilities will be rounded up to these values. Must be NA (default for all arms) if no boundary is wanted.

max_probs numeric vector, upper threshold for adaptive allocation probabilities, higher probabilities will be rounded down to these values. Must be NA (default for all arms) if no boundary is wanted.

data_looks vector of increasing integers, specifies when to conduct adaptive analyses (= the total number of patients randomised at each adaptive analysis). The last number in the vector represents the maximum sample size. Instead of specifying data_looks, the max_n and look_after_every arguments can be used in combination (then data_looks must be NULL, the default).

max_n single integer, maximum total sample size (defaults to NULL). Must only be specified if data_looks is NULL. Requires specification of the look_after_every argument.

look_after_every single integer, specified together with max_n. Adaptive analyses will be conducted after every look_after_every patients randomised, and at the total sample size as specified by max_n (max_n does not need to be a multiple of look_after_every). If specified, data_looks must be NULL (as default).

control single character string, name of one of the arms or NULL (default). If specified, this arm will serve as a common control arm, to which all other arms will be compared and the inferiority/superiority/equivalence thresholds (see below) will be for those comparisons. See setup_trial() Details below for information on behaviour with respect to these comparisons.

control_prob_fixed if a common control arm is specified, this must be set to either NULL (the default), in which case the control arm allocation probability will not be fixed if control arms change (the allocation probability to the first control arm may still be fixed using fixed_probs) Otherwise a vector of probabilities of either length 1 or number of arms - 1 can be provided, or one of the special arguments "sqrt-based", "sqrt-based start", "sqrt-based fixed" or "match". See setup_trial() Details below for details in behaviour.

inferiority single numeric (> 0 and <1, default is 0.01) specifying the inferiority threshold. An arm will be considered inferior and dropped if the probability that it is best (when comparing all arms) or better than the control arm (when a common control is used) drops below this threshold.

superiority single numeric (>0 and <1, default is 0.99) specifying the superiority threshold. If the probability that an arm is best (when comparing all arms) or better than the control arm (when a common control is used) exceeds this number, said arm will be declared the winner and the trial will be stopped (if no common control is used or if the last comparator is dropped in a design with a common control) or become the new control and the trial will continue (if a common control is specified).

equivalence_prob single numeric (> 0 and < 1) or NULL (default, corresponding to no equivalence assessment). If a numeric value is specified, arms will be stopped for equivalence if the probability of either (a) equivalence compared to a common control
or (b) equivalence between all arms remaining (designs without a common control) exceeds this threshold. Requires specification of equivalence_diff, equivalence_only_first, and a common control arm.

equivalence_diff
single numeric value (> 0) or NULL (default, corresponding to no equivalence assessment). If a numeric value is specified, estimated differences below this threshold will be considered equivalent when assessing equivalence. For designs with a common control arm, the differences between each non-control arm and the control arm is used, and for trials without a common control arm, the difference between the highest and lowest estimated outcome rates are used and the trial is only stopped for equivalence if all remaining arms are thus equivalent.

equivalence_only_first
single logical in trial specifications where equivalence_prob and equivalence_diff are specified, otherwise NULL (default). Must be NULL for designs without a common control arm. If a common control arm is used, this specifies whether equivalence will only be assessed for the first control (if TRUE) or also for subsequent control arms (if FALSE) if one arm is superior to the first control and becomes the new control.

futility_prob
single numeric (> 0 and < 1) or NULL (default, corresponds to no futility assessment). If a numeric value is specified, arms will be stopped for futility when the probability for futility compared to the common control exceeds this threshold. Requires a common control arm, specification of futility_diff and futility_only_first.

futility_diff
single numeric value (> 0) or NULL (default, corresponding to no futility assessment). If a numeric value is specified, estimated differences below this threshold in the beneficial direction (as specified in highest_is_best) will be considered futile when assessing futility in designs with a common control arm. If only 1 arm remains after dropping arms for futility, the trial will be stopped without declaring the last arm superior.

futility_only_first
single logical in trial specifications where futility_prob and futility_diff are specified, otherwise NULL (default). Must be NULL for designs without a common control arm. Specifies whether futility will only be assessed against the first control (if TRUE) or also for subsequent control arms (if FALSE) if one arm is superior to the first control and becomes the new control.

highest_is_best
single logical, specifies whether larger estimates of the outcome are favourable or not; defaults to FALSE, corresponding to, e.g., an undesirable binary outcomes (e.g., mortality) or a continuous outcome where lower numbers are preferred (e.g., hospital length of stay).

soften_power
either a single numeric value or a numeric vector of exactly the same length as the maximum number of looks/adaptive analyses. Values must be between 0 and 1 (default); if < 1, then re-allocated non-fixed allocation probabilities are all raised to this power to make allocation probabilities less extreme, in turn used to redistribute remaining probability while respecting limits when defined by min_probs and/or max_probs. If 1, then no softening is applied.

fun_raw_est
function that takes a numeric vector and returns a single numeric value, used to calculate a raw summary estimate of the outcomes in each arm. Defaults to mean(), which is always used in the setup_trial_binom() and setup_trial_norm()
functions.

Note: the function is called one time per arm during setup to validate the output structure.

cri_width

single numeric $\geq 0$ and $< 1$, the width of the percentile-based credible intervals used when summarising individual trial results. Defaults to $0.95$, corresponding to 95% credible intervals.

n_draws

single integer, the number of draws from the posterior distributions (for each arm) used when running the trial. Defaults to 5000; can be reduced for a speed gain (at the potential loss of stability of results if too low) or increased for increased precision (takes longer). Values $< 100$ are not allowed and values $< 1000$ are not recommended and warned against.

robust

single logical, if TRUE (default) the medians and median absolute deviations (scaled to be comparable to the standard deviation for normal distributions; MAD_SD) are used to summarise the posterior distributions; if FALSE, the means and standard deviations (SDs) are used instead (slightly faster, but may be less appropriate for posteriors skewed on the natural scale).

description

optional single character string describing the trial design, will only be used in print functions if not NULL (the default).

add_info

optional single string containing additional information regarding the trial design or specifications, will only be used in print functions if not NULL (the default).

Details

**How to specify the** fun_y_gen **function**

The function must take the following inputs:

- allocs: character vector, the trial arms that new patients allocated since the last adaptive analysis are randomised to.

The function must return a single numeric vector, corresponding to the outcomes for all patients allocated since the last adaptive analysis, in the same order as allocs.

See the Examples vignette (vignette("Examples", "adaptr")) for an example with further details.

**How to specify the** fun_draws **function**

The function must take the following inputs:

- arms: character vector, the unique trial arms, in the same order as above, but only the currently active arms are specified when the function is called.
- allocs: a vector of allocations for all patients, corresponding to the trial arms, including patients allocated to currently inactive arms when called.
- ys: a vector of outcomes for all patients in the same order as allocs, including outcomes for patients allocated to currently inactive arms when called.
- control: single character, the current control arm, will be NULL for designs without a common control arm, but required regardless as the argument is supplied by run_trial()/run_trials().
- n_draws: single integer, the number of posterior draws for each arm.
The function must return a matrix (with numeric values) with arms columns and \( n_{\text{draws}} \) rows. The matrix must have columns only for currently active arms (when called). Each row should contain a single posterior draw for each arm on the original outcome scale: if they are estimated as, e.g., the log(odds), these estimates must be transformed to probabilities and similarly for other measures.

Important: the matrix cannot contain NAs, even if no patients have been randomised to an arm yet. See the provided example for one way to alleviate this.

See the Examples vignette (vignette("Examples", "adaptr");) for an example with further details.

Notes

- Different estimation methods and prior distributions may be used; complex functions will lead to slower simulations compared to simpler methods for obtaining posterior draws, including those specified using the \( \text{setup_trial} \_\text{binom()} \) and \( \text{setup_trial} \_\text{norm()} \) functions.
- Technically, using log relative effect measures — e.g. log(odds ratio) or log(risk ratios) - or differences compared to a reference arm (e.g., mean differences or absolute risk differences) instead of absolute values in each arm will work to some extent (be cautious!):
  - Stopping for superiority/inferiority/max sample sizes will work.
  - Stopping for equivalence/futility may be used with relative effect measures on the log scale.
  - Several summary statistics from \( \text{run_trial}() \) (sum_ys and posterior estimates) may be nonsensical if relative effect measures are used (depending on calculation method).
  - In the same vein, extract_results() (sum_ys, sq_err, and sq_err_te), and \( \text{summary}() \) (sum_ys_mean/sd/median/q25/q75, rmse, rmse_te and idp) may be equally nonsensical when calculated on the relative scale.

Using additional custom or functions from loaded packages in the custom functions

If the \fun_y_gen, \fun_draws, or \fun_raw_est functions calls other user-specified functions (or uses objects defined by the user outside these functions or the \text{setup_trial}()-call) or functions from external packages and simulations are conducted on multiple cores, these objects or functions must be exported or prefixed with their namespaces, respectively, as described in \text{run_trials}().

More information on arguments

- \text{control}: if one or more treatment arms are superior to the control arm (i.e., passes the superiority threshold as defined above), this arm will become the new control (if multiple arms are superior, the one with the highest probability of being the overall best will become the new control), the previous control will be dropped for inferiority, and all remaining arms will be immediately compared to the new control in the same adaptive analysis and dropped if inferior (or possibly equivalent/futile, see below) compared to this new control arm. Only applies in trials with a common control.
- \text{control_prob_fixed}: If the length is 1, then this allocation probability will be used for the control group (including if a new arm becomes the control and the original control is dropped). If multiple values are specified the first value will be used when all arms are active, the second when one arm has been dropped, and so forth. If 1 or more values are specified, previously set \text{fixed_probs}, \text{min_probs} or \text{max_probs} for new control arms will be ignored. If all allocation probabilities do not sum to 1 (e.g, due to multiple limits) they will be re-scaled to do so.
  
  Can also be set to one of the special arguments "sqrt-based", "sqrt-based start", "sqrt-based
fixed" or "match" (written exactly as one of those, case sensitive). This requires start_probs to be NULL and relevant fixed_probs to be NULL (or NA for the control arm).

If one of the "sqrt-based"/"sqrt-based start"/"sqrt-based fixed" options are used, the function will set square-root-transformation-based starting allocation probabilities. These are defined as:

square root of number of non-control arms to 1-ratio for other arms scaled to sum to 1, which will generally increase power for comparisons against the common control, as discussed in, e.g., Park et al, 2020 doi: 10.1016/j.jclinepi.2020.04.025.

If "sqrt-based", square-root-transformation-based allocation probabilities will also be used for new controls when arms are dropped. If "sqrt-based start", the control arm will be fixed to this allocation probability at all times (also after arm dropping, with re-scaling as necessary, as specified above). If "sqrt-based fixed" is chosen, square-root-transformation-based allocation probabilities will be used and all allocation probabilities will be fixed throughout the trial (with re-scaling when arms are dropped).

If "match" is specified, the control group allocation will always be matched to be similar to the highest non-control arm allocation ratio.

Superiority and inferiority

In trial designs without a common control arm, superiority and inferiority are assessed by comparing all currently active groups. This means that if a "final" analysis of a trial without a common control and > 2 arms is conducted including all arms (as will often be done in practice) after an adaptive trial have stopped, the final probabilities of the best arm being superior may differ slightly. For example, in a trial with three arms and no common control arm, one arm may be dropped early for inferiority defined as < 1% probability of being the overall best arm. The trial may then continue with the two remaining arms, and stopped when one is declared superior to the other defined as > 99% probability of being the overall best arm. If a final analysis is then conducted including all arms, the final probability of the best arm being overall superior will generally be slightly lower as the probability of the first dropped arm being the best will generally be > 0%, even if very low and below the inferiority threshold.

This is not relevant trial designs with a common control, as pairwise assessments of superiority/inferiority compared to the common control will not be influenced similarly by previously dropped arms (and previously dropped arms may be included in the analyses, even if posterior distributions are not returned for those). Similarly, in actual clinical trials, final probabilities may change slightly as the most recently randomised patients will generally not have outcome data available at the final adaptive analysis where the trial is stopped.

Equivalence

Equivalence is assessed after both inferiority and superiority have been assessed (and in case of superiority, it will be assessed against the new control arm in designs with a common control, if specified - see above).

Futility

Futility is assessed after inferiority, superiority, and equivalence have been assessed (and in case of superiority, it will be assessed against the new control arm in designs with a common control, if specified - see above). Arms will thus be dropped for equivalence before futility.

Value

A trial_spec object used to run simulations by run_trial() or run_trials(). The output is essentially a list containing the input values (some combined in a data.frame called trial_arms),
but its class signals that these inputs have been validated and inappropriate combinations and settings have been ruled out. Also contains best_arm holding the arm(s) with the best value(s) in true_ys. Use str() to peruse the actual content of the returned object

Examples

# Setup a custom trial specification with right-skewed, log-normally
# distributed continuous outcomes (higher values are worse)

# Define the function that will generate the outcomes in each arm
# Notice: contents should match arms/true_ys in the setup_trial() call below
get_ys_lognorm <- function(allocs) {
  y <- numeric(length(allocs))
  # arms (names and order) and values (except for exponentiation) should match
  # those used in setup_trial (below)
  means <- c("Control" = 2.2, "Experimental A" = 2.1, "Experimental B" = 2.3)
  for (arm in names(means)) {
    ii <- which(allocs == arm)
    y[ii] <- rlnorm(length(ii), means[arm], 1.5)
  }
  y
}

# Define the function that will generate posterior draws
# In this example, the function uses no priors (corresponding to improper
# flat priors) and calculates results on the log-scale, before exponentiating
# back to the natural scale, which is required for assessments of
# equivalence, futility and general interpretation
get_draws_lognorm <- function(arms, allocs, ys, control, n_draws) {
  draws <- list()
  logys <- log(ys)
  for (arm in arms){
    ii <- which(allocs == arm)
    n <- length(ii)
    if (n > 1) {
      # Necessary to avoid errors if too few patients randomised to this arm
      draws[[arm]] <- exp(rnorm(n_draws, mean = mean(logys[ii]), sd = sd(logys[ii])/sqrt(n - 1))))
    } else {
      # Too few patients randomised to this arm - extreme uncertainty
      draws[[arm]] <- exp(rnorm(n_draws, mean = mean(logys), sd = 1000 * (max(logys) - min(logys))))
    }
  }
  do.call(cbind, draws)
}

# The actual trial specification is then defined
lognorm_trial <- setup_trial(  
  # arms should match those above
  arms = c("Control", "Experimental A", "Experimental B"),
  # true_ys should match those above
  true_ys = exp(c(2.2, 2.1, 2.3)),
  fun_y_gen = get_ys_lognorm, # as specified above
  fun_draws = get_draws_lognorm, # as specified above
max_n = 5000,
look_after_every = 200,
control = "Control",
# Square-root-based, fixed control group allocation ratio
# and response-adaptive randomisation for other arms
control_prob_fixed = "sqrt-based",
# Equivalence assessment
equivalence_prob = 0.9,
equivalence_diff = 0.5,
equivalence_only_first = TRUE,
highest_is_best = FALSE,
# Summarise raw results by taking the mean on the
# log scale and back-transforming
fun_raw_est = function(x) exp(mean(log(x)))
# Summarise posteriors using medians with MAD-SDs,
# as distributions will not be normal on the actual scale
robust = TRUE,
# Description/additional info used when printing
description = "continuous, log-normally distributed outcome",
add_info = "SD on the log scale for all arms: 1.5"
)

# Print trial specification with 3 digits for all probabilities
print(lognorm_trial, prob_digits = 3)

Description

Specifies the design of an adaptive trial with a binary, binomially distributed outcome and validates all inputs. Uses beta-binomial conjugate models with beta(1, 1) prior distributions, corresponding to a uniform prior (or the addition of 2 patients, 1 with an event and 1 without) to the trial. Use run_trial() or run_trials() to conduct single/multiple simulations of the specified trial, respectively.

Note: add_info as specified in setup_trial() is set to NULL for trial specifications setup by this function.

Further details: please see setup_trial(). See setup_trial_norm() for simplified setup of trials with normally distributed continuous outcomes.

For additional trial specification examples, see the Basic examples vignette (vignette("Basic-examples", package = "adaptr").)

Usage

setup_trial_binom(
  arms,
true_ys,
start_probs = NULL,
fixed_probs = NULL,
min_probs = rep(NA, length(arms)),
max_probs = rep(NA, length(arms)),
data_looks = NULL,
max_n = NULL,
look_after_every = NULL,
control = NULL,
control_prob_fixed = NULL,
inferiority = 0.01,
superiority = 0.99,
equivalence_prob = NULL,
equivalence_diff = NULL,
equivalence_only_first = NULL,
futility_prob = NULL,
futility_diff = NULL,
futility_only_first = NULL,
highest_is_best = FALSE,
soften_power = 1,
cri_width = 0.95,
n_draws = 5000,
robust = TRUE,
description = "generic binomially distributed outcome trial"
)

Arguments

arms character vector with unique names for the trial arms.
true_ys numeric vector, true probabilities (between 0 and 1) of outcomes in all trial arms.
start_probs numeric vector, allocation probabilities for each arm at the beginning of the trial.
The default (NULL) is automatically changed to equal randomisation.
fixed_probs numeric vector, fixed allocation probabilities for each arm - must be either a numeric vector with NA for arms without fixed probabilities and values between 0 and 1 for the other arms or NULL (default), if adaptive randomisation is used for all arms or if one of the special settings ("sqrt-based", "sqrt-based start", "sqrt-based fixed", or "match") is specified for control_prob_fixed (described below).
min_probs numeric vector, lower threshold for adaptive allocation probabilities, lower probabilities will be rounded up to these values. Must be NA (default for all arms) if no boundary is wanted.
max_probs numeric vector, upper threshold for adaptive allocation probabilities, higher probabilities will be rounded down to these values. Must be NA (default for all arms) if no boundary is wanted.
data_looks vector of increasing integers, specifies when to conduct adaptive analyses (= the total number of patients randomised at each adaptive analysis). The last
number in the vector represents the maximum sample size. Instead of specifying `data_looks`, the `max_n` and `look_after_every` arguments can be used in combination (then `data_looks` must be NULL, the default).

**max_n**

Single integer, maximum total sample size (defaults to NULL). Must only be specified if `data_looks` is NULL. Requires specification of the `look_after_every` argument.

**look_after_every**

Single integer, specified together with `max_n`. Adaptive analyses will be conducted after every `look_after_every` patients randomised, and at the total sample size as specified by `max_n` (`max_n` does not need to be a multiple of `look_after_every`). If specified, `data_looks` must be NULL (as default).

**control**

Single character string, name of one of the arms or NULL (default). If specified, this arm will serve as a common control arm, to which all other arms will be compared and the inferiority/superiority/equivalence thresholds (see below) will be for those comparisons. See `setup_trial()` Details below for information on behaviour with respect to these comparisons.

**control_prob_fixed**

If a common control arm is specified, this must be set to either NULL (the default), in which case the control arm allocation probability will not be fixed if control arms change (the allocation probability to the first control arm may still be fixed using `fixed_probs`). Otherwise a vector of probabilities of either length 1 or number of arms - 1 can be provided, or one of the special arguments "sqrt-based", "sqrt-based start", "sqrt-based fixed" or "match". See `setup_trial()` Details below for details in behaviour.

**inferiority**

Single numeric (> 0 and <1, default is 0.01) specifying the inferiority threshold. An arm will be considered inferior and dropped if the probability that it is best (when comparing all arms) or better than the control arm (when a common control is used) drops below this threshold.

**superiority**

Single numeric (>0 and <1, default is 0.99) specifying the superiority threshold. If the probability that an arm is best (when comparing all arms) or better than the control arm (when a common control is used) exceeds this number, said arm will be declared the winner and the trial will be stopped (if no common control is used or if the last comparator is dropped in a design with a common control) or become the new control and the trial will continue (if a common control is specified).

**equivalence_prob**

Single numeric (> 0 and < 1) or NULL (default, corresponding to no equivalence assessment). If a numeric value is specified, arms will be stopped for equivalence if the probability of either (a) equivalence compared to a common control or (b) equivalence between all arms remaining (designs without a common control) exceeds this threshold. Requires specification of `equivalence_diff`, `equivalence_only_first`, and a common control arm.

**equivalence_diff**

Single numeric value (> 0) or NULL (default, corresponding to no equivalence assessment). If a numeric value is specified, estimated differences below this threshold will be considered equivalent when assessing equivalence. For designs with a common control arm, the differences between each non-control arm and
the control arm is used, and for trials without a common control arm, the
difference between the highest and lowest estimated outcome rates are used and
the trial is only stopped for equivalence if all remaining arms are thus equivalent.

equivalence_only_first
   single logical in trial specifications where equivalence_prob and equivalence_diff
   are specified, otherwise NULL (default). Must be NULL for designs without a
   common control arm. If a common control arm is used, this specifies whether
   equivalence will only be assessed for the first control (if TRUE) or also for sub-
   sequent control arms (if FALSE) if one arm is superior to the first control and
   becomes the new control.

futility_prob
   single numeric (> 0 and < 1) or NULL (default, corresponds to no futility assess-
   ment). If a numeric value is specified, arms will be stopped for futility when the
   probability for futility compared to the common control exceeds this thresh-
   old. Requires a common control arm, specification of futility_diff and
   futility_only_first.

futility_diff
   single numeric value (> 0) or NULL (default, corresponding to no futility assess-
   ment). If a numeric value is specified, estimated differences below this threshold
   in the beneficial direction (as specified in highest_is_best) will be considered
   futile when assessing futility in designs with a common control arm. If only
   1 arm remains after dropping arms for futility, the trial will be stopped without
   declaring the last arm superior.

futility_only_first
   single logical in trial specifications designs where futility_prob and futility_diff
   are specified, otherwise NULL (default). Must be NULL for designs without a common control arm.
   if one arm is superior to the first control and becomes the new control.

highest_is_best
   single logical, specifies whether larger estimates of the outcome are favourable
   or not; defaults to FALSE, corresponding to, e.g., an undesirable binary outcomes
   (e.g., mortality) or a continuous outcome where lower numbers are preferred
   (e.g., hospital length of stay).

soften_power
   either a single numeric value or a numeric vector of exactly the same length as
   the maximum number of looks/adaptive analyses. Values must be between 0
   and 1 (default); if < 1, then re-allocated non-fixed allocation probabilities are all
   raised to this power to make allocation probabilities less extreme, in turn used
   to redistribute remaining probability while respecting limits when defined by
   min_probs and/or max_probs. If 1, then no softening is applied.

cri_width
   single numeric >= 0 and < 1, the width of the percentile-based credible intervals
   used when summarising individual trial results. Defaults to 0.95, corresponding
   to 95% credible intervals.

n_draws
   single integer, the number of draws from the posterior distributions (for each
   arm) used when running the trial. Defaults to 5000; can be reduced for a speed
   gain (at the potential loss of stability of results if too low) or increased for
   increased precision (takes longer). Values < 100 are not allowed and values
   < 1000 are not recommended and warned against.

robust
   single logical, if TRUE (default) the medians and median absolute deviations
   (scaled to be comparable to the standard deviation for normal distributions;
MAD_SD) are used to summarise the posterior distributions; if FALSE, the means and standard deviations (SDs) are used instead (slightly faster, but may be less appropriate for posteriors skewed on the natural scale).

description
character string, default is "generic binomially distributed outcome trial". See arguments of setup_trial().

Value
A trial_spec object used to run simulations by run_trial() or run_trials(). The output is essentially a list containing the input values (some combined in a data.frame called trial_arms), but its class signals that these inputs have been validated and inappropriate combinations and settings have been ruled out. Also contains best_arm holding the arm(s) with the best value(s) in true_ys. Use str() to peruse the actual content of the returned object.

Examples
# Setup a trial specification a binary, binomially distributed, undesirable outcome
binom_trial <- setup_trial_binom(
  arms = c("Arm A", "Arm B", "Arm C"),
  true_ys = c(0.25, 0.20, 0.30),
  min_probs = rep(0.15, 3),
  # Minimum allocation of 15% in all arms
  data_looks = seq(from = 300, to = 2000, by = 100),
  # Stop for equivalence if > 90% probability of differences < 5 percentage points
  equivalence_prob = 0.9,
  equivalence_diff = 0.05,
  soften_power = 0.5 # Limit extreme allocation ratios
)

# Print using 3 digits for probabilities
print(binom_trial, prob_digits = 3)

setup_trial_norm

Setup a trial specification using a continuous, normally distributed outcome

Description
Specifies the design of an adaptive trial with a continuous, normally distributed outcome and validates all inputs. Uses normally distributed posterior distributions for the mean values in each trial arm; technically, no priors are used (as using normal-normal conjugate prior models with extremely wide or uniform priors gives similar results for these simple, unadjusted estimates). Technically, this thus corresponds to using improper, flat priors, although not explicitly specified as such. Use run_trial() or run_trials() to conduct single/multiple simulations of the specified trial, respectively.

Note: add_info as specified in setup_trial() is set to the arms and standard deviations used for
trials specified using this function.

**Further details:** please see `setup_trial()`. See `setup_trial_binom()` for simplified setup of trials with binomially distributed binary outcomes.

For additional trial specification examples, see the the Basic examples vignette (vignette("Basic-examples", package = "adaptr")) and the Advanced example vignette (vignette("Advanced-example", package = "adaptr")).

**Usage**

```r
setup_trial_norm(
  arms,
  true_ys,
  sds,
  start_probs = NULL,
  fixed_probs = NULL,
  min_probs = rep(NA, length(arms)),
  max_probs = rep(NA, length(arms)),
  data_looks = NULL,
  max_n = NULL,
  look_after_every = NULL,
  control = NULL,
  control_prob_fixed = NULL,
  inferiority = 0.01,
  superiority = 0.99,
  equivalence_prob = NULL,
  equivalence_diff = NULL,
  equivalence_only_first = NULL,
  futility_prob = NULL,
  futility_diff = NULL,
  futility_only_first = NULL,
  highest_is_best = FALSE,
  soften_power = 1,
  cri_width = 0.95,
  n_draws = 5000,
  robust = FALSE,
  description = "generic normally distributed outcome trial"
)
```

**Arguments**

- **arms** character vector with unique names for the trial arms.
- **true_ys** numeric vector, simulated means of the outcome in all trial arms.
- **sds** numeric vector, true standard deviations (must be > 0) of the outcome in all trial arms.
- **start_probs** numeric vector, allocation probabilities for each arm at the beginning of the trial. The default (NULL) is automatically changed to equal randomisation.
- **fixed_probs** numeric vector, fixed allocation probabilities for each arm - must be either a numeric vector with NA for arms without fixed probabilities and values between 0
and 1 for the other arms or NULL (default), if adaptive randomisation is used for all arms or if one of the special settings ("sqrt-based", "sqrt-based start", "sqrt-based fixed", or "match") is specified for control_prob_fixed (described below).

min_probs numeric vector, lower threshold for adaptive allocation probabilities, lower probabilities will be rounded up to these values. Must be NA (default for all arms) if no boundary is wanted.

max_probs numeric vector, upper threshold for adaptive allocation probabilities, higher probabilities will be rounded down to these values. Must be NA (default for all arms) if no boundary is wanted.

data_looks vector of increasing integers, specifies when to conduct adaptive analyses (= the total number of patients randomised at each adaptive analysis). The last number in the vector represents the maximum sample size. Instead of specifying data_looks, the max_n and look_after_every arguments can be used in combination (then data_looks must be NULL, the default).

max_n single integer, maximum total sample size (defaults to NULL). Must only be specified if data_looks is NULL. Requires specification of the look_after_every argument.

look_after_every single integer, specified together with max_n. Adaptive analyses will be conducted after every look_after_every patients randomised, and at the total sample size as specified by max_n (max_n does not need to be a multiple of look_after_every). If specified, data_looks must be NULL (as default).

control single character string, name of one of the arms or NULL (default). If specified, this arm will serve as a common control arm, to which all other arms will be compared and the inferiority/superiority/equivalence thresholds (see below) will be for those comparisons. See setup_trial() Details below for information on behaviour with respect to these comparisons.

control_prob_fixed if a common control arm is specified, this must be set to either NULL (the default), in which case the control arm allocation probability will not be fixed if control arms change (the allocation probability to the first control arm may still be fixed using fixed_probs) Otherwise a vector of probabilities of either length 1 or number of arms - 1 can be provided, or one of the special arguments "sqrt-based", "sqrt-based start", "sqrt-based fixed" or "match". See setup_trial() Details below for details in behaviour.

inferiority single numeric (> 0 and <1, default is 0.01) specifying the inferiority threshold. An arm will be considered inferior and dropped if the probability that it is best (when comparing all arms) or better than the control arm (when a common control is used) drops below this threshold.

superiority single numeric (>0 and <1, default is 0.99) specifying the superiority threshold. If the probability that an arm is best (when comparing all arms) or better than the control arm (when a common control is used) exceeds this number, said arm will be declared the winner and the trial will be stopped (if no common control is used or if the last comparator is dropped in a design with a common control) or become the new control and the trial will continue (if a common control is specified).
setup_trial_norm

equivalence_prob
single numeric (> 0 and < 1) or NULL (default, corresponding to no equivalence assessment). If a numeric value is specified, arms will be stopped for equivalence if the probability of either (a) equivalence compared to a common control or (b) equivalence between all arms remaining (designs without a common control) exceeds this threshold. Requires specification of equivalence_diff, equivalence_only_first, and a common control arm.

equivalence_diff
single numeric value (> 0) or NULL (default, corresponding to no equivalence assessment). If a numeric value is specified, estimated differences below this threshold will be considered equivalent when assessing equivalence. For designs with a common control arm, the differences between each non-control arm and the control arm is used, and for trials without a common control arm, the difference between the highest and lowest estimated outcome rates are used and the trial is only stopped for equivalence if all remaining arms are thus equivalent.

equivalence_only_first
single logical in trial specifications where equivalence_prob and equivalence_diff are specified, otherwise NULL (default). Must be NULL for designs without a common control arm. If a common control arm is used, this specifies whether equivalence will only be assessed for the first control (if TRUE) or also for subsequent control arms (if FALSE) if one arm is superior to the first control and becomes the new control.

futility_prob
single numeric (> 0 and < 1) or NULL (default, corresponds to no futility assessment). If a numeric value is specified, arms will be stopped for futility when the probability for futility compared to the common control exceeds this threshold. Requires a common control arm, specification of futility_diff and futility_only_first.

futility_diff
single numeric value (> 0) or NULL (default, corresponding to no futility assessment). If a numeric value is specified, estimated differences below this threshold in the beneficial direction (as specified in highest_is_best) will be considered futile when assessing futility in designs with a common control arm. If only 1 arm remains after dropping arms for futility, the trial will be stopped without declaring the last arm superior.

futility_only_first
single logical in trial specifications designs where futility_prob and futility_diff are specified, otherwise NULL (default). Must be NULL for designs without a common control arm. Specifies whether futility will only be assessed against the first control (if TRUE) or also for subsequent control arms (if FALSE) if one arm is superior to the first control and becomes the new control.

highest_is_best
single logical, specifies whether larger estimates of the outcome are favourable or not; defaults to FALSE, corresponding to, e.g., an undesirable binary outcomes (e.g., mortality) or a continuous outcome where lower numbers are preferred (e.g., hospital length of stay).

soften_power
either a single numeric value or a numeric vector of exactly the same length as the maximum number of looks/adaptive analyses. Values must be between 0 and 1 (default); if < 1, then re-allocated non-fixed allocation probabilities are all raised to this power to make allocation probabilities less extreme, in turn used to redistribute remaining probability while respecting limits when defined by min_probs and/or max_probs. If 1, then no softening is applied.
cri_width single numeric \( \geq 0 \) and \(< 1\), the width of the percentile-based credible intervals used when summarising individual trial results. Defaults to \(0.95\), corresponding to 95\% credible intervals.

n_draws single integer, the number of draws from the posterior distributions (for each arm) used when running the trial. Defaults to 5000; can be reduced for a speed gain (at the potential loss of stability of results if too low) or increased for increased precision (takes longer). Values \(< 100\) are not allowed and values \(< 1000\) are not recommended and warned against.

robust single logical, if TRUE (default) the medians and median absolute deviations (scaled to be comparable to the standard deviation for normal distributions; MAD_SD) are used to summarise the posterior distributions; if FALSE, the means and standard deviations (SDs) are used instead (slightly faster, but may be less appropriate for posteriors skewed on the natural scale).

description character string, default is "generic normally distributed outcome trial". See arguments of setup_trial().

Details

Because the posteriors used in this type of trial (with a generic, continuous, normally distributed outcome) are by definition normally distributed, FALSE is used as the default value for the robust argument.

Value

A trial_spec object used to run simulations by run_trial() or run_trials(). The output is essentially a list containing the input values (some combined in a data.frame called trial_arms), but its class signals that these inputs have been validated and inappropriate combinations and settings have been ruled out. Also contains best_arm holding the arm(s) with the best value(s) in true_ys. Use str() to peruse the actual content of the returned object.

Examples

# Setup a trial specification using a continuous, normally distributed, desirable outcome norm_trial <- setup_trial_norm(
  arms = c("Control", "New A", "New B", "New C"),
  true_ys = c(15, 20, 14, 13),
  sds = c(2, 2.5, 1.9, 1.8), # SDs in each arm
  max_n = 500,
  look_after_every = 50,
  control = "Control", # Common control arm
  control_prob_fixed = "sqrt-based fixed", # Square-root-based, fixed control group allocation ratios
  highest_is_best = TRUE,
  soften_power = 0.5 # Limit extreme allocation ratios
)

# Print using 3 digits for probabilities
print(norm_trial, prob_digits = 3)
Summary of simulated trial results

Description

Summarises simulation results from the run_trials() function. Uses extract_results(), which may be used directly to extract key trial results without summarising.

Usage

```r
## S3 method for class 'trial_results'
summary(
  object, 
  select_strategy = "control if available", 
  select_last_arm = FALSE, 
  select_preferences = NULL, 
  te_comp = NULL, 
  raw_est = FALSE, 
  restrict = NULL, 
  ... 
)
```

Arguments

- **object** trial_results object, output from the run_trials() function.
- **select_strategy** single character string. For trials not stopped due to superiority (or with only 1 arm remaining, if select_last_arm is set to TRUE in trial designs with a common control arm; see below), this parameter specifies which arm will be considered selected when calculating trial design performance metrics (described below; this corresponds to the consequence of an inconclusive trial, i.e., which arm would then be used in practice). The following options are available and must be written exactly as below (case sensitive, cannot be abbreviated):
  - "control if available" (default): selects the first control arm for trials with a common control arm if this arm is active at end-of-trial, otherwise no arm will be selected. For trial designs without a common control, no arm will be selected.
  - "none": selects no arm in trials not ending with superiority.
  - "control": similar to "control if available", but will throw an error for trial designs without a common control arm.
  - "final control": selects the final control arm regardless of whether the trial was stopped for practical equivalence, futility, or at the maximum sample size; this strategy can only be specified for trial designs with a common control arm.
- "control or best": selects the first control arm if still active at end-of-trial, otherwise selects the best remaining arm (defined as the remaining arm with the highest probability of being the best in the final analysis). Only works for trial designs with a common control arm.
- "best": selects the best remaining arm (as described under "control or best").
- "list or best": selects the first remaining arm from a specified list (specified using select_preferences, technically a character vector). If none of these arms are are active at end-of-trial, the best remaining arm will be selected (as described above).
- "list": as specified above, but if no arms on the provided list remain active at end-of-trial, no arm is selected.

**select_last_arm**

single logical, defaults to FALSE. If TRUE, the only remaining active arm (the last control) will be selected in trials with a common control arm ending with equivalence or futility, before considering the options specified in select_strategy. Must be FALSE for trial designs without a common control arm.

**select_preferences**

character vector specifying a number of arms used for selection if one of the "list or best" or "list" options are specified for select_strategy. Can only contain valid arms available in the trial.

**te_comp**

character string, treatment-effect comparator. Can be either NULL (the default) in which case the first control arm is used for trial designs with a common control arm, or a single trial arm. Will be used when calculating sq_err_te (the squared error of the treatment effect comparing the selected arm to the comparator arm, as described below).

**raw_est**

single logical. If FALSE (default), the posterior estimates (post_est, see setup_trial() and run_trial()) will be used to calculate sq_err (the squared error of the estimated compared to the specified effect in the selected arm) and sq_err_te (the squared error of the treatment effect comparing the selected arm to the comparator arm, as described for te_comp and below). If TRUE, the raw estimates (raw_est, see setup_trial() and run_trial()) will be used instead of the posterior estimates.

**restrict**

single character string or NULL. If NULL (default), results are summarised for all simulations; if "superior", results are summarised for simulations ending with superiority only; if "selected", results are summarised for simulations ending with a selected arm (according to the specified arm selection strategy for simulations not ending with superiority). Some summary measures (e.g., prob_conclusive) can only be calculated across all simulations and several are calculated regardless of restrict settings, but have substantially different interpretations if restricted.

... additional arguments, not used.

**Details**

The ideal design percentage (IDP) returned (described below) is based on Viele et al, 2020 doi: 10.1177/1740774519877836 and has been adapted to work for trials with both desirable/undesirable out-
comes and non-binary outcomes. Briefly, the expected outcome is calculated as the sum of the true outcomes in each arm multiplied by the corresponding selection probabilities (ignoring simulations with no selected arm). The IDP is then calculated as:

- For desirable outcomes:
  \[100 \times \frac{{\text{expected outcome} - \text{lowest true outcome}}}{{\text{highest true outcome} - \text{lowest true outcome}}}\]
- For undesirable outcomes:
  \[100 - \text{IDP calculated for desirable outcomes}\]

Value

A "trial_results_summary" object containing the following:
- n_rep: the number of simulations.
- n_summarised: the number of simulations summarised.
- highest_is_best: as specified in setup_trial().
- elapsed_time: the total simulation time.
- size_mean, size_sd, size_median, size_p25, size_p75: the mean, standard deviation, median as well as 25- and 75-percentiles of the sample sizes of the summarised trial simulations.
- sum_ys_mean, sum_ys_sd, sum_ys_median, sum_ys_p25, sum_ys_p75: the mean, standard deviation, median as well as 25- and 75-percentiles of the total sum_ys (e.g., the total number of events in trials with a binary outcome, or the sums of continuous values for all patients across all arms in trials with a continuous outcome) across all arms in the summarised trial simulations.
- ratio_ys_mean, ratio_ys_sd, ratio_ys_median, ratio_ys_p25, ratio_ys_p75: the mean, standard deviation, median as well as 25- and 75-percentiles of the final ratio_ys (sum_ys/final_n) across all arms in the summarised trial simulations.
- prob_conclusive: the proportion of conclusive trial simulations (simulations not stopped at the maximum sample size without a superiority, equivalence or futility decision).
- prob_superior, prob_equivalence, prob_futility, prob_max: the proportion (0-1) of trial simulations stopped for superiority, equivalence, futility or inconclusive at the maximum allowed sample size, respectively.
- prob_select_*: the selection probabilities for each arm and for no selection, according to the specified selection strategy. Contains one element per arm, named as prob_select_arm_<arm name> and prob_select_none for the probability of selecting no arm.
- rmse, rmse_te: the root mean squared error of the estimates for the selected arm and for the treatment effect, as described further in extract_results().
- idp: the ideal design percentage (IDP; 0-100%), see Details.
- select_strategy, select_last_arm, select_preferences, te_comp, raw_ests, restrict: as specified above.
- control: the control arm specified by setup_trial(), setup_trial_binom() or setup_trial_norm(); NULL if no control.
- equivalence_assessed, futility_assessed: single logicals, specifies whether the trial design specification includes assessments of equivalence and/or futility.
- base_seed: as specified in run_trials().
- cri_width, n_draws, robust, description, add_info: as specified in setup_trial(), setup_trial_binom() or setup_trial_norm().
Examples

# Setup a trial specification
binom_trial <- setup_trial_binom(arms = c("A", "B", "C", "D"),
control = "A",
true_ys = c(0.20, 0.18, 0.22, 0.24),
data_looks = 1:20 * 100)

# Run 10 simulations with a specified random base seed
res <- run_trials(binom_trial, n_rep = 10, base_seed = 12345)

# Summarise simulations - select the control arm if available in trials not
# ending with a superiority decision
res_sum <- summary(res, select_strategy = "control")

# Print summary
print(res_sum, digits = 1)
Index

adaptr (adaptr-package), 2
adaptr-package, 2

extract_results, 3
extract_results(), 2, 3, 17, 22, 34, 36

find_beta_params, 5

library(), 17

mean(), 20

parallel::clusterExport(), 16, 17
parallel::detectCores(), 16
plot_history, 6
plot_history(), 2, 3, 9, 13, 16
plot_status, 8
plot_status(), 2, 3, 7, 16
print, 9
print(), 3
print.trial_results(), 17

readRDS(), 15
require(), 17
run_trial, 12
run_trial(), 2–6, 11, 12, 15–17, 21–23, 25, 29, 33, 35
run_trials, 15
run_trials(), 2, 3, 6–8, 12, 13, 16, 17, 21–23, 25, 29, 33, 34, 36

saveRDS(), 15, 16
setup_trial, 2, 17
setup_trial(), 2–4, 11–16, 18, 19, 22, 25, 27, 29–31, 33, 35, 36
setup_trial_binom, 25
setup_trial_binom(), 2, 3, 5, 12–15, 17, 20, 22, 30, 36
setup_trial_norm, 29
setup_trial_norm(), 2, 3, 5, 12–15, 17, 20, 22, 25, 36

summary, 34
summary(), 2, 3, 12, 17, 22

38