

Package: simaerep (via r-universe)

August 31, 2024

Title Find Clinical Trial Sites Under-Reporting Adverse Events

Version 0.5.0

Description Monitoring of Adverse Event (AE) reporting in clinical trials is important for patient safety. Sites that are under-reporting AEs can be detected using Bootstrap-based simulations that simulate overall AE reporting. Based on the simulation an AE under-reporting probability is assigned to each site in a given trial (Koneswarakantha 2021 <doi:10.1007/s40264-020-01011-5>).

URL <https://openpharma.github.io/simaerep/>,
<https://github.com/openpharma/simaerep>

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Encoding UTF-8

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aggr_duplicated_visits
Aggregate duplicated visits.

Description

Internal function called by [check_df_visit\(\)](#).

Usage

```
aggr_duplicated_visits(df_visit)
```

Arguments

df_visit dataframe with columns: study_id, site_number, patnum, visit, n_ae

Value

df_visit corrected

check_df_visit *Integrity check for df_visit.*

Description

Internal function used by all functions that accept df_visit as a parameter. Checks for NA columns, numeric visits and AEs, implicitly missing and duplicated visits.

Usage

```
check_df_visit(df_visit)
```

Arguments

df_visit dataframe with columns: study_id, site_number, patnum, visit, n_ae

Value

corrected df_visit

Examples

```
df_visit <- sim_test_data_study(
  n_pat = 100,
  n_sites = 5,
  frac_site_with_ur = 0.4,
  ur_rate = 0.6
)

df_visit$study_id <- "A"

df_visit_filt <- df_visit %>%
  dplyr::filter(visit != 3)

df_visit_corr <- check_df_visit(df_visit_filt)
3 %in% df_visit_corr$visit
nrow(df_visit_corr) == nrow(df_visit)

df_visit_corr <- check_df_visit(dplyr::bind_rows(df_visit, df_visit))
nrow(df_visit_corr) == nrow(df_visit)
```

eval_sites

Evaluate sites.

Description

Correct under-reporting probabilities using [p.adjust](#).

Usage

```
eval_sites(df_sim_sites, method = "BH", under_only = TRUE, ...)
```

Arguments

df_sim_sites	dataframe generated by sim_sites
method	character, passed to stats::p.adjust(), if NULL <code>eval_sites_deprecated()</code> is used instead, Default = "BH"
under_only	compute under-reporting probabilities only, default = TRUE check_df_visit() , computationally expensive on large data sets. Default: TRUE
...	use to pass <code>r_sim_sites</code> parameter to <code>eval_sites_deprecated()</code>

Value

dataframe with the following columns:

study_id study identification

site_number site identification

visit_med75 median(max(visit)) * 0.75
mean_ae_site_med75 mean AE at visit_med75 site level
mean_ae_study_med75 mean AE at visit_med75 study level
pval p-value as returned by [poisson.test](#)
prob_low bootstrapped probability for having mean_ae_site_med75 or lower
pval_adj adjusted p-values
prob_low_adj adjusted bootstrapped probability for having mean_ae_site_med75 or lower
pval_prob_ur probability under-reporting as 1 - pval_adj, poisson.test (use as benchmark)
prob_low_prob_ur probability under-reporting as 1 - prob_low_adj, bootstrapped (use)

See Also

[site_aggr](#), [sim_sites](#), [p.adjust](#)

Examples

```

df_visit <- sim_test_data_study(n_pat = 100, n_sites = 5,
  frac_site_with_ur = 0.4, ur_rate = 0.6)

df_visit$study_id <- "A"
df_site <- site_aggr(df_visit)

df_sim_sites <- sim_sites(df_site, df_visit, r = 100)

df_eval <- eval_sites(df_sim_sites)
df_eval

# use deprecated method -----
df_eval <- eval_sites(df_sim_sites, method = NULL, r_sim_sites = 100)
df_eval
  
```

eval_sites_deprecated *Evaluate sites.*

Description

Correct under-reporting probabilities by the expected number of false positives (fp). This has been deprecated in favor of more conventional methods available via [p.adjust](#).

Usage

```
eval_sites_deprecated(df_sim_sites, r_sim_sites)
```

Arguments

df_sim_sites dataframe generated by [sim_sites\(\)](#)
r_sim_sites integer, number of repeats for bootstrap resampling for site simulation, needed for zero probability correction for fp calculation, Default: 1000

Details

If by chance expected number of false positives (fp) is greater than the total number of positives (p) we set `p_vs_fp_ratio = 1` and `prob_ur = 0`.

Value

dataframe with the following columns:

study_id study identification

site_number site identification

visit_med75 median(max(visit)) * 0.75

mean_ae_site_med75 mean AE at visit_med75 site level

mean_ae_study_med75 mean AE at visit_med75 study level

pval p-value as returned by `poisson.test`

prob_low bootstrapped probability for having mean_ae_site_med75 or lower

n_site number of study sites

pval_n_detected sites with the same p-value or lower

pval_fp expected number of fp, `pval * n_site`

pval_p_vs_fp_ratio odds under-reporting as `p/fp`, `poisson.test` (use as benchmark)

pval_prob_ur probability under-reporting as `1 - fp/p`, `poisson.test` (use as benchmark)

prob_low_n_detected sites with same bootstrapped probability or lower

prob_low_fp expected number of fp, `prob_lower * n_site`

prob_low_p_vs_fp_ratio odds under-reporting as `p/fp`, bootstrapped (use)

prob_low_prob_ur probability under-reporting as `1 - fp/p`, bootstrapped (use)

See Also

[site_aggr\(\)](#), [sim_sites\(\)](#)

Examples

```
df_visit <- sim_test_data_study(n_pat = 100, n_sites = 5,
  frac_site_with_ur = 0.4, ur_rate = 0.6)

df_visit$study_id <- "A"
df_site <- site_aggr(df_visit)

df_sim_sites <- sim_sites(df_site, df_visit, r = 100)

df_eval <- eval_sites_deprecated(df_sim_sites, r_sim_sites = 100)
df_eval
```

exp_implicit_missing_visits
Expose implicitly missing visits.

Description

Internal function called by [check_df_visit\(\)](#).

Usage

```
exp_implicit_missing_visits(df_visit)
```

Arguments

df_visit dataframe with columns: study_id, site_number, patnum, visit, n_ae

Value

df_visit corrected

get_config *Get Portfolio Configuration*

Description

Get Portfolio configuration from a dataframe aggregated on patient level with max_ae and max_visit. Will filter studies with only a few sites and patients and will anonymize IDs. Portfolio configuration can be used by [sim_test_data_portfolio](#) to generate data for an artificial portfolio.

Usage

```
get_config(  
  df_site,  
  min_pat_per_study = 100,  
  min_sites_per_study = 10,  
  anonymize = TRUE,  
  pad_width = 4  
)
```

Arguments

df_site dataframe aggregated on patient level with max_ae and max_visit
 min_pat_per_study minimum number of patients per study, Default: 100
 min_sites_per_study minimum number of sites per study, Default: 10
 anonymize logical, Default: TRUE
 pad_width padding width for newly created IDs, Default: 4

Value

dataframe with the following columns:

study_id study identification
ae_per_visit_mean mean AE per visit per study
site_number site
max_visit_sd standard deviation of maximum patient visits per site
max_visit_mean mean of maximum patient visits per site
n_pat number of patients

See Also

[sim_test_data_study](#) [get_config](#) [sim_test_data_portfolio](#) [sim_ur_scenarios](#) [get_portf_perf](#)

Examples

```
df_visit1 <- sim_test_data_study(n_pat = 100, n_sites = 10,
                                frac_site_with_ur = 0.4, ur_rate = 0.6)

df_visit1$study_id <- "A"

df_visit2 <- sim_test_data_study(n_pat = 100, n_sites = 10,
                                frac_site_with_ur = 0.2, ur_rate = 0.1)

df_visit2$study_id <- "B"

df_visit <- dplyr::bind_rows(df_visit1, df_visit2)

df_site_max <- df_visit %>%
  dplyr::group_by(study_id, site_number, patnum) %>%
  dplyr::summarise(max_visit = max(visit),
                  max_ae = max(n_ae),
                  .groups = "drop")

df_config <- get_config(df_site_max)

df_config
```



```
df_portf <- sim_test_data_portfolio(df_config)

df_portf

df_scen <- sim_ur_scenarios(df_portf,
                           extra_ur_sites = 2,
                           ur_rate = c(0.5, 1))

df_scen

df_perf <- get_portf_perf(df_scen)

df_perf
```

get_ecd_values	<i>Get empirical cumulative distribution values of pval or prob_lower</i>
----------------	---

Description

Test function, test applicability of poisson test, by calculating

- the bootstrapped probability of obtaining a specific p-value or lower, use in combination with [sim_studies\(\)](#).

Usage

```
get_ecd_values(df_sim_studies, df_sim_sites, val_str)
```

Arguments

```
df_sim_studies  dataframe, generated by sim\_studies\(\)
df_sim_sites    dataframe, generated by sim\_sites\(\)
val_str         c("prob_low", "pval")
```

Details

trains a ecdf function for each studies based on the results of [sim_studies\(\)](#)

Value

dataframe with the following columns:

```
study_id  study identification
site_number  site identification
visit_med75  median(max(visit)) * 0.75
mean_ae_site_med75  mean AE at visit_med75 site level
```

mean_ae_study_med75 mean AE at visit_med75 study level
pval/prob_low p-value as returned by poisson.test
pval/prob_low_eed p-value as returned by poisson.test

Examples

```
df_visit <- sim_test_data_study(n_pat = 100, n_sites = 5,
  frac_site_with_ur = 0.4, ur_rate = 0.3)

df_visit$study_id <- "A"
df_site <- site_aggr(df_visit)

df_sim_sites <- sim_sites(df_site, df_visit, r = 100)

df_sim_studies <- sim_studies(
  df_site = df_site,
  df_visit = df_visit,
  r = 3,
  parallel = FALSE,
  poisson_test = TRUE,
  prob_lower = TRUE
)

get_eed_values(df_sim_studies, df_sim_sites, "prob_low")
get_eed_values(df_sim_studies, df_sim_sites, "pval")
```

get_pat_pool_config *Configure study patient pool by site parameters.*

Description

Internal Function used by [sim_sites\(\)](#)

Usage

```
get_pat_pool_config(df_visit, df_site, min_n_pat_with_med75 = 1)
```

Arguments

df_visit	dataframe
df_site	dataframe as created by site_aggr()
min_n_pat_with_med75	minimum number of patients with visit_med_75 for simulation, Default: 1

Details

For simulating a study we need to configure the study patient pool to match the configuration of the sites

Value

dataframe

Examples

```
df_visit1 <- sim_test_data_study(n_pat = 100, n_sites = 5,
                                frac_site_with_ur = 0.4, ur_rate = 0.6)

df_visit1$study_id <- "A"

df_visit2 <- sim_test_data_study(n_pat = 1000, n_sites = 3,
                                frac_site_with_ur = 0.2, ur_rate = 0.1)

df_visit2$study_id <- "B"

df_visit <- dplyr::bind_rows(df_visit1, df_visit2)

df_site <- site_aggr(df_visit)

df_config <- get_pat_pool_config(df_visit, df_site)

df_config
```

get_portf_perf

*Get Portfolio Performance***Description**

Performance as true positive rate (tpr as tp/P) on the basis of desired false positive rates (fpr as fp/P).

Usage

```
get_portf_perf(df_scen, stat = "prob_low_prob_ur", fpr = c(0.001, 0.01, 0.05))
```

Arguments

df_scen	dataframe as returned by sim_ur_scenarios
stat	character denoting the column name of the under-reporting statistic, Default: 'prob_low_prob_ur'
fpr	numeric vector specifying false positive rates, Default: c(0.001, 0.01, 0.05)

Details

DETAILS

Value

dataframe

See Also

[sim_test_data_study](#) [get_config](#) [sim_test_data_portfolio](#) [sim_ur_scenarios](#) [get_portf_perf](#)

Examples

```
df_visit1 <- sim_test_data_study(n_pat = 100, n_sites = 10,
                                frac_site_with_ur = 0.4, ur_rate = 0.6)

df_visit1$study_id <- "A"

df_visit2 <- sim_test_data_study(n_pat = 100, n_sites = 10,
                                frac_site_with_ur = 0.2, ur_rate = 0.1)

df_visit2$study_id <- "B"

df_visit <- dplyr::bind_rows(df_visit1, df_visit2)

df_site_max <- df_visit %>%
  dplyr::group_by(study_id, site_number, patnum) %>%
  dplyr::summarise(max_visit = max(visit),
                  max_ae = max(n_ae),
                  .groups = "drop")

df_config <- get_config(df_site_max)

df_config

df_portf <- sim_test_data_portfolio(df_config)

df_portf

df_scen <- sim_ur_scenarios(df_portf,
                           extra_ur_sites = 2,
                           ur_rate = c(0.5, 1))

df_scen

df_perf <- get_portf_perf(df_scen)

df_perf
```

get_site_mean_ae_dev *Get site mean ae development.*

Description

Internal function used by [site_aggr\(\)](#), [plot_visit_med75\(\)](#), returns mean AE development from visit 0 to visit_med75.

Usage

```
get_site_mean_ae_dev(df_visit, df_pat, df_site)
```

Arguments

df_visit	dataframe
df_pat	dataframe as returned by pat_aggr()
df_site	dataframe as returned by site_aggr()

Value

dataframe

get_visit_med75	<i>Get visit_med75.</i>
-----------------	-------------------------

Description

Internal function used by [site_aggr\(\)](#).

Usage

```
get_visit_med75(df_pat, method = "med75_adj", min_pat_pool = 0.2)
```

Arguments

df_pat	dataframe as returned by pat_aggr()
method	character, one of c("med75", "med75_adj") defining method for defining evaluation point visit_med75 (see details), Default: "med75_adj"
min_pat_pool	double, minimum ratio of available patients available for sampling. Determines maximum visit_med75 value see Details. Default: 0.2

Value

dataframe

`is_orivisit`*is orivisit class*

Description

internal function

Usage`is_orivisit(x)`**Arguments**`x` object**Value**logical

`is_simaerep`*is simaerep class*

Description

internal function

Usage`is_simaerep(x)`**Arguments**`x` object**Value**

logical

orivisit	<i>create orivisit object</i>
----------	-------------------------------

Description

Internal S3 object, stores lazy reference to original visit data.

Usage

```
orivisit(df_visit, call = NULL, env = parent.frame())
```

Arguments

<code>df_visit</code>	dataframe with original visit data
<code>call</code>	optional, provide call, Default: NULL
<code>env</code>	optional, provide environment of original visit data, Default: <code>parent.frame()</code>

Details

Saves variable name of original visit data, checks whether it can be retrieved from parent environment and stores summary. Original data can be retrieved using `as.data.frame(x)`.

Value

orivisit object

Examples

```
df_visit <- sim_test_data_study(  
  n_pat = 100,  
  n_sites = 5,  
  frac_site_with_ur = 0.4,  
  ur_rate = 0.6  
)  
  
df_visit$study_id <- "A"  
  
visit <- orivisit(df_visit)  
  
object.size(df_visit)  
object.size(visit)  
  
as.data.frame(visit)
```

pat_aggr	<i>Aggregate visit to patient level.</i>
----------	--

Description

Internal function used by `site_aggr()` and `plot_visit_med75()`, adds the maximum visit for each patient.

Usage

```
pat_aggr(df_visit)
```

Arguments

df_visit dataframe

Value

dataframe

pat_pool	<i>Create a study specific patient pool for sampling</i>
----------	--

Description

Internal function for `sim_sites`, filter all visits greater than `max_visit_med75_study` returns dataframe with one column for studies and one column with nested patient data.

Usage

```
pat_pool(df_visit, df_site)
```

Arguments

df_visit dataframe, created by `sim_sites`
df_site dataframe created by `site_aggr`

Value

dataframe with nested pat_pool column

Examples

```
df_visit <- sim_test_data_study(
  n_pat = 100,
  n_sites = 5,
  frac_site_with_ur = 0.4,
  ur_rate = 0.6
)

df_visit$study_id <- "A"

df_site <- site_aggr(df_visit)

df_pat_pool <- pat_pool(df_visit, df_site)

df_pat_pool
```

plot.simaerep

plot AE under-reporting simulation results

Description

generic plot function for simaerep objects

Usage

```
## S3 method for class 'simaerep'
plot(
  x,
  ...,
  study = NULL,
  what = "ur",
  n_sites = 16,
  df_visit = NULL,
  env = parent.frame()
)
```

Arguments

x	simaerep object
...	additional parameters passed to plot_study() or plot_visit_med75()
study	character specifying study to be plotted, Default: NULL
what	one of c("ur", "med75"), specifying whether to plot site AE under-reporting or visit_med75 values, Default: 'ur'
n_sites	number of sites to plot, Default: 16
df_visit	optional, pass original visit data if it cannot be retrieved from parent environment, Default: NULL
env	optional, pass environment from which to retrieve original visit data, Default: parent.frame()

Details

see [plot_study\(\)](#) and [plot_visit_med75\(\)](#)

Value

ggplot object

Examples

```
df_visit <- sim_test_data_study(  
  n_pat = 100,  
  n_sites = 5,  
  frac_site_with_ur = 0.4,  
  ur_rate = 0.6  
)  
  
df_visit$study_id <- "A"  
  
aerep <- simaerep(df_visit)  
  
plot(aerep, what = "ur", study = "A")  
plot(aerep, what = "med75", study = "A")
```

plot_dots

Plots AE per site as dots.

Description

This plot is meant to supplement the package documentation.

Usage

```
plot_dots(  
  df,  
  nrow = 10,  
  ncols = 10,  
  col_group = "site",  
  thresh = NULL,  
  color_site_a = "#BDBDBD",  
  color_site_b = "#757575",  
  color_site_c = "gold3",  
  color_high = "#00695C",  
  color_low = "#25A69A",  
  size_dots = 10  
)
```

Arguments

df	dataframe, cols = c('site', 'patients', 'n_ae')
nrow	integer, number of rows, Default: 10
ncols	integer, number of columns, Default: 10
col_group	character, grouping column, Default: 'site'
thresh	numeric, threshold to determine color of mean_ae annotation, Default: NULL
color_site_a	character, hex color value, Default: '#BDBDBD'
color_site_b	character, hex color value, Default: '#757575'
color_site_c	character, hex color value, Default: 'gold3'
color_high	character, hex color value, Default: '#00695C'
color_low	character, hex color value, Default: '#25A69A'
size_dots	integer, Default: 10

Value

ggplot object

Examples

```
study <- tibble::tibble(
  site = LETTERS[1:3],
  patients = c(list(seq(1, 50, 1)), list(seq(1, 40, 1)), list(seq(1, 10, 1)))
) %>%
  tidyr::unnest(patients) %>%
  dplyr::mutate(n_ae = as.integer(runif(min = 0, max = 10, n = nrow(.))))

plot_dots(study)
```

plot_sim_example *Plot simulation example.*

Description

This plots supplements the package documentation.

Usage

```
plot_sim_example(
  subtract_ae_per_pat = 0,
  size_dots = 10,
  size_raster_label = 12,
  color_site_a = "#BDBDBD",
  color_site_b = "#757575",
  color_site_c = "gold3",
```

```
    color_high = "#00695C",
    color_low = "#25A69A",
    title = TRUE,
    legend = TRUE,
    seed = 5
  )
```

Arguments

subtract_ae_per_pat	integer, subtract aes from patients at site C, Default: 0
size_dots	integer, Default: 10
size_raster_label	integer, Default: 12
color_site_a	character, hex color value, Default: '#BDBDBD'
color_site_b	character, hex color value, Default: '#757575'
color_site_c	character, hex color value, Default: 'gold3'
color_high	character, hex color value, Default: '#00695C'
color_low	character, hex color value, Default: '#25A69A'
title	logical, include title, Default: T
legend	logical, include legend, Default: T
seed	pass seed for simulations Default: 5

Details

uses [plot_dots\(\)](#) and adds 2 simulation panels, uses made-up site config with three sites A,B,C simulating site C

Value

ggplot

See Also

[get_legend](#), [plot_grid](#)

Examples

```
plot_sim_example(size_dots = 5)
```

plot_sim_examples *Plot multiple simulation examples.*

Description

This plot is meant to supplement the package documentation.

Usage

```
plot_sim_examples(substract_ae_per_pat = c(0, 1, 3), ...)
```

Arguments

```
substract_ae_per_pat
  integer, Default: c(0, 1, 3)
...
  parameters passed to plot_sim_example()
```

Details

This function is a wrapper for plot_sim_example()

Value

ggplot

See Also

[ggdraw](#), [draw_label](#), [plot_grid](#)

Examples

```
plot_sim_examples(size_dot = 3, size_raster_label = 10)
plot_sim_examples()
```

plot_study *Plot ae development of study and sites highlighting at risk sites.*

Description

Most suitable visual representation of the AE under-reporting statistics.

Usage

```
plot_study(
  df_visit,
  df_site,
  df_eval,
  study,
  df_al = NULL,
  n_sites = 16,
  pval = FALSE,
  prob_col = "prob_low_prob_ur"
)
```

Arguments

df_visit	dataframe, created by <code>sim_sites()</code>
df_site	dataframe created by <code>site_aggr()</code>
df_eval	dataframe created by <code>eval_sites()</code>
study	study
df_al	dataframe containing study_id, site_number, alert_level_site, alert_level_study (optional), Default: NA
n_sites	integer number of most at risk sites, Default: 16
pval	logical show p-value, Default:FALSE
prob_col	character, denotes probability column, Default: "prob_low_prob_ur"

Details

Left panel shows mean AE reporting per site (lightblue and darkblue lines) against mean AE reporting of the entire study (golden line). Single sites are plotted in descending order by AE under-reporting probability on the right panel in which grey lines denote cumulative AE count of single patients. Grey dots in the left panel plot indicate sites that were picked for single plotting. AE under-reporting probability of dark blue lines crossed threshold of 95%. Numbers in the upper left corner indicate the ratio of patients that have been used for the analysis against the total number of patients. Patients that have not been on the study long enough to reach the evaluation point (visit_med75) will be ignored.

Value

ggplot

Examples

```
df_visit <- sim_test_data_study(n_pat = 1000, n_sites = 10,
  frac_site_with_ur = 0.2, ur_rate = 0.15, max_visit_sd = 8)

df_visit$study_id <- "A"
df_site <- site_aggr(df_visit)
```

```
df_sim_sites <- sim_sites(df_site, df_visit, r = 100)

df_eval <- eval_sites(df_sim_sites)

plot_study(df_visit, df_site, df_eval, study = "A")
```

plot_visit_med75	<i>Plot patient visits against visit_med75.</i>
------------------	---

Description

Plots cumulative AEs against visits for patients at sites of given study and compares against visit_med75.

Usage

```
plot_visit_med75(
  df_visit,
  df_site = NULL,
  study_id_str,
  n_sites = 6,
  min_pat_pool = 0.2,
  verbose = TRUE
)
```

Arguments

df_visit	dataframe
df_site	dataframe, as returned by site_aggr()
study_id_str	character, specify study in study_id column
n_sites	integer, Default: 6
min_pat_pool	double, minimum ratio of available patients available for sampling. Determines maximum visit_med75 value see Details. Default: 0.2
verbose	logical, Default: TRUE

Value

ggplot

Examples

```
df_visit <- sim_test_data_study(n_pat = 120, n_sites = 6,
  frac_site_with_ur = 0.4, ur_rate = 0.6)

df_visit$study_id <- "A"
df_site <- site_aggr(df_visit)

plot_visit_med75(df_visit, df_site, study_id_str = "A", n_site = 6)
```

`poiss_test_site_ae_vs_study_ae`*Poisson test for vector with site AEs vs vector with study AEs.*

Description

Internal function used by `sim_sites()`.

Usage

```
poiss_test_site_ae_vs_study_ae(site_ae, study_ae, visit_med75)
```

Arguments

<code>site_ae</code>	vector with AE numbers
<code>study_ae</code>	vector with AE numbers
<code>visit_med75</code>	integer

Details

sets pvalue=1 if mean AE site is greater than mean AE study or ttest gives error

Value

pval

See Also

[sim_sites\(\)](#)

Examples

```
poiss_test_site_ae_vs_study_ae(  
  site_ae = c(5, 3, 3, 2, 1, 6),  
  study_ae = c(9, 8, 7, 9, 6, 7, 8),  
  visit_med75 = 10  
)
```

```
poiss_test_site_ae_vs_study_ae(  
  site_ae = c(11, 9, 8, 6, 3),  
  study_ae = c(9, 8, 7, 9, 6, 7, 8),  
  visit_med75 = 10  
)
```

prep_for_sim	<i>Prepare data for simulation.</i>
--------------	-------------------------------------

Description

Internal function called by [sim_sites](#). Collect AEs per patient at visit_med75 for site and study as a vector of integers.

Usage

```
prep_for_sim(df_site, df_visit)
```

Arguments

df_site	dataframe created by site_aggr
df_visit	dataframe, created by sim_sites

Value

dataframe

See Also

[sim_sites](#), [sim_after_prep](#)

Examples

```
df_visit <- sim_test_data_study(  
  n_pat = 100,  
  n_sites = 5,  
  frac_site_with_ur = 0.4,  
  ur_rate = 0.2  
)  
  
df_visit$study_id <- "A"  
  
df_site <- site_aggr(df_visit)  
  
df_prep <- prep_for_sim(df_site, df_visit)  
df_prep
```

```
prob_lower_site_ae_vs_study_ae
```

Calculate bootstrapped probability for obtaining a lower site mean AE number.

Description

Internal function used by [sim_sites\(\)](#)

Usage

```
prob_lower_site_ae_vs_study_ae(  
  site_ae,  
  study_ae,  
  r = 1000,  
  parallel = FALSE,  
  under_only = TRUE  
)
```

Arguments

site_ae	vector with AE numbers
study_ae	vector with AE numbers
r	integer, denotes number of simulations, default = 1000
parallel	logical, toggles parallel processing on and of, default = F
under_only	compute under-reporting probabilities only, default = TRUE

Details

sets pvalue=1 if mean AE site is greater than mean AE study

Value

pval

See Also

[safely](#)

Examples

```
prob_lower_site_ae_vs_study_ae(  
  site_ae = c(5, 3, 3, 2, 1, 6),  
  study_ae = c(9, 8, 7, 9, 6, 7, 8),  
  parallel = FALSE  
)
```

`purrr_bar`*Execute a purrr or furrr function with a progress bar.*

Description

Internal utility function.

Usage

```
purrr_bar(  
  ...,  
  .purrr,  
  .f,  
  .f_args = list(),  
  .purrr_args = list(),  
  .steps,  
  .slow = FALSE,  
  .progress = TRUE  
)
```

Arguments

<code>...</code>	iterable arguments passed to <code>.purrr</code>
<code>.purrr</code>	purrr or furrr function
<code>.f</code>	function to be executed over iterables
<code>.f_args</code>	list of arguments passed to <code>.f</code> , Default: <code>list()</code>
<code>.purrr_args</code>	list of arguments passed to <code>.purrr</code> , Default: <code>list()</code>
<code>.steps</code>	integer number of iterations
<code>.slow</code>	logical slows down execution, Default: <code>FALSE</code>
<code>.progress</code>	logical, show progress bar, Default: <code>TRUE</code>

Details

Call still needs to be wrapped in [with_progress](#) or [with_progress_cnd\(\)](#)

Value

result of function passed to `.f`

Examples

```
# purrr::map  
progressr::with_progress(  
  purrr_bar(rep(0.25, 5), .purrr = purrr::map, .f = Sys.sleep, .steps = 5)  
)
```

```
# purrr::walk
progressr::with_progress(
  purrr_bar(rep(0.25, 5), .purrr = purrr::walk, .f = Sys.sleep, .steps = 5)
)

# progress bar off
progressr::with_progress(
  purrr_bar(
    rep(0.25, 5), .purrr = purrr::walk, .f = Sys.sleep, .steps = 5, .progress = FALSE
  )
)

# purrr::map2
progressr::with_progress(
  purrr_bar(
    rep(1, 5), rep(2, 5),
    .purrr = purrr::map2,
    .f = `+`,
    .steps = 5,
    .slow = TRUE
  )
)

# purrr::pmap
progressr::with_progress(
  purrr_bar(
    list(rep(1, 5), rep(2, 5)),
    .purrr = purrr::pmap,
    .f = `+`,
    .steps = 5,
    .slow = TRUE
  )
)

# define function within purrr_bar() call
progressr::with_progress(
  purrr_bar(
    list(rep(1, 5), rep(2, 5)),
    .purrr = purrr::pmap,
    .f = function(x, y) {
      paste0(x, y)
    },
    .steps = 5,
    .slow = TRUE
  )
)

# with mutate
progressr::with_progress(
  tibble::tibble(x = rep(0.25, 5)) %>%
  dplyr::mutate(x = purrr_bar(x, .purrr = purrr::map, .f = Sys.sleep, .steps = 5))
)
```

simaerep	<i>create simaerep object</i>
----------	-------------------------------

Description

simulate AE under-reporting probabilities

Usage

```
simaerep(
  df_visit,
  param_site_aggr = list(method = "med75_adj", min_pat_pool = 0.2),
  param_sim_sites = list(r = 1000, poisson_test = FALSE, prob_lower = TRUE),
  param_eval_sites = list(method = "BH"),
  progress = TRUE,
  check = TRUE,
  env = parent.frame(),
  under_only = TRUE
)
```

Arguments

df_visit	data frame with columns: study_id, site_number, patnum, visit, n_ae
param_site_aggr	list of parameters passed to site_aggr() , Default: list(method = "med75_adj", min_pat_pool = 0.2)
param_sim_sites	list of parameters passed to sim_sites() , Default: list(r = 1000, poisson_test = FALSE, prob_lower = TRUE)
param_eval_sites	list of parameters passed to eval_sites() , Default: list(method = "BH")
progress	logical, display progress bar, Default = TRUE
check	logical, perform data check and attempt repair with check_df_visit() , computationally expensive on large data sets. Default: TRUE
env	optional, provide environment of original visit data, Default: parent.frame()
under_only	logical compute under-reporting probabilities only, superseeds under_only parameter passed to eval_sites() and sim_sites() , Default: TRUE

Details

executes [site_aggr\(\)](#), [sim_sites\(\)](#) and [eval_sites\(\)](#) on original visit data and stores all intermediate results. Stores lazy reference to original visit data for facilitated plotting using generic plot(x).

Value

simaerep object

See Also

[site_aggr\(\)](#), [sim_sites\(\)](#), [eval_sites\(\)](#), [orivisit\(\)](#), [plot.simaerep\(\)](#)

Examples

```
df_visit <- sim_test_data_study(  
  n_pat = 100,  
  n_sites = 5,  
  frac_site_with_ur = 0.4,  
  ur_rate = 0.6  
)  
  
df_visit$study_id <- "A"  
  
aerep <- simaerep(df_visit)  
  
aerep  
  
str(aerep)
```

sim_after_prep	<i>Start simulation after preparation.</i>
----------------	--

Description

Internal function called by [sim_sites](#) after [prep_for_sim](#)

Usage

```
sim_after_prep(  
  df_sim_prep,  
  r = 1000,  
  poisson_test = FALSE,  
  prob_lower = TRUE,  
  progress = FALSE,  
  under_only = TRUE  
)
```

Arguments

df_sim_prep	dataframe as returned by prep_for_sim
r	integer, denotes number of simulations, default = 1000
poisson_test	logical, calculates poisson.test pvalue

prob_lower	logical, calculates probability for getting a lower value
progress	logical, display progress bar, Default = TRUE
under_only	compute under-reporting probabilities only, default = TRUE check_df_visit() , computationally expensive on large data sets. Default: TRUE

Value

dataframe

See Also[sim_sites](#), [prep_for_sim](#)**Examples**

```
df_visit <- sim_test_data_study(
  n_pat = 100,
  n_sites = 5,
  frac_site_with_ur = 0.4,
  ur_rate = 0.2
)

df_visit$study_id <- "A"

df_site <- site_aggr(df_visit)

df_prep <- prep_for_sim(df_site, df_visit)

df_sim <- sim_after_prep(df_prep)

df_sim
```

sim_scenario	<i>simulate single scenario</i>
--------------	---------------------------------

Descriptioninternal function called by `simulate_scenarios()`**Usage**

```
sim_scenario(n_ae_site, n_ae_study, frac_pat_with_ur, ur_rate)
```

Arguments

n_ae_site	integer vector
n_ae_study	integer vector
frac_pat_with_ur	double
ur_rate	double

Value

list

Examples

```

sim_scenario(c(5,5,5,5), c(8,8,8,8), 0.2, 0.5)
sim_scenario(c(5,5,5,5), c(8,8,8,8), 0.75, 0.5)
sim_scenario(c(5,5,5,5), c(8,8,8,8), 1, 0.5)
sim_scenario(c(5,5,5,5), c(8,8,8,8), 1, 1)
sim_scenario(c(5,5,5,5), c(8,8,8,8), 0, 0.5)
sim_scenario(c(5,5,5,5), c(8,8,8,8), 2, 0.5)

```

sim_sites

Calculate prob_lower and poisson.test pvalue for study sites.

Description

Collects the number of AEs of all eligible patients that meet visit_med75 criteria of site. Then calculates poisson.test pvalue and bootstrapped probability of having a lower mean value.

Usage

```

sim_sites(
  df_site,
  df_visit,
  r = 1000,
  poisson_test = TRUE,
  prob_lower = TRUE,
  progress = TRUE,
  check = TRUE,
  under_only = TRUE
)

```

Arguments

df_site	dataframe created by site_aggr
df_visit	dataframe, created by sim_sites
r	integer, denotes number of simulations, default = 1000
poisson_test	logical, calculates poisson.test pvalue
prob_lower	logical, calculates probability for getting a lower value
progress	logical, display progress bar, Default = TRUE
check	logical, perform data check and attempt repair with
under_only	compute under-reporting probabilities only, default = TRUE check_df_visit() , computationally expensive on large data sets. Default: TRUE

Value

dataframe with the following columns:

study_id study identification

site_number site identification

n_pat number of patients at site

visit_med75 median(max(visit)) * 0.75

n_pat_with_med75 number of patients at site with med75

mean_ae_site_med75 mean AE at visit_med75 site level

mean_ae_study_med75 mean AE at visit_med75 study level

n_pat_with_med75_study number of patients at study with med75 excl. site

pval p-value as returned by [poisson.test](#)

prob_low bootstrapped probability for having mean_ae_site_med75 or lower

See Also

[sim_sites](#), [site_aggr](#), [pat_pool](#), [prob_lower_site_ae_vs_study_ae](#), [poiss_test_site_ae_vs_study_ae](#), [sim_sites](#), [prep_for_sim](#)

Examples

```
df_visit <- sim_test_data_study(
  n_pat = 100,
  n_sites = 5,
  frac_site_with_ur = 0.4,
  ur_rate = 0.2
)

df_visit$study_id <- "A"

df_site <- site_aggr(df_visit)

df_sim_sites <- sim_sites(df_site, df_visit, r = 100)

df_sim_sites %>%
  knitr::kable(digits = 2)
```

Description

Test function, test applicability of poisson test, by calculating a the bootstrapped probability of obtaining a specific p-value or lower, use in combination with [get_ecd_values\(\)](#).

Usage

```

sim_studies(
  df_visit,
  df_site,
  r = 100,
  poisson_test = TRUE,
  prob_lower = TRUE,
  r_prob_lower = 1000,
  under_only = TRUE,
  parallel = FALSE,
  keep_ae = FALSE,
  min_n_pat_with_med75 = 1,
  studies = NULL,
  .progress = TRUE
)

```

Arguments

df_visit	dataframe
df_site	dataframe
r	integer, denotes number of simulations, Default: 1000
poisson_test	logical, calculates poisson.test pvalue, Default: TRUE
prob_lower	logical, calculates probability for getting a lower value, Default: FALSE
r_prob_lower	integer, denotes number of simulations for prob_lower value calculation,, Default: 1000
under_only	compute under-reporting probabilities only, default = TRUE
parallel	logical, see examples for registering parallel processing framework , Default: FALSE
keep_ae	logical, keep ae numbers in output dataframe memory increase roughly 30 percent, Default: F
min_n_pat_with_med75	integer, min number of patients with med75 at site to simulate, Default: 1
studies	vector with study names, Default: NULL
.progress	logical, show progress bar

Details

Here we simulate study replicates maintaining the same number of sites, patients and visit_med75 by bootstrap resampling, then probabilities for obtaining lower or same mean_ae count and p-values using poisson.test are calculated.

adds column with simulated probabilities for equal or lower mean_ae at visit_med75

Value

dataframe

Examples

```

df_visit1 <- sim_test_data_study(n_pat = 100, n_sites = 5,
                                frac_site_with_ur = 0.4, ur_rate = 0.6)

df_visit1$study_id <- "A"

df_visit2 <- sim_test_data_study(n_pat = 1000, n_sites = 3,
                                frac_site_with_ur = 0.2, ur_rate = 0.1)

df_visit2$study_id <- "B"

df_visit <- dplyr::bind_rows(df_visit1, df_visit2)

df_site <- site_aggr(df_visit)

sim_studies(df_visit, df_site, r = 3, keep_ae = TRUE)

## Not run:
# parallel processing -----
library(future)
future::plan(multiprocess)
sim_studies(df_visit, df_site, r = 3, keep_ae = TRUE, parallel = TRUE)
future::plan(sequential)

## End(Not run)

```

sim_test_data_patient *simulate patient ae reporting test data*

Description

helper function for [sim_test_data_study\(\)](#)

Usage

```

sim_test_data_patient(
  .f_sample_max_visit = function() rnorm(1, mean = 20, sd = 4),
  .f_sample_ae_per_visit = function(max_visit) rpois(max_visit, 0.5)
)

```

Arguments

```

.f_sample_max_visit
    function used to sample the maximum number of aes, Default: function() rnorm(1,
    mean = 20, sd = 4)
.f_sample_ae_per_visit
    function used to sample the aes for each visit, Default: function(x) rpois(x, 0.5)

```

Details

```
"""
```

Value

vector containing cumulative aes

Examples

```
replicate(5, sim_test_data_patient())
replicate(5, sim_test_data_patient(
  .f_sample_ae_per_visit = function(x) rpois(x, 1.2))
)
replicate(5, sim_test_data_patient(
  .f_sample_max_visit = function() rnorm(1, mean = 5, sd = 5))
)
```

```
sim_test_data_portfolio
```

Simulate Portfolio Test Data

Description

Simulate visit level data from a portfolio configuration.

Usage

```
sim_test_data_portfolio(
  df_config,
  df_ae_rates = NULL,
  parallel = FALSE,
  progress = TRUE
)
```

Arguments

df_config	dataframe as returned by get_config
df_ae_rates	dataframe with ae rates. Default: NULL
parallel	logical activate parallel processing, see details, Default: FALSE
progress	logical, Default: TRUE

Details

uses [sim_test_data_study](#). We use the `furrr` package to implement parallel processing as these simulations can take a long time to run. For this to work we need to specify the plan for how the code should run, e.g. `'plan(multisession, workers = 3)`

Value

dataframe with the following columns:

study_id study identification

ae_per_visit_mean mean AE per visit per study

site_number site

max_visit_sd standard deviation of maximum patient visits per site

max_visit_mean mean of maximum patient visits per site

patnum number of patients

visit visit number

n_ae cumulative sum of AEs

See Also

[sim_test_data_study_get_config](#) [sim_test_data_portfolio](#) [sim_ur_scenarios](#) [get_portf_perf](#)

Examples

```
df_visit1 <- sim_test_data_study(n_pat = 100, n_sites = 10,
                                frac_site_with_ur = 0.4, ur_rate = 0.6)

df_visit1$study_id <- "A"

df_visit2 <- sim_test_data_study(n_pat = 100, n_sites = 10,
                                frac_site_with_ur = 0.2, ur_rate = 0.1)

df_visit2$study_id <- "B"

df_visit <- dplyr::bind_rows(df_visit1, df_visit2)

df_site_max <- df_visit %>%
  dplyr::group_by(study_id, site_number, patnum) %>%
  dplyr::summarise(max_visit = max(visit),
                  max_ae = max(n_ae),
                  .groups = "drop")

df_config <- get_config(df_site_max)

df_config

df_portf <- sim_test_data_portfolio(df_config)

df_portf

df_scen <- sim_ur_scenarios(df_portf,
                            extra_ur_sites = 2,
                            ur_rate = c(0.5, 1))
```

```
df_scen
df_perf <- get_portf_perf(df_scen)
df_perf
```

sim_test_data_study *simulate study test data*

Description

evenly distributes a number of given patients across a number of given sites. Then simulates ae development of each patient reducing the number of reported AEs for patients distributed to AE-under-reporting sites.

Usage

```
sim_test_data_study(
  n_pat = 1000,
  n_sites = 20,
  frac_site_with_ur = 0,
  ur_rate = 0,
  max_visit_mean = 20,
  max_visit_sd = 4,
  ae_per_visit_mean = 0.5,
  ae_rates = NULL
)
```

Arguments

n_pat	integer, number of patients, Default: 1000
n_sites	integer, number of sites, Default: 20
frac_site_with_ur	fraction of AE under-reporting sites, Default: 0
ur_rate	AE under-reporting rate, will lower mean ae per visit used to simulate patients at sites flagged as AE-under-reporting. Negative Values will simulate over-reporting., Default: 0
max_visit_mean	mean of the maximum number of visits of each patient, Default: 20
max_visit_sd	standard deviation of maximum number of visits of each patient, Default: 4
ae_per_visit_mean	mean ae per visit per patient, Default: 0.5
ae_rates	vector with visit-specific ae rates, Default: Null

Details

maximum visit number will be sampled from normal distribution with characteristics derived from `max_visit_mean` and `max_visit_sd`, while the ae per visit will be sampled from a poisson distribution described by `ae_per_visit_mean`.

Value

tibble with columns `site_number`, `patnum`, `is_ur`, `max_visit_mean`, `max_visit_sd`, `ae_per_visit_mean`, `visit`, `n_ae`

Examples

```
set.seed(1)
df_visit <- sim_test_data_study(n_pat = 100, n_sites = 5)
df_visit[which(df_visit$patnum == "P000001"),]
df_visit <- sim_test_data_study(n_pat = 100, n_sites = 5,
  frac_site_with_ur = 0.2, ur_rate = 0.5)
df_visit[which(df_visit$patnum == "P000001"),]
ae_rates <- c(0.7, rep(0.5, 8), rep(0.3, 5))
sim_test_data_study(n_pat = 100, n_sites = 5, ae_rates = ae_rates)
```

 sim_ur_scenarios

Simulate Under-Reporting Scenarios

Description

Use with simulated portfolio data to generate under-reporting stats for specified scenarios.

Usage

```
sim_ur_scenarios(
  df_portf,
  extra_ur_sites = 3,
  ur_rate = c(0.25, 0.5),
  r = 1000,
  poisson_test = FALSE,
  prob_lower = TRUE,
  parallel = FALSE,
  progress = TRUE,
  site_aggr_args = list(),
  eval_sites_args = list()
)
```

Arguments

df_portf	dataframe as returned by sim_test_data_portfolio
extra_ur_sites	numeric, set maximum number of additional under-reporting sites, see details Default: 3
ur_rate	numeric vector, set under-reporting rates for scenarios Default: c(0.25, 0.5)
r	integer, denotes number of simulations, default = 1000
poisson_test	logical, calculates poisson.test pvalue
prob_lower	logical, calculates probability for getting a lower value
parallel	logical, use parallel processing see details, Default: FALSE
progress	logical, show progress bar, Default: TRUE
site_aggr_args	named list of parameters passed to site_aggr , Default: list()
eval_sites_args	named list of parameters passed to eval_sites , Default: list()

Details

The function will apply under-reporting scenarios to each site. Reducing the number of AEs by a given under-reporting (ur_rate) for all patients at the site and add the corresponding under-reporting statistics. Since the under-reporting probability is also affected by the number of other sites that are under-reporting we additionally calculate under-reporting statistics in a scenario where additional under reporting sites are present. For this we use the median number of patients per site at the study to calculate the final number of patients for which we lower the AEs in a given under-reporting scenario. We use the furrr package to implement parallel processing as these simulations can take a long time to run. For this to work we need to specify the plan for how the code should run, e.g. plan(multisession, workers = 18)

Value

dataframe with the following columns:

study_id	study identification
site_number	site identification
n_pat	number of patients at site
n_pat_with_med75	number of patients at site with visit_med75
visit_med75	median(max(visit)) * 0.75
mean_ae_site_med75	mean AE at visit_med75 site level
mean_ae_study_med75	mean AE at visit_med75 study level
n_pat_with_med75_study	number of patients at site with visit_med75 at study excl site
extra_ur_sites	additional sites with under-reporting patients
frac_pat_with_ur	ratio of patients in study that are under-reporting
ur_rate	under-reporting rate
pval	p-value as returned by poisson.test

prob_low bootstrapped probability for having mean_ae_site_med75 or lower
pval_adj adjusted p-values
prob_low_adj adjusted bootstrapped probability for having mean_ae_site_med75 or lower
pval_prob_ur probability under-reporting as 1 - pval_adj, poisson.test (use as benchmark)
prob_low_prob_ur probability under-reporting as 1 - prob_low_adj, bootstrapped (use)

See Also

[sim_test_data_study](#) [get_config](#) [sim_test_data_portfolio](#) [sim_ur_scenarios](#) [get_portf_perf](#)

Examples

```
df_visit1 <- sim_test_data_study(n_pat = 100, n_sites = 10,
                                frac_site_with_ur = 0.4, ur_rate = 0.6)

df_visit1$study_id <- "A"

df_visit2 <- sim_test_data_study(n_pat = 100, n_sites = 10,
                                frac_site_with_ur = 0.2, ur_rate = 0.1)

df_visit2$study_id <- "B"

df_visit <- dplyr::bind_rows(df_visit1, df_visit2)

df_site_max <- df_visit %>%
  dplyr::group_by(study_id, site_number, patnum) %>%
  dplyr::summarise(max_visit = max(visit),
                  max_ae = max(n_ae),
                  .groups = "drop")

df_config <- get_config(df_site_max)

df_config

df_portf <- sim_test_data_portfolio(df_config)

df_portf

df_scen <- sim_ur_scenarios(df_portf,
                           extra_ur_sites = 2,
                           ur_rate = c(0.5, 1))

df_scen

df_perf <- get_portf_perf(df_scen)

df_perf
```

site_aggr *Aggregate from visit to site level.*

Description

Calculates visit_med75, n_pat_with_med75 and mean_ae_site_med75

Usage

```
site_aggr(df_visit, method = "med75_adj", min_pat_pool = 0.2, check = TRUE)
```

Arguments

df_visit	dataframe with columns: study_id, site_number, patnum, visit, n_ae
method	character, one of c("med75", "med75_adj") defining method for defining evaluation point visit_med75 (see details), Default: "med75_adj"
min_pat_pool	double, minimum ratio of available patients available for sampling. Determines maximum visit_med75 value see Details. Default: 0.2
check	logical, perform data check and attempt repair with check_df_visit() , computationally expensive on large data sets. Default: TRUE

Details

For determining the visit number at which we are going to evaluate AE reporting we take the maximum visit of each patient at the site and take the median. Then we multiply with 0.75 which will give us a cut-off point determining which patient will be evaluated. Of those patients we will evaluate we take the minimum of all maximum visits hence ensuring that we take the highest visit number possible without excluding more patients from the analysis. In order to ensure that the sampling pool for that visit is large enough we limit the visit number by the 80% quantile of maximum visits of all patients in the study.

Value

dataframe with the following columns:

study_id study identification

site_number site identification

n_pat number of patients, site level

visit_med75 adjusted median(max(visit)) * 0.75 see Details

n_pat_with_med75 number of patients that meet visit_med75 criterion, site level

mean_ae_site_med75 mean AE at visit_med75, site level

Examples

```
df_visit <- sim_test_data_study(
  n_pat = 100,
  n_sites = 5,
  frac_site_with_ur = 0.4,
  ur_rate = 0.6
)

df_visit$study_id <- "A"

df_site <- site_aggr(df_visit)

df_site %>%
  knitr::kable(digits = 2)
```

with_progress_cnd	<i>Conditional</i> with_progress .
-------------------	--

Description

Internal function. Use instead of [with_progress](#) within custom functions with progress bars.

Usage

```
with_progress_cnd(ex, progress = TRUE)
```

Arguments

ex	expression
progress	logical, Default: TRUE

Details

This wrapper adds a progress parameter to [with_progress](#) so that we can control the progress bar in the user facing functions. The progressbar only shows in interactive mode.

Value

No return value, called for side effects

See Also

[with_progress](#)

Examples

```

if (interactive()) {

  with_progress_cnd(
    purrr_bar(rep(0.25, 5), .purrr = purrr::map, .f = Sys.sleep, .steps = 5),
    progress = TRUE
  )

  with_progress_cnd(
    purrr_bar(rep(0.25, 5), .purrr = purrr::map, .f = Sys.sleep, .steps = 5),
    progress = FALSE
  )

  # wrap a function with progress bar with another call with progress bar

  f1 <- function(x, progress = TRUE) {
    with_progress_cnd(
      purrr_bar(x, .purrr = purrr::walk, .f = Sys.sleep, .steps = length(x), .progress = progress),
      progress = progress
    )
  }

  # inner progress bar blocks outer progress bar
  progressr::with_progress(
    purrr_bar(
      rep(rep(1, 3),3), .purrr = purrr::walk, .f = f1, .steps = 3,
      .f_args = list(progress = TRUE)
    )
  )

  # inner progress bar turned off
  progressr::with_progress(
    purrr_bar(
      rep(list(rep(0.25, 3)), 5), .purrr = purrr::walk, .f = f1, .steps = 5,
      .f_args = list(progress = FALSE)
    )
  )
}

```

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