

Package ‘msprog’

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Type Package

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compute_delta	<i>Definition of minimum clinically meaningful shift for different scales.</i>
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Description

compute_delta() computes the default minimum clinically meaningful change from baseline in the outcome measure (EDSS, NHPT, T25FW, or SDMT). Note: default thresholds are meant to apply to all versions of each test (e.g., dominant or non-dominant hand for NHPT, best time or mean of two trials, etc.).

Usage

```
compute_delta(baseline, outcome = "edss")
```

Arguments

baseline	Outcome value at baseline.
outcome	One of: <ul style="list-style-type: none"> 'edss' (Extended Disability Status Scale, default); 'nhpt' (Nine-Hole Peg Test); 't25fw' (Timed 25-Foot Walk); 'sdmt' (Symbol Digit Modalities Test).

Value

Minimum clinically meaningful change from the provided baseline value. Specifically:

- EDSS: 1.5 if baseline=0, 1 if 0<baseline<=5.0, 0.5 if baseline>5.0
- NHPT and T25FW: 20% of baseline
- SDMT: either 4 points or 20% of baseline.

Examples

```
compute_delta(4.5) # default outcome is 'edss'
compute_delta(55, outcome='sdmt')
```

is_event	<i>Compare value to reference.</i>
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Description

is_event() checks if an outcome value determines a valid worsening, or improvement, or change, from a given reference value.

Usage

```
is_event(
  x,
  baseline,
  type,
  outcome = "edss",
  worsening = NULL,
  delta_fun = NULL,
  sub_threshold = FALSE
)
```

Arguments

x	Outcome value to test.
baseline	Outcome value at baseline.
type	One of: <ul style="list-style-type: none"> • 'wors' (worsening); • 'impr' (improvement); • 'change' (any valid change).
outcome	One of: <ul style="list-style-type: none"> • 'edss' (Extended Disability Status Scale, default); • 'nhpt' (Nine-Hole Peg Test); • 't25fw' (Timed 25-Foot Walk); • 'sdmt' (Symbol Digit Modalities Test); • NULL (only accepted when specifying custom worsening – and delta_fun as well, if sub_threshold=F). Outcome type determines a default direction of worsening (see worseningargument) and default definition of clinically meaningful change given the reference value (using the built-in function compute_delta()). This can be replaced by a custom function using the delta_fun argument.
worsening	The direction of worsening ('increase' if higher values correspond to worse disease course, 'decrease' otherwise). This argument is only used when outcome is set to NULL. If outcome is specified, worsening is automatically set to 'increase' for EDSS, NHPT, T25FW, and to 'decrease' for SDMT.
delta_fun	Custom function specifying the minimum clinically meaningful change in the outcome measure from the provided reference value. The function provided must take a numeric value (reference score) as input, and return a numeric value corresponding to the minimum shift from baseline, see example below. If none is specified (default), the user must provide a non-NULL value for the outcome argument (see above) in order to use the built-in function compute_delta() . The argument is ignored if 'sub_threshold=T'.
sub_threshold	If TRUE, any confirmed worsening, or improvement, or change in the outcome measure is valid, regardless of delta_fun.

Value

A boolean value specifying if a valid event was found.

Examples

```
is_event(x=4.5, baseline=4, type='wors', outcome='edss')
is_event(x=50, baseline=57, type='wors', outcome='sdtmt')
```

MSprog

Assess multiple sclerosis disability course from longitudinal data.

Description

MSprog() detects and characterises the confirmed disability worsening (CDW) or improvement (CDI) events of an outcome measure (EDSS, NHPT, T25FW, or SDMT; or any custom outcome) for one or more subjects, based on repeated assessments through time (and on the dates of acute episodes, if any). Several qualitative and quantitative options are given as arguments that can be set by the user and reported as a complement to the results to ensure reproducibility.

Usage

```
MSprog(
  data,
  subj_col,
  value_col,
  date_col,
  outcome,
  relapse = NULL,
  rsubj_col = NULL,
  rdate_col = NULL,
  renddate_col = NULL,
  subjects = NULL,
  delta_fun = NULL,
  worsening = NULL,
  event = "firstCDW",
  baseline = "fixed",
  proceed_from = "firstconf",
  sub_threshold_rebl = "none",
  bl_geq = F,
  relapse_rebl = F,
  skip_local_extrema = "none",
  validconf_col = NULL,
  conf_days = 12 * 7,
  conf_tol_days = c(7, 2 * 365.25),
  require_sust_days = 0,
  check_intermediate = T,
  relapse_to_bl = 30,
  relapse_to_event = 0,
  relapse_to_conf = 30,
  relapse_assoc = 90,
  relapse_indep = NULL,
  impute_last_visit = 0,
  date_format = NULL,
  include_dates = F,
  include_value = F,
```

```

    include_stable = T,
    verbose = 1
)

```

Arguments

<code>data</code>	<code>data.frame</code> containing longitudinal data, including: subject ID, outcome value, date of visit.
<code>subj_col</code>	Name of data column with subject ID.
<code>value_col</code>	Name of data column with outcome value.
<code>date_col</code>	Name of data column with date of visit.
<code>outcome</code>	Specifies the outcome type. Must be one of the following: <ul style="list-style-type: none"> 'edss' (Expanded Disability Status Scale) 'nhpt' (Nine-Hole Peg Test) 't25fw' (Timed 25-Foot Walk) 'sdmt' (Symbol Digit Modalities Test) NULL (only accepted when specifying a custom <code>delta_fun</code>) Outcome type determines a default direction of worsening (see <code>worsening</code> argument) and default definition of clinically meaningful change given the reference value (using the built-in function <code>compute_delta()</code>). This can be replaced by a custom function using the <code>delta_fun</code> argument.
<code>relapse</code>	Optional <code>data.frame</code> containing longitudinal data, including: subject ID and relapse date.
<code>rsubj_col</code>	Name of subject ID column for relapse data, if different from outcome data.
<code>rdate_col</code>	Name of onset date column for relapse data, if different from outcome data.
<code>renddate_col</code>	Name of end date column for relapse data (if present).
<code>subjects</code>	Subset of subjects (list of IDs). If none is specified, all subjects listed in <code>data</code> are included.
<code>delta_fun</code>	Custom function specifying the minimum clinically meaningful change in the outcome measure from the provided reference value. The function provided must take a numeric value (reference score) as input, and return a numeric value corresponding to the minimum shift from baseline, see example below. If none is specified (default), the user must provide a non-NULL value for the outcome argument (see above) in order to use the built-in function <code>compute_delta()</code> .
<code>worsening</code>	The direction of worsening ('increase' if higher values correspond to worse disease course, 'decrease' otherwise). The given value is only used when outcome is set to NULL. Otherwise, worsening is automatically set to 'increase' if outcome is set to 'edss', 'nhpt', 't25fw', and to 'decrease' if outcome is set to 'sdmt'.
<code>event</code>	Specifies which events to detect. Must be one of the following: <ul style="list-style-type: none"> 'firstCDW' (first CDW, default) 'firstCDI' (first CDI) 'multiple' (all confirmed events in chronological order) 'firstPIRA' (first PIRA) 'firstRAW' (first RAW) 'first' (only the very first confirmed event – CDI or CDW).

baseline	<p>Specifies the baseline scheme. Must be one of the following.</p> <ul style="list-style-type: none"> 'fixed': first valid outcome value, default. 'roving': updated after each CDI or CDW event to the visit determined by <code>proceed_from</code>; suitable for a multiple-event setting (i.e., when event is set to 'multiple') or when searching for a specific type of CDW (i.e., when event is set to 'firstPIRA' or 'firstRAW') – not recommended for randomised data. 'roving_impr': updated after every CDI (to the visit determined by <code>proceed_from</code>); suitable for a first-CDW setting to discard fluctuations around baseline – not recommended for multiple events, or for randomised data. 'roving_wors': updated after every CDW (to the visit determined by <code>proceed_from</code>); suitable when searching for a specific type of CDW (i.e., when event is set to 'firstPIRA' or 'firstRAW').
proceed_from	<p>After detecting a confirmed disability event, continue searching:</p> <ul style="list-style-type: none"> from the next visit after the first qualifying confirmation visit if <code>proceed_from</code>='firstconf' from the next visit after the event onset if <code>proceed_from</code>='event'. <p>If baseline is set to 'roving', 'roving_impr', or 'roving_wors', when re-baselining after a confirmed disability event, the baseline is moved to:</p> <ul style="list-style-type: none"> the first qualifying confirmation visit if <code>proceed_from</code>='firstconf' the event visit if <code>proceed_from</code>='event'.
sub_threshold_rebl	<p>This argument is only used if baseline is not set to 'fixed'. Must be one of the following.</p> <ul style="list-style-type: none"> 'event': any confirmed sub-threshold event (i.e. any <i>confirmed</i> change in the outcome measure, possibly below clinically meaningful threshold) can potentially trigger a re-baseline. 'improvement': any confirmed sub-threshold improvement (i.e. any <i>confirmed</i> improvement in the outcome measure, possibly below clinically meaningful threshold) can potentially trigger a re-baseline. 'worsening': any confirmed sub-threshold worsening (i.e. any <i>confirmed</i> worsening in the outcome measure, possibly below clinically meaningful threshold) can potentially trigger a re-baseline. 'none': only use clinically meaningful confirmed changes for re-baseline. <p>See <code>delta_fun</code> argument and <code>compute_delta()</code> function for more details.</p>
bl_geq	<p>This argument is only used if the baseline is moved. If TRUE, the new reference value must always be greater or equal than the previous one; when it is not, the old reference value is assigned to it [2].</p>
relapse_rebl	<p>If TRUE, re-baseline after every relapse.</p>
skip_local_extrema	<p>This argument is only used if the baseline is moved. It controls function behaviour in the presence of local minima or maxima. A visit <i>i</i> is a local minimum point for outcome if <code>outcome[i+1]>outcome[i]</code> and <code>outcome[i-1]>outcome[i]</code>; local maxima are defined similarly. A visit <i>i</i> is a <i>strict</i> local minimum point for outcome if <code>outcome[i+1]-outcome[i]>=delta_fun(outcome[i]); outcome[i-1]-outcome[i]></code>; Strict local maxima are defined similarly. When <code>outcome[i]=outcome[i-2]</code>, visit <i>i</i> is <i>not</i> considered a local extremum point even if the above conditions hold. This controls for cases where the outcome has an undulating course. The following argument values are accepted.</p>

	<ul style="list-style-type: none"> • 'none': local extrema are always accepted as valid baseline values. • 'strict': the baseline cannot be placed at a <i>strict</i> local minimum or maximum. • 'all': the baseline cannot be placed at a local minimum or maximum.
validconf_col	Name of data column specifying which visits can (T) or cannot (F) be used as confirmation visits. The input data does not necessarily have to include such a column. If validconf_col=NULL, all visits are potentially used as confirmation visits.
conf_days	Period before confirmation (days). Can be a single value or list-like of any length if multiple windows are to be considered.
conf_tol_days	Tolerance window for confirmation visit (days); can be an integer (same tolerance on left and right) or list-like of length 2 (different tolerance on left and right). The right end of the interval can be set to Inf (confirmation window unbounded on the right – e.g., "confirmed over 12 <i>or more</i> weeks").
require_sust_days	Minimum number of days over which a confirmed change must be sustained (i.e., confirmed at <i>all</i> visits occurring in the specified period) to be retained as an event. Events sustained for the remainder of the follow-up period are always retained regardless of follow-up duration. If require_sust_days=Inf, events are retained only when sustained for the remainder of the follow-up period. (Warning: if check_intermediate is set to FALSE, sustained change will be established based <i>only on the end</i> of the specified period.)
check_intermediate	If TRUE (default), events are confirmed <i>over all intermediate visits</i> up to the confirmation visit. If set to FALSE (not recommended in most cases, as it may discard meaningful fluctuations), events will be confirmed <i>only at</i> the specified confirmation visit (and <i>only at the end</i> of the period defined by require_sust_days, if any).
relapse_to_bl	Minimum distance from a relapse (days) for a visit to be used as baseline. Can be an integer (minimum distance from <i>last</i> relapse) or list-like of length 2 (minimum distance from <i>last</i> relapse, minimum distance from <i>next</i> relapse). Note that setting the distance to zero means keeping the baseline where it is regardless of surrounding relapses. If relapse end dates are available (renddate_col), the minimum distance from last relapse is overwritten by the relapse duration, unless it was set to zero (in which case it stays 0). If the designated baseline does not respect this constraint, the baseline is moved to the next available visit.
relapse_to_event	Minimum distance from a relapse (days) for an event to be considered as such. Can be an integer (minimum distance from <i>last</i> relapse) or list-like of length 2 (minimum distance from <i>last</i> relapse, minimum distance from <i>next</i> relapse). Note that setting the distance to zero means retaining the event regardless of surrounding relapses. If relapse end dates are available (renddate_col), the minimum distance from last relapse is overwritten by the relapse duration, unless it was set to zero (in which case it stays 0).
relapse_to_conf	Minimum distance from a relapse (days) for a visit to be a valid confirmation visit. Can be an integer (minimum distance from <i>last</i> relapse) or list-like of length 2 (minimum distance from <i>last</i> relapse, minimum distance from <i>next</i> relapse). Note that setting the distance to zero means using any visit for confirmation regardless of surrounding relapses. If relapse end dates are available

	(renddate_col), the minimum distance from last relapse is overwritten by the relapse duration, unless it was set to zero (in which case it stays 0).
relapse_assoc	Maximum distance from a relapse (days) for a CDW event to be classified as RAW. Can be an integer (maximum distance from <i>last</i> relapse) or list-like of length 2 (maximum distance from <i>last</i> relapse, maximum distance from <i>next</i> relapse). If relapse end dates are available (renddate_col), the maximum distance from last relapse is overwritten by the relapse duration.
relapse_indep	Specifies relapse-free intervals for PIRA definition. Must be given in the form produced by function relapse_indep_from_bounds() by calling <code>relapse_indep_from_bounds(p0, p1, e0, e1, c0, c1)</code> to specify the intervals around (any subset of) three checkpoints: (i) a preceding visit, e.g., baseline or last visit before the worsening (p0 and p1), (ii) the event onset (e0 and e1), and (iii) the first available confirmation visit (c0 and c1). See relapse_indep_from_bounds() function docs for more details on how to define the intervals. If relapse end dates are available (renddate_col), it is possible to also define PIRA based on those by setting <code>use_end_dates=T</code> in relapse_indep_from_bounds() .
impute_last_visit	Imputation probability for worsening events occurring at last visit (i.e. with no confirmation). Unconfirmed worsening events occurring at the last visit are never imputed if <code>impute_last_visit=0</code> ; they are always imputed if <code>impute_last_visit=1</code> ; they are imputed with probability p , $0 < p < 1$, if <code>impute_last_visit=p</code> . If a value $N > 1$ is passed, unconfirmed worsening events are imputed only if occurring within N days of follow-up (e.g., in case of early discontinuation).
date_format	<p>Format of dates in the date_col and rdate_col columns of the input data. Can be specified as:</p> <ul style="list-style-type: none"> • Standard format for dates (e.g., "%d-%m-%Y"; see strptime() docs for correct syntax). • 'day' if dates in are given as "days from start" (the starting point can be different for each subject – e.g., days from randomisation in a clinical trial); negative values are accepted. <p>If not specified, function as.Date() will try to infer it automatically.</p>
include_dates	If TRUE, output\$results will include the date of each event ('date' column) and the date of the corresponding baseline ('bldate' column).
include_value	If TRUE, output\$results will include the outcome value at each event ('value' column) and at the corresponding baseline ('blvalue' column).
include_stable	If TRUE, subjects with no confirmed events are included in output\$results, with <code>time2event</code> = total follow up.
verbose	<p>One of:</p> <ul style="list-style-type: none"> • 0 (print no info); • 1 (print concise info, default); • 2 (print extended info).

Details

The events are detected sequentially by scanning the outcome values in chronological order. Time windows for confirmation visits are determined by arguments `conf_days`, `conf_tol_days`, `relapse_to_conf`.

CDW events are classified as relapse-associated or relapse-independent based on their relative timing with respect to the relapses. Specifically, relapse-associated worsening (RAW) events are defined as CDW events occurring within a specified interval (`relapse_assoc` argument) from a relapse; the definition of progression independent of relapse activity (PIRA) is established by specifying relapse-free intervals (`relapse_indep` argument).

Value

An object of class 'MSprogOutput' with the following attributes:

- `event_count`: a `data.frame` containing the event sequence detected for each subject, and the counts for each event type
- `results`: a `data.frame` with extended info on each event for all subjects
- `settings`: a list containing all the arguments used to compute the output
- `unconfirmed`: a `data.frame` with info on unconfirmed events (initial change from baseline, but no confirmation) for all subjects.

References

[1] Müller J, Cagol A, Lorscheider J, Tsagkas C, Benkert P, Yaldizli Ö, et al. Harmonizing definitions for progression independent of relapse activity in multiple sclerosis: A systematic review. *JAMA Neurol.* 2023;80:1232–45.

[2] Kappos L, Wolinsky JS, Giovannoni G, Arnold DL, Wang Q, Bernasconi C, et al. Contribution of relapse-independent progression vs relapse-associated worsening to overall confirmed disability accumulation in typical relapsing multiple sclerosis in a pooled analysis of 2 randomized clinical trials. *JAMA Neurol.* 2020;77:1132–40.

Examples

```
# 1. EDSS course
output <- MSprog(toydata_visits, subj_col='id', value_col='EDSS', date_col='date', outcome='edss',
  relapse=toydata_relapses, conf_days=12*7, conf_tol_days=30,
  event='multiple', baseline='roving', verbose=1)
print(output$results) # extended info on each event for all subjects
print(output$event_count) # summary of event sequence for each subject

# 2. SDMT course
output <- MSprog(toydata_visits, subj_col='id', value_col='SDMT', date_col='date', outcome='sdmt',
  relapse=toydata_relapses, conf_days=12*7, conf_tol_days=30,
  event='multiple', baseline='roving', verbose=1)
print(output$results) # extended info on each event for all subjects
print(output$event_count) # summary of event sequence for each subject

# 3. SDMT course, with a custom delta function
my_sdmtdelta <- function(reference_value) {min(c(reference_value/5, 4))}
output <- MSprog(toydata_visits, subj_col='id', value_col='SDMT', date_col='date', outcome='sdmt',
  delta_fun=my_sdmtdelta,
  relapse=toydata_relapses, conf_days=12*7, conf_tol_days=30,
  event='multiple', baseline='roving', verbose=1)
print(output$results) # extended info on each event for all subjects
print(output$event_count) # summary of event sequence for each subject
```

print.MSprogOutput	<i>Textual description of criteria used to assess disability course.</i>
--------------------	--

Description

print method for class 'MSprogOutput'.

Usage

```
## S3 method for class 'MSprogOutput'
print(x, web = F, ...)
```

Arguments

x	An object of class 'MSprogOutput' (result of a call to MSprog()).
web	Adapt for printing in web app.
...	Optional arguments for print methods. They are ignored in this function.

Details

The method prints out (1) the package version, (2) a full list of function arguments, and (3) a short paragraph describing the full set of criteria used to obtain the output.

Examples

```
output <- MSprog(toydata_visits, 'id', 'EDSS', 'date', 'edss',
  relapse=toydata_relapses, conf_days=7*12, conf_tol_days=30,
  event='multiple', baseline='roving', verbose=2)
print(output) # textual description of parameters used to obtain output
```

relapse_indep_from_bounds	<i>Define relapse-free intervals for PIRA definition.</i>
---------------------------	---

Description

relapse_indep_from_bounds() organises the given interval bounds into a named list to be given as argument relapse_indep to function [MSprog\(\)](#). The relapse-free intervals may be anchored to (any subset of) the following three data-driven checkpoints.

- 'prec': a visit preceding the event: can be (i) the current baseline, (ii) the last visit before event onset, or (iii) the last visit before event onset with a clinically meaningful score distance from the event score (i.e., i such that $\text{outcome}[\text{event}] - \text{outcome}[i] \geq \text{delta_fun}(\text{outcome}[i])$, and same for the confirmation visit);
- 'event': the disability worsening event onset;
- 'conf': the (first) confirmation visit.

Usage

```
relapse_indep_from_bounds(
  p0 = 0,
  p1 = 0,
  e0 = 0,
  e1 = 0,
  c0 = 0,
  c1 = 0,
  prec_type = "baseline",
  use_end_dates = F
)
```

Arguments

p0	Days before preceding visit (≥ 0).
p1	Days after preceding visit (≥ 0), or NULL.
e0	Days before event onset (≥ 0), or NULL.
e1	Days after event onset (≥ 0), or NULL.
c0	Days before confirmation (≥ 0), or NULL.
c1	Days after confirmation (≥ 0).
prec_type	Which visit to use as "preceding visit". Must be one of: <ul style="list-style-type: none"> 'baseline': the current baseline; 'last': the last visit before event onset; 'last_lower': the last visit before event onset with a clinically meaningful score distance from the event score, i.e., the last visit i where $\text{outcome}[\text{event}] - \text{outcome}[i] \geq \text{delta_fun}(\text{outcome}[i])$.
use_end_dates	If TRUE, only the right bounds (e1, c1) are used, as the right bounds will be defined by the onset-to-end interval of each relapse. This option is only relevant when relapse <i>end</i> dates are available.

Details

If both ends of an interval are 0 (e.g., if both $p0=0$ and $p1=0$), the checkpoint is ignored. If the right end is NULL, the interval is assumed to extend up to the left end of the next interval. If the left end is NULL, the interval is assumed to extend up to the right end of the previous interval. Here are some examples:

- No relapses from 90dd before to 30dd after the event, and from 90dd before to 30dd after the confirmation [1]:
relapse_indep_from_bounds(e0=90, e1=30, c0=90, c1=30);
- No relapses between baseline and confirmation (high-specificity definition from [1]):
relapse_indep_from_bounds(p0=0, p1=NULL, e0=NULL, e1=NULL, c0=NULL, c1=0);
- No relapses from baseline to 30dd after the event, and within confirmation+-30dd [2]:
relapse_indep_from_bounds(p0=0, p1=NULL, e0=NULL, e1=30, c0=30, c1=30).

Value

A named list to be given as argument relapse_indep to function [MSprog\(\)](#)

References

- [1] Müller J, Cagol A, Lorscheider J, Tsagkas C, Benkert P, Yaldizli Ö, et al. Harmonizing definitions for progression independent of relapse activity in multiple sclerosis: A systematic review. *JAMA Neurol.* 2023;80:1232–45.
- [2] Kappos L, Wolinsky JS, Giovannoni G, Arnold DL, Wang Q, Bernasconi C, et al. Contribution of relapse-independent progression vs relapse-associated worsening to overall confirmed disability accumulation in typical relapsing multiple sclerosis in a pooled analysis of 2 randomized clinical trials. *JAMA Neurol.* 2020;77:1132–40.

toydata_relapses	<i>Synthetic Relapse Data</i>
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Description

Artificially generated relapse dates for some example patients in [toydata_visits](#) to illustrate the use of the package.

Usage

```
data(toydata_relapses)
```

Format

An object of class `data.frame`

id Subject ID

date The relapse date

References

This data set was artificially created for the `msprog` package.

Examples

```
data(toydata_relapses)
head(toydata_relapses)
```

toydata_visits

*Synthetic Longitudinal EDSS and SDMT Data***Description**

Artificially generated toy data set providing Extended Disability Status Scale (EDSS) and Symbol Digit Modalities Test (SDMT) scores in a small cohort of example patients to illustrate the use of the package.

Usage

```
data(toydata_visits)
```

Format

An object of class `data.frame`

id Subject ID

date The visit date

EDSS A value between 0 and 10

SDMT A value between 0 and 110

References

This data set was artificially created for the `msprog` package.

Examples

```
head(toydata_visits)
```

value_milestone

*Time to disability milestone.***Description**

`value_milestone()` scans the visits in chronological order to detect the first outcome value exceeding a specified disability milestone (e.g., `EDSS>=6`), *with confirmation*. Note: "exceeding" means either `value>=milestone` or `value<=milestone`, depending on the outcome measure (see arguments `outcome` and `worsening`).

Usage

```
value_milestone(
  data,
  milestone,
  subj_col,
  value_col,
  date_col,
  outcome,
  worsening = NULL,
  relapse = NULL,
  rsubj_col = NULL,
  rdate_col = NULL,
  validconf_col = NULL,
  conf_days = 24 * 7,
  conf_tol_days = c(7, 2 * 365.25),
  require_sust_days = 0,
  relapse_to_event = 0,
  relapse_to_conf = 30,
  impute_last_visit = 0,
  date_format = NULL,
  verbose = 0
)
```

Arguments

<code>data</code>	a <code>data.frame</code> containing longitudinal data, including: subject ID, outcome value, date of visit.
<code>milestone</code>	Disability milestone (outcome value to check data against).
<code>subj_col</code>	Name of data column with subject ID.
<code>value_col</code>	Name of data column with outcome value.
<code>date_col</code>	Name of data column with date of visit.
<code>outcome</code>	Specifies the outcome type. Must be one of the following: <ul style="list-style-type: none"> 'edss' (Expanded Disability Status Scale); 'nhpt' (Nine-Hole Peg Test); 't25fw' (Timed 25-Foot Walk); 'sdmt' (Symbol Digit Modalities Test); NULL (only accepted when specifying argument <code>worsening</code>)
<code>worsening</code>	The direction of worsening ('increase' if higher values correspond to worse disease course, 'decrease' otherwise). The given value is only used when <code>outcome</code> is set to NULL. Otherwise, <code>worsening</code> is automatically set to 'increase' if <code>outcome</code> is set to 'edss', 'nhpt', 't25fw', and to 'decrease' if <code>outcome</code> is set to 'sdmt'.
<code>relapse</code>	<code>data.frame</code> containing longitudinal data, including: subject ID and relapse date.
<code>rsubj_col</code>	Name of subject column for relapse data, if different from outcome data.
<code>rdate_col</code>	Name of date column for relapse data, if different from outcome data.
<code>validconf_col</code>	Name of data column specifying which visits can (T) or cannot (F) be used as confirmation visits. The input data does not necessarily have to include such a

	column. If <code>validconf_col=NULL</code> , all visits are potentially used as confirmation visits.
<code>conf_days</code>	Period before confirmation (days).
<code>conf_tol_days</code>	Tolerance window for confirmation visit (days); can be an integer (same tolerance on left and right) or list-like of length 2 (different tolerance on left and right). The right end of the interval can be set to <code>Inf</code> (confirmation window unbounded on the right – e.g., "confirmed over 12 <i>or more</i> weeks").
<code>require_sust_days</code>	Minimum number of days over which the milestone must be sustained (i.e., confirmed at <i>all</i> visits occurring in the specified period). If the milestone is sustained for the remainder of the follow-up period, it is considered reached regardless of follow-up duration. If <code>require_sust_days=Inf</code> , values are retained only when sustained for the remainder of the follow-up period.
<code>relapse_to_event</code>	Minimum distance from a relapse (days) for the milestone to be considered reached. Can be an integer (minimum distance from <i>last</i> relapse) or list-like of length 2 (minimum distance from <i>last</i> relapse, minimum distance from <i>next</i> relapse). Note that setting the distance to zero means retaining the event regardless of surrounding relapses.
<code>relapse_to_conf</code>	Minimum distance from a relapse (days) for a visit to be a valid confirmation visit. Can be an integer (minimum distance from <i>last</i> relapse) or list-like of length 2 (minimum distance from <i>last</i> relapse, minimum distance from <i>next</i> relapse). Note that setting the distance to zero means using any visit for confirmation regardless of surrounding relapses.
<code>impute_last_visit</code>	Imputation probability when the milestone is reached at the last visit (i.e. with no confirmation). Unconfirmed values exceeding the milestone at the last visit are never imputed if <code>impute_last_visit=0</code> ; they are always imputed if <code>impute_last_visit=1</code> ; they are imputed with probability p , $0 < p < 1$, if <code>impute_last_visit=p</code> . If a value $N > 1$ is passed, unconfirmed values exceeding the milestone are imputed only if occurring within N days of follow-up (e.g., in case of early discontinuation).
<code>date_format</code>	Format of dates in the input data. Can be: <ul style="list-style-type: none"> • 'day' if dates are given as "days from start" (the starting point can be different for each subject – e.g., days from randomisation in a clinical trial); negative values are accepted. • Standard format for dates (e.g., "%d-%m-%Y"; see <code>strptime()</code> docs for correct syntax). <p>If not specified, function <code>as.Date()</code> will try to infer it automatically.</p>
<code>verbose</code>	One of: <ul style="list-style-type: none"> • 0 (print no info); • 1 (print concise info, default); • 2 (print extended info).

Details

An event is only retained if **confirmed**, i.e., if all values *up to* the confirmation visit exceed the milestone. Valid time windows for confirmation visits are determined by arguments `conf_days`, `conf_tol_days`, `relapse_to_conf`.

Value

A `data.frame` containing the following columns:

- `date_col`: the date of first reaching or exceeding the milestone (or last date of follow-up if milestone is not reached);
- `value_col`: the first value reaching or exceeding the milestone, if present, otherwise no value;
- `'time2event'`: the time taken to reach or exceed the milestone (or total follow-up length if milestone is not reached);
- `'observed'`: whether the milestone was reached (1) or not (0).

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