AdhereR: Estimate Adherence from Electronic Healthcare Data

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Why EHD?

- data available from routine care for large samples with minimal extra costs
  - Estimate prevalence of (non-)adherence
  - Identify predictors of (non-)adherence
  - Model impact of adherence on clinical outcomes
  - Identify individuals with suboptimal adherence for targeted interventions
- limitations:
  - low granularity
  - variable data entry quality & standards
  - limited info recorded

Typically available information

- Patient identifier
- Date of event
- Type of medication
- Quantity prescribed/dispensed/billed

Methodology matters

- Different adherence estimates from the same data
- Insufficiently reported algorithms
- Lack of standardization and transparency
- Misinformed clinical decisions

Example: Method-related variation in adherence to sibutramine

Measure	Formula	Value	Result (Standard Deviation)
CMA[17]	cumulative days' supply of medication obtained/total days to next fill or to end of observation period	adherence value for cumulative time period	0.635 (0.29)
CMG[17]	total days of treatment gaps/total days to next fill or end of observation period	nonadherence value for cumulative period, winsorized at zero	0.370 (0.28)
CMOS[13]	total days of treatment gaps (+) or surplus[a] (–)/total days in observation period	nonadherence value for cumulative period, allowing for surplus	0.365 (0.29)
CR[24]	(total days supplied – last days' supply)/(last claim date – first claim date) × 100	adherence value for period between fills	84.4% (0.22)[b]
CSA[17]	days' supply obtained at beginning of interval/days in interval	adherence value for interval of study participation	1.097 (1.73)
DBR[22]	1 – {[(last claim date – first claim date) – total days' supply]/(last claim date – first claim date)} × 100	overall adherence percentage	104.8% (38.6)
MPR[16]	days' supply: days in period	ratio of medication available	0.635:1 (0.29)
MPRm[26]	[total days supplied/(last claim date – first claim date + last days' supply)] × 100	adherence percentage, adjusted to include final refill period	86.6% (16.6)
MRA[23]	(total days' supply/total number of days evaluated) × 100	overall adherence percentage	63.5% (29.1)
PDC[27]	(total days supply/total number of days evaluated) × 100%, capped at 1.0[a]	percentage of days with medication available	63.0% (28.3)
RCR[25]	[(sum of quantity dispensed over interval/quantity to be taken per day) × 100]/number of days in interval between first and last refill	overall adherence percentage	104.8% (38.6)

LM Hess - 2006. https://doi.org/10.1345/aph.1H018 (https://doi.org/10.1345/aph.1H018).

AdhereR

- Open-source package for the statistical software R
- Computation of adherence from EHD
- (Interactive) visualization
- Transparent and reproducible reporting
- Under active development

Assumptions

- The regimen requires the use of a fixed daily dosage of medication
- All medication supplied for that patient in that period of time is recorded
- The patient does not use medication from other sources
- The medication is used by the patient it has been supplied for
- Medication is supposed to be supplied at least two times during the observed period
- Several other assumptions apply to individual algorithms

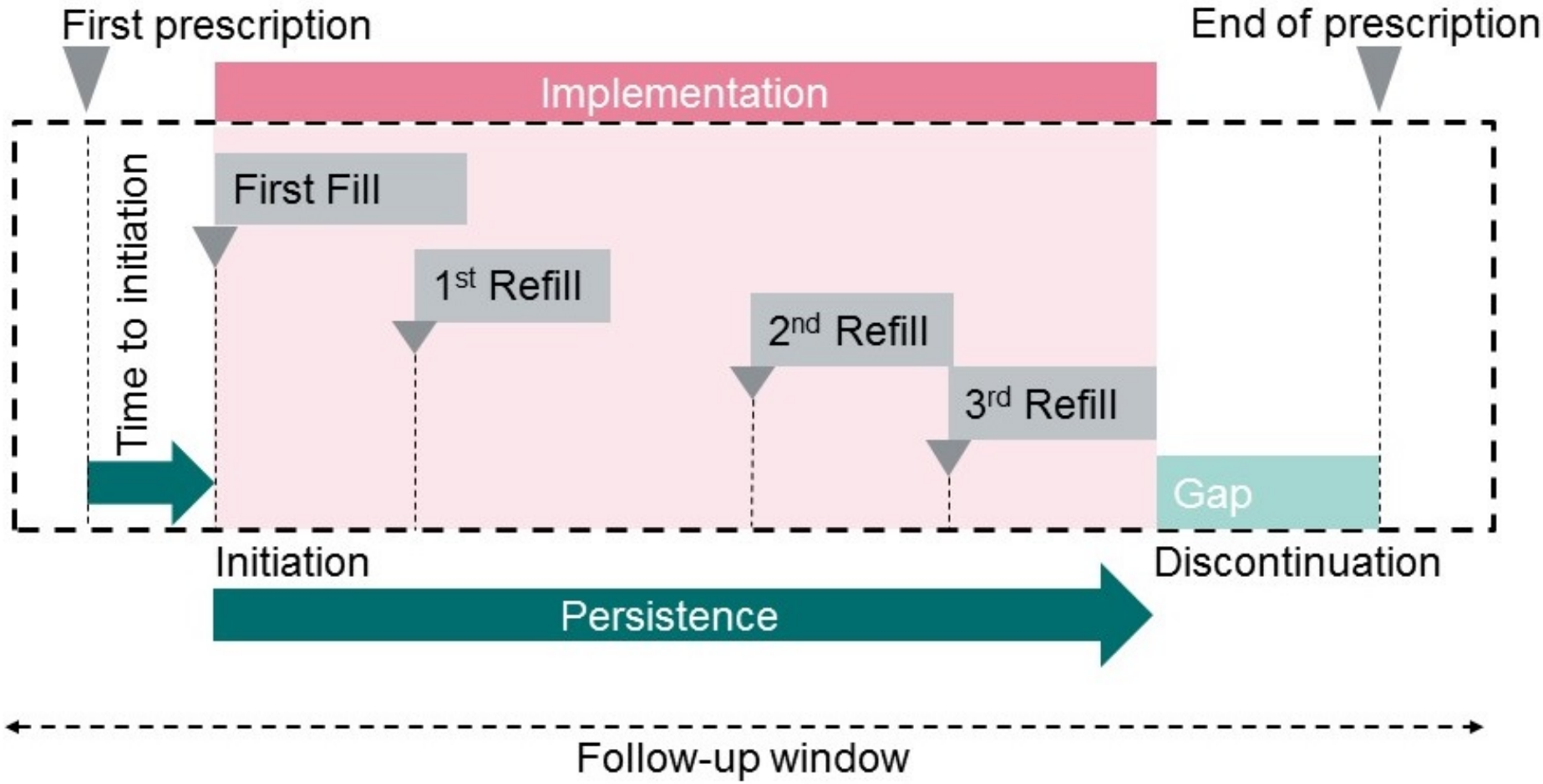
Definitions: Data source

- *Medication event* = prescribing or dispensing event of a given medication for a given patient
- *Duration* = number of days the quantity of supplied medication would last if used as recommended
- *Quantity* = number of doses supplied at a medication event
- *Daily dosage* = number of doses recommended to be taken daily
- *Medication type* = classification performed by the researcher depending on study aims

Definitions: Adherence taxonomy

- *Adherence*
  - continuous multiple-interval measures of medication availability (CMA)
- *Initiation*
  - the length of time between the first prescribing event and the first dispensing event
- *Persistence*
  - the length of time with repeated medication events, before discontinuing for a time period longer than a pre-specified permissible gap
- *Implementation*
  - CMA during treatment episodes or observation windows with no treatment gaps longer than a pre-specified period

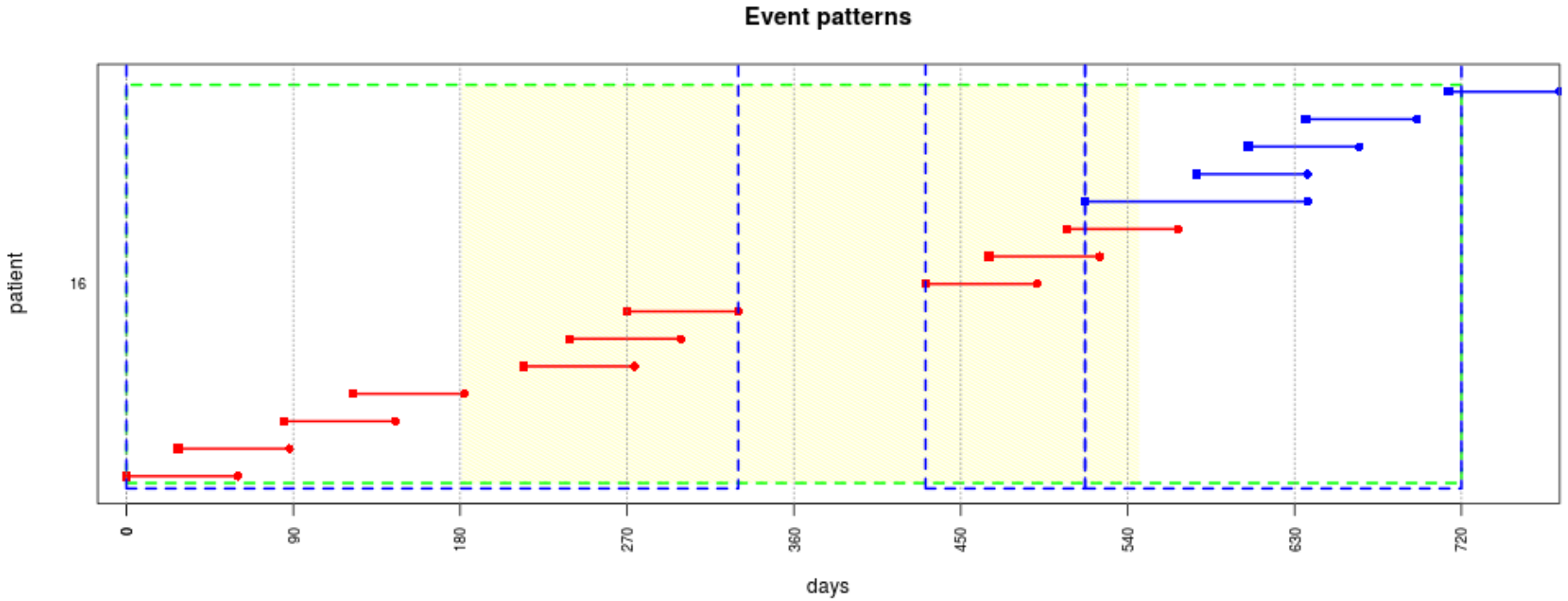
ABC Taxonomy for EHD



ABC taxonomy figure adapted for EHD

Definitions: Time frames

- *Follow-up window* (FUW)
- *Observation window* (OW)
- *Treatment episode* (TE)



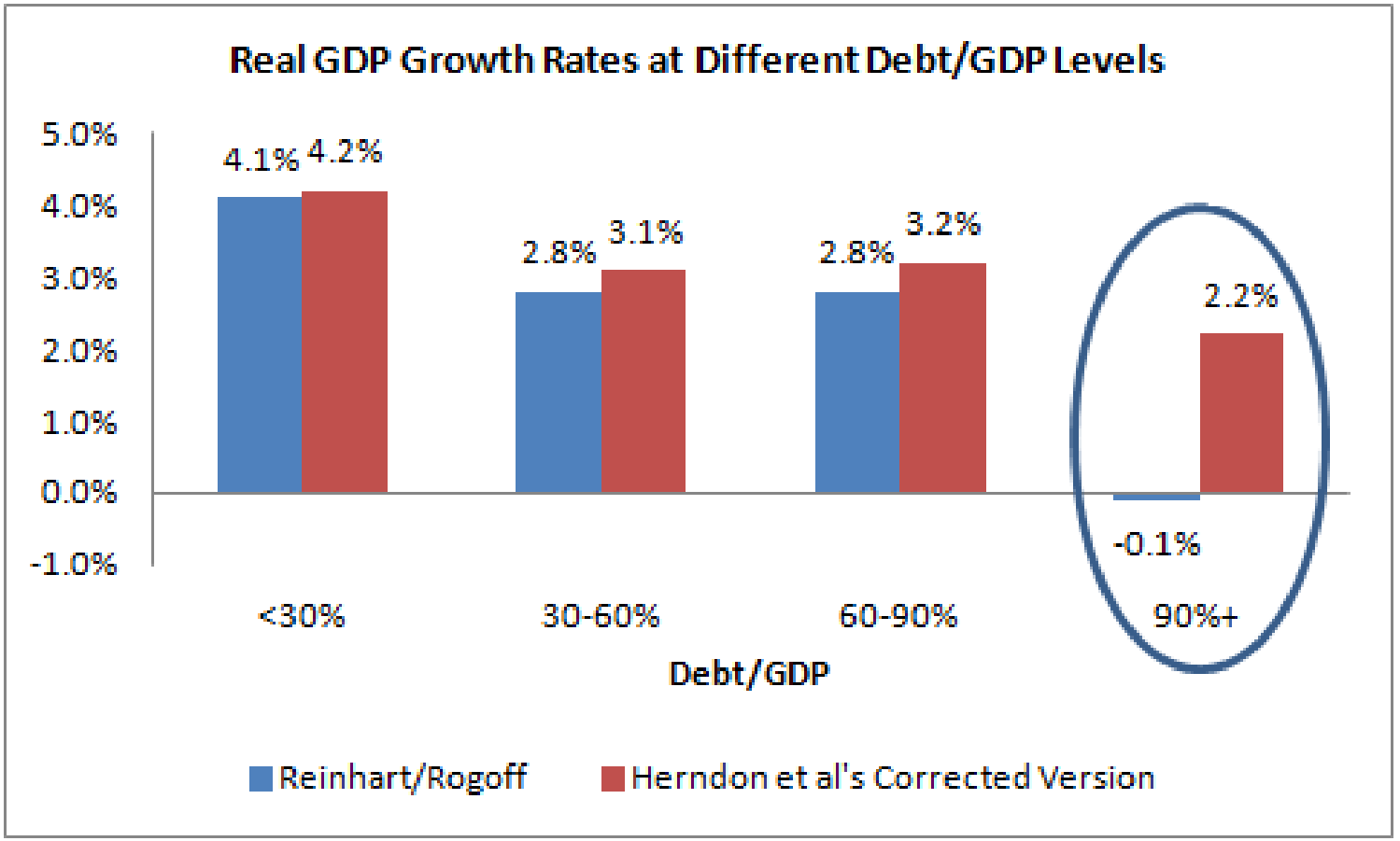
Working with AdhereR

1. Data preparation
2. Data exploration / Visualization
3. Adherence calculation
4. Reporting

Prerequisites

- The raw data (A),
- A tidy data set (B),
- A code book with all variables and values in the tidy data set,
- A reproducible recipe how to go from A to B.

Why reproducibility is important



Herndon, T., Ash, M., & Pollin, R. (2014). Cambridge journal of economics, 38(2), 257-279.

1. Data preparation

- selecting medication events applicable to the research question
- coding medication type depending on clinical considerations
- calculate medication event durations (if necessary)
- check plausible values and correcting any deviations
- handle missing data
- see Huang, Yunyu, Jaco Voorham, und Flora M Haaijer-Ruskamp. Journal of Comparative Effectiveness Research 5, Nr. 4 (27. Juni 2016): 345-54. https://doi.org/10.2217/cer-2015-0022 (https://doi.org/10.2217/cer-2015-0022).

R Basics: structure of analysis (1/2)

- load necessary packages
  - `library(Adherer)`
  - `library(data.table)`
- import data
  - `load("path/to/data.rda")` to load R data objects
  - `fread("path/to/data.csv")` to import csv-files
  - `dbConnect(...)` to connect to a (remote) database

R Basics: Data structures

- data.frames or data.tables hold the data similar to an excel spreadsheet
- each row is an observation
- each column is a variable

R Basics: structure of analysis (2/2)

- manipulate data
  - `data.table` syntax: `data[*subset*, *do*, *by*]`
- store results
  - Basic `R` syntax: `object <- function(data, argument)`
  - `save(data, ... , file="path/to/file.rda")` to save R data object
  - `write.csv(data, file = "path.to.file.csv")` to export to csv-file

Link multiple data sources

- Necessary data recorded in different databases
- Prescription changes or hospitalizations affect adherence estimation
- New AdhereR function to:
  1. automatically select the last prescribed dose to calculate supply duration,
  2. check for prescription changes, hospitalizations, and other treatment interruptions during this period, and
  3. adjust the supply duration based on prescription changes and hospitalizations

Link multiple data sources

Show ▾ entries Search:

ID	DATE.PRESC	VISIT	ATC.CODE	FORM	UNIT	PRESC.DURATION	DAILY.DOSE
1	2056-12-08	0	A09AA02	ORAL FORM	UI		36000
1	2057-02-23	1	A09AA02	ORAL FORM	UI		86000
1	2057-03-03	2	A09AA02	ORAL FORM	UI		86000

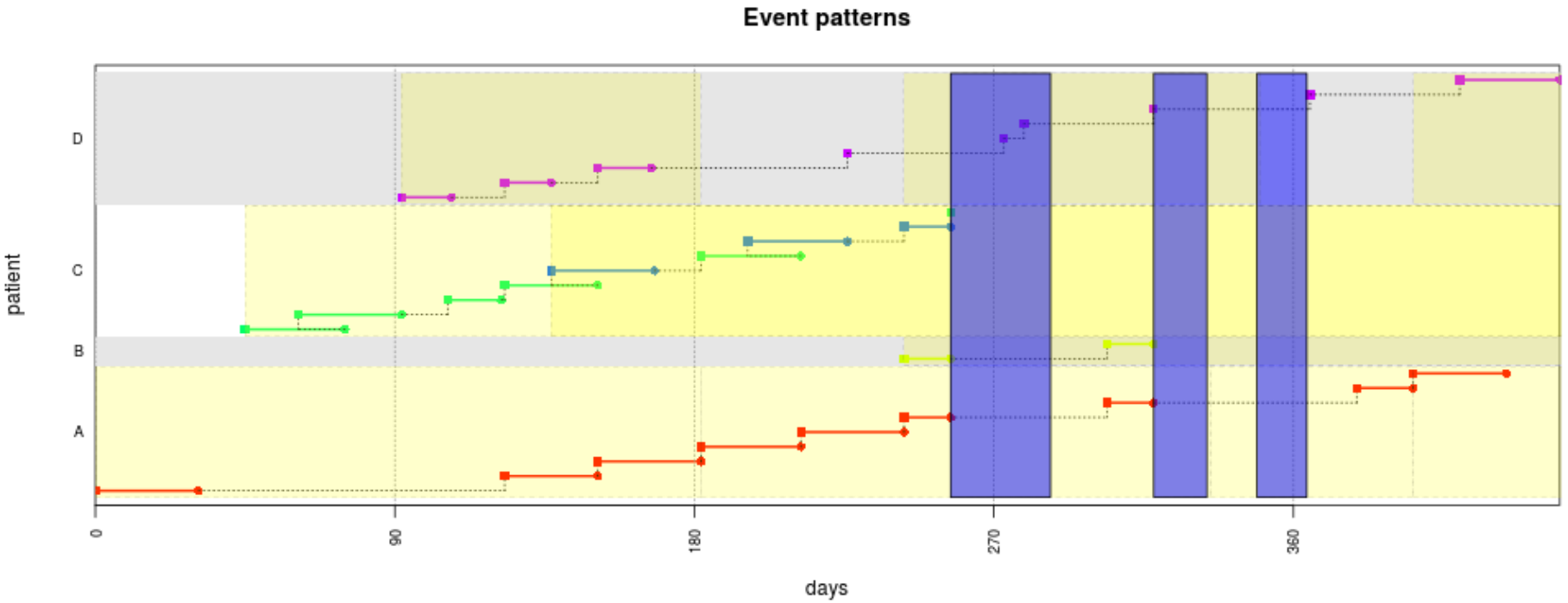
ID	DATE.PRESC	VISIT	ATC.CODE	FORM	UNIT	PRESC.DURATION	DAILY.DOSE

Showing 1 to 3 of 1,502 entries

Previous 1 2 3 4 5 … 501 Next

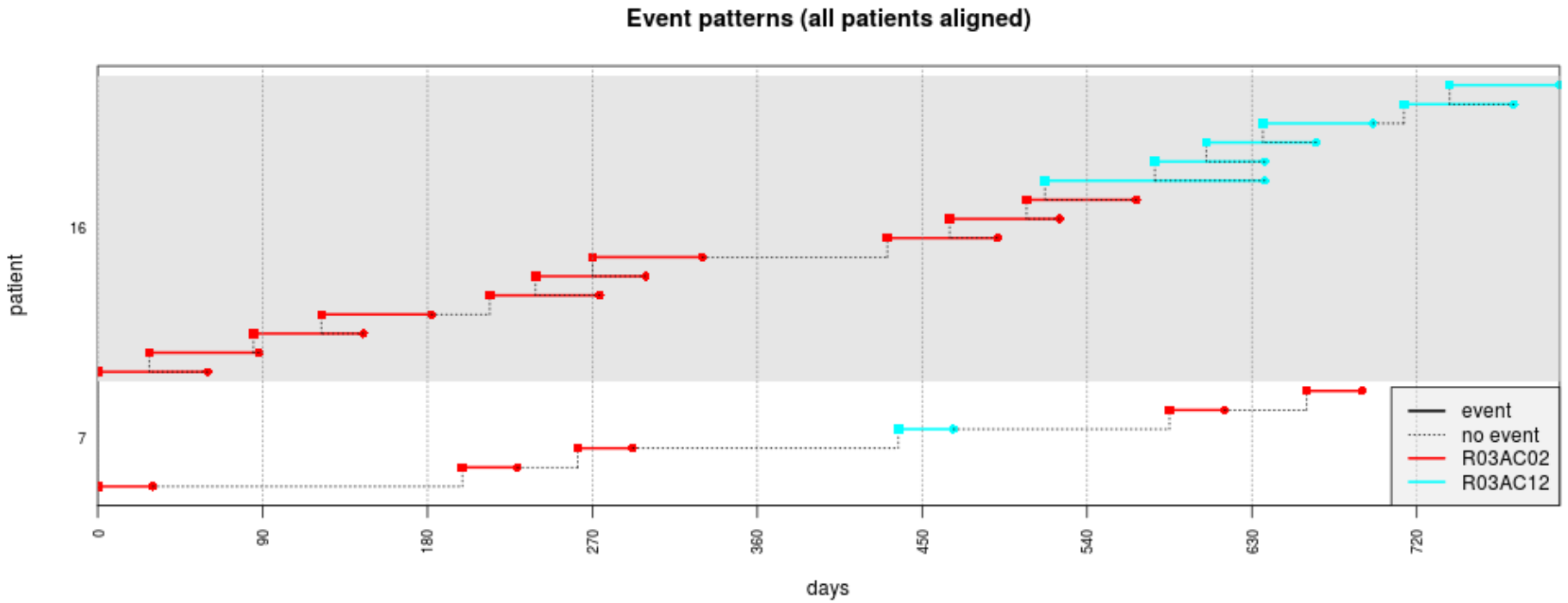
Link multiple data sources

```
compute_event_durations(disp.data, presc.data, hosp.data, ...)
```



2. Data exploration/Visualization

- Exploration during preparation stage
- Illustration for scientific communication
- Guidance in clinical practice



Interactive Plotting

General settings...

Select CMA type

simple

Select CMA to compute

CMA1

Select patient to plot

1

Follow-up window...

Follow-up wnd. start unit

days

Follow-up wnd. start

0 1,825

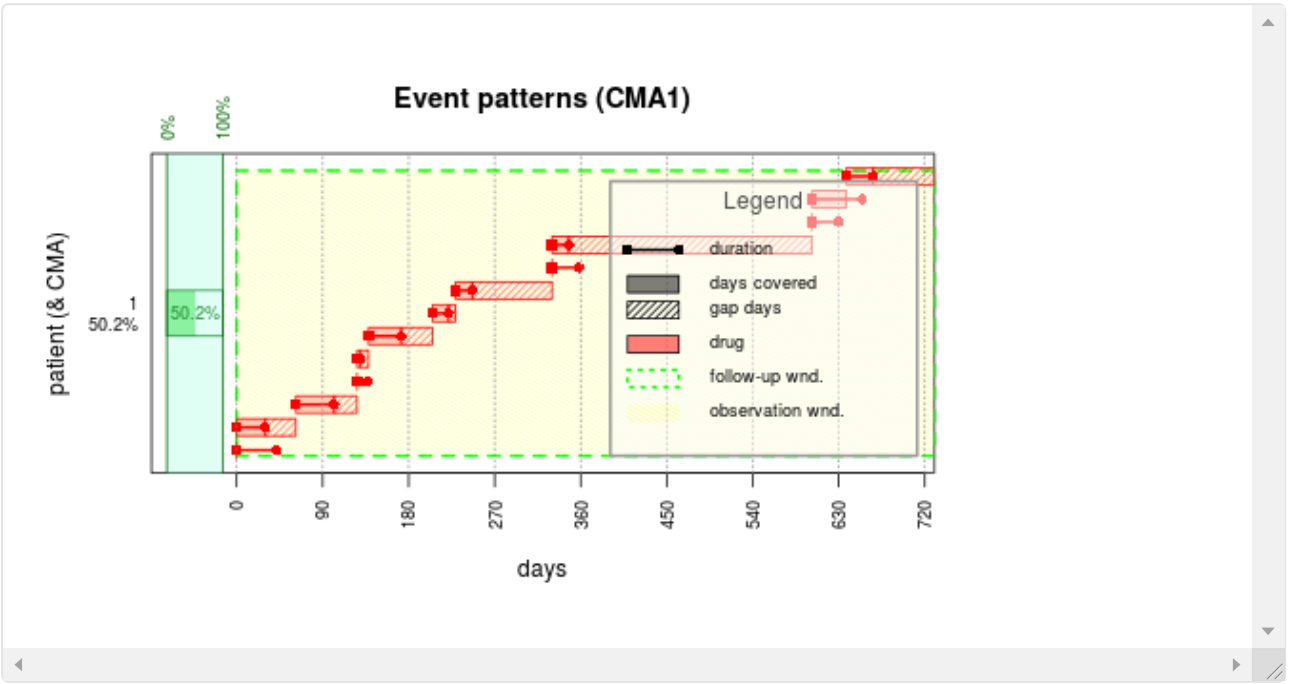
Plot width

500 5,000

0 1,000 2,000 3,000 4,000 5,000

keep ratio Save plot! Exit...

Messages: Plotting patient ID '1' with CMA 'CMA1'



3. Adherence calculations

- `AdhereR` estimates adherence as *Continuous Medication Availability* (CMA)
- *simple* CMA measures: `CMA1` - `CMA9`
    - Delimitation of OW,
    - Capping of CMA values,
    - Carry-over of medication oversupply within the OW, and
    - Carry-over of medication supply into OW.
- *iterated* CMA measures: `CMA_per_episode` and `CMA_sliding_window`

Overall adherence - implementation & persistence

- CMA itself makes no difference between persistence/non-persistence
- CMA = implementation only if sample/individual is on treatment
  - *simple* CMA for sample that initiated and did not discontinue OR
  - *per episode* CMA first identifies treatment episodes then computes CMA for each

Overall adherence with CMA7

```
cma7 <- CMA7(data=example_data,
             ID.colname="ID",
             event.date.colname="DATE.DISP",
             event.duration.colname="DURATION",
             event.daily.dose.colname="DAILY.DOSE",
             medication.class.colname="ATC.CODE",
             carry.only.for.same.medication=FALSE,
             consider.dosage.change=TRUE,
             followup.window.start="START.PRESC",
             followup.window.duration=3*365,
             observation.window.start=0,
             observation.window.duration=365,
             date.format="%Y-%m-%d")
```

Initiation

- Requires prescription and dispensing data for the same follow-up period
- yes/no - availability of a dispensing date (within a period of time after prescription)
- time to dispensing - `time_to_initiation()` function

Time to initiation

```
time_to_initiation(disp.data, presc.data, ...)
```

Show ▾ entries Search:

ID	ATC.CODE	FORM	UNIT	first.presc	first.disp	time.to.initialization
1	R03AC12	METERED INHALER	MICROG	2057-02-23	2056-10-09	-137
2	R03AC02	METERED INHALER	MICROG		2058-02-08	
2	R03AC03	METERED INHALER	MICROG		2056-07-28	

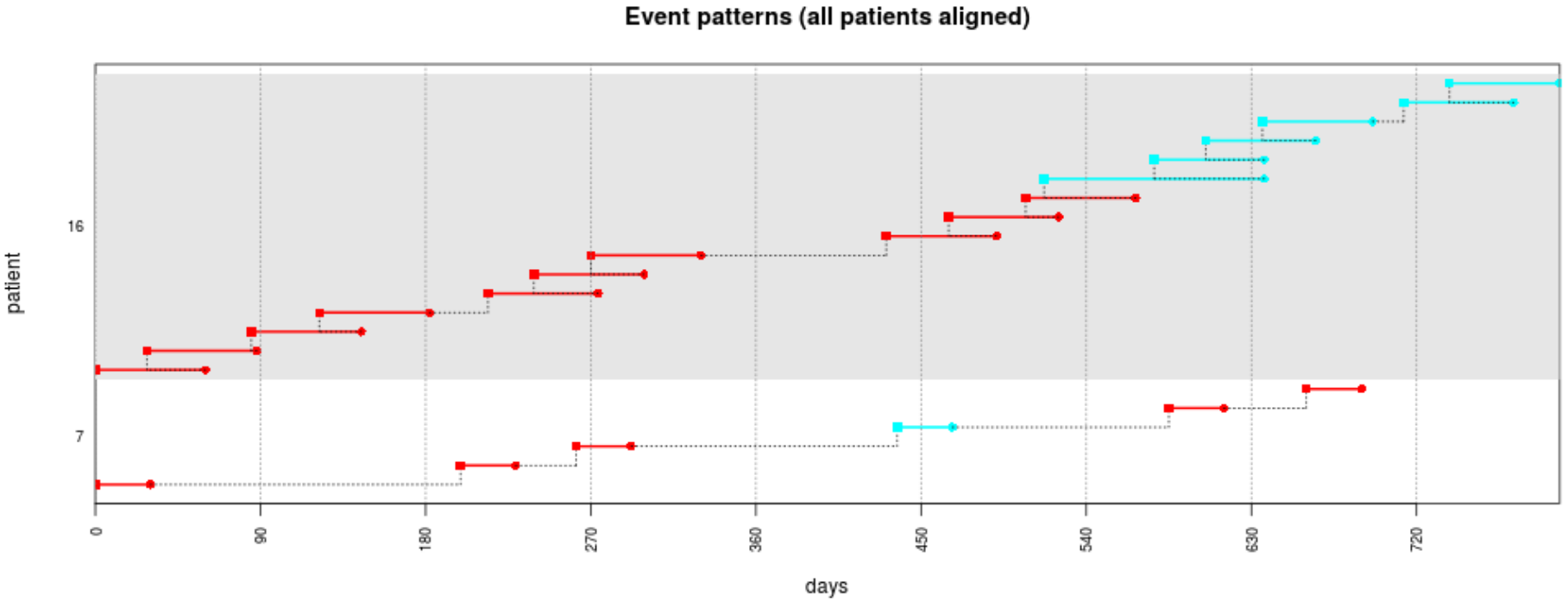
ID ATC.CODE FORM UNIT first.presc first.disp time.to.initialization

Showing 1 to 3 of 26 entries

Previous 1 2 3 4 5 … 9 Next

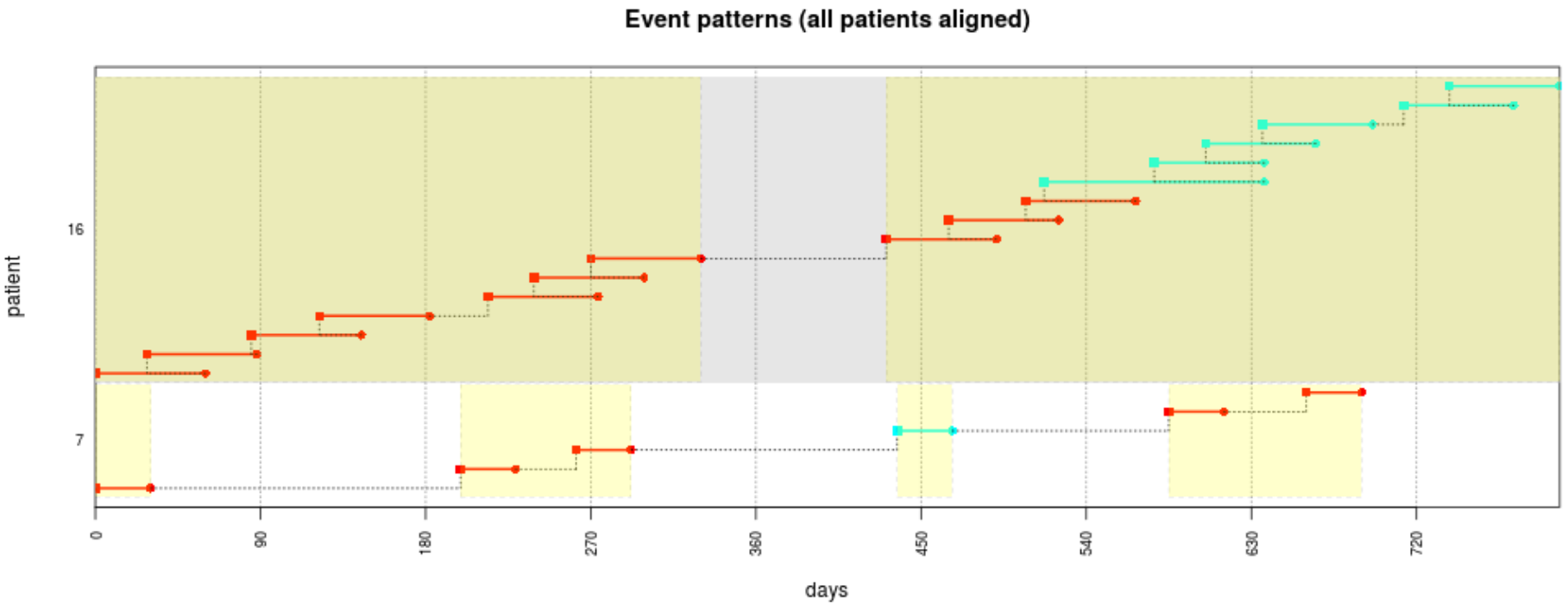
Persistence

- differentiate between persistence with treatment and quality of implementation



Persistence

- `compute.treatment.episodes(data, ...)`

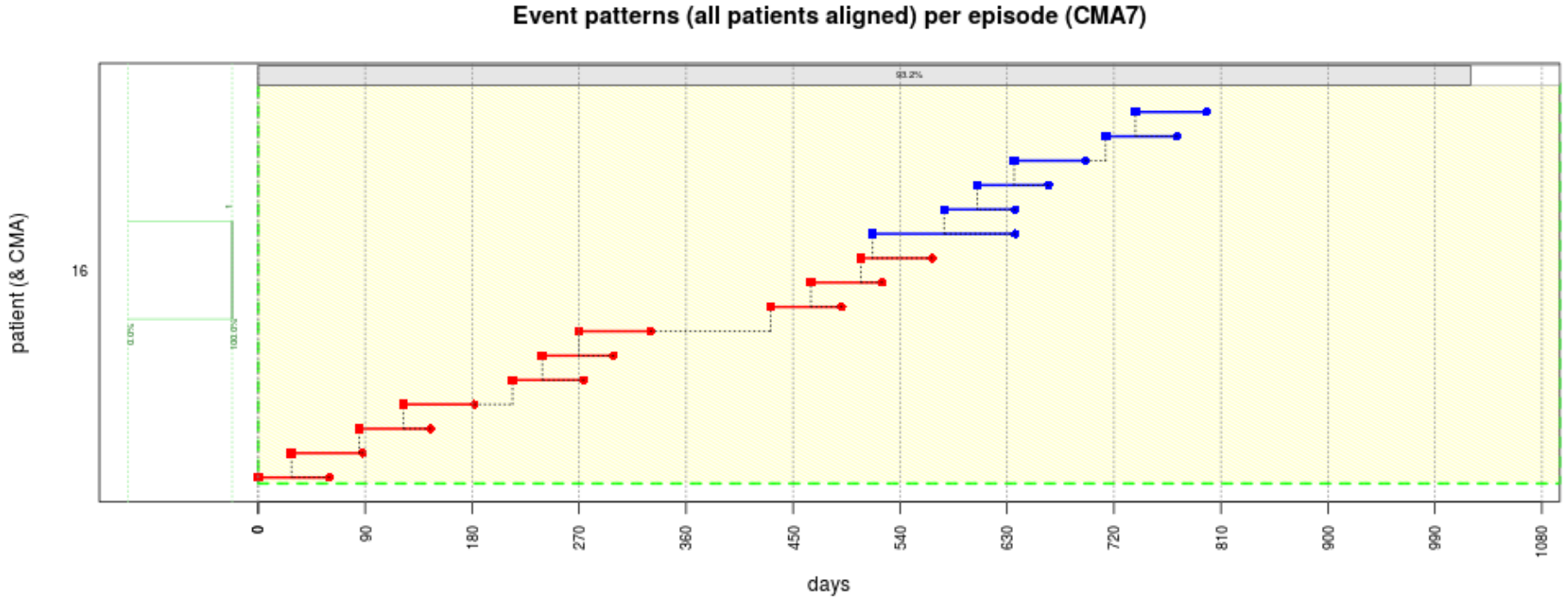


Persistence output

ID	episode.ID	episode.start	end.episode.gap.days	episode.duration	episode.end
7	1	2056-07-07	169	30	2056-08-06
7	2	2057-01-22	145	93	2057-04-25
7	3	2057-09-17	118	30	2057-10-17
7	4	2058-02-12	405	105	2058-05-28
16	1	2056-07-04	0	517	2057-12-03
16	2	2057-12-03	158	420	2059-01-27

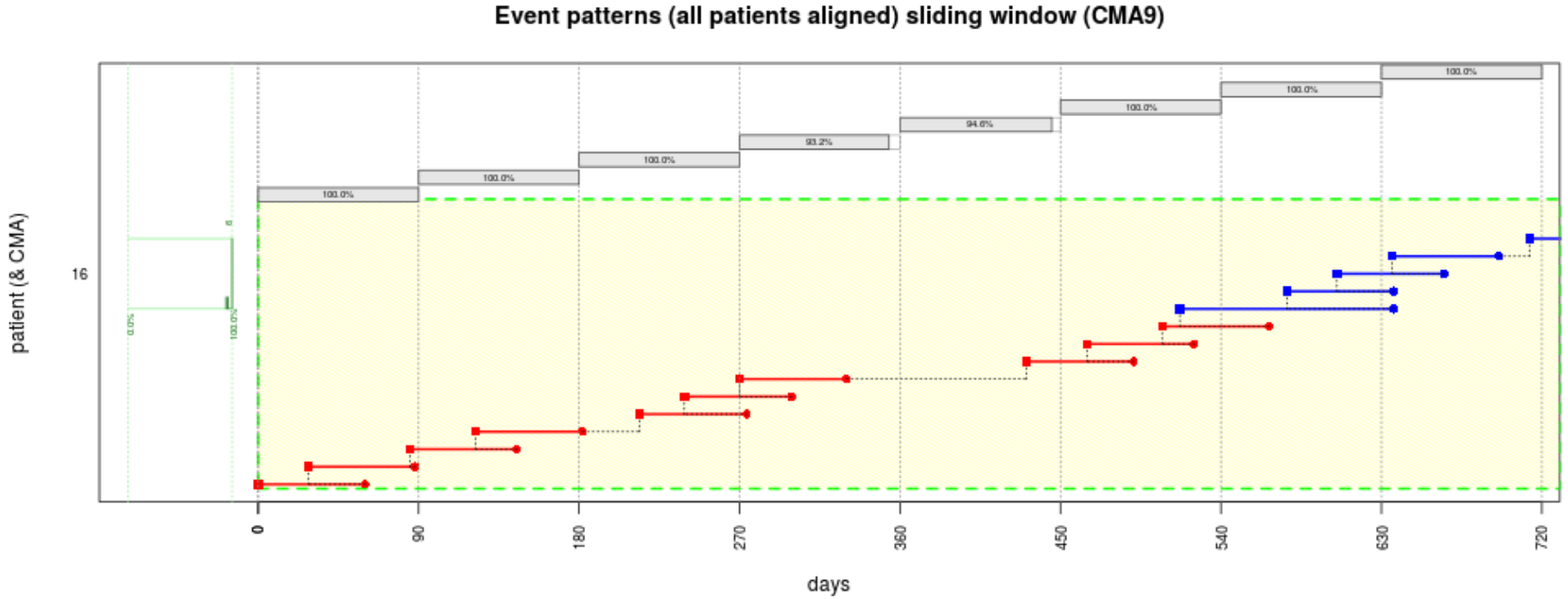
Implementation

- CMA per episode
- `CMA_per_episode(CMA, data, ...)`



Longitudinal analysis

- for time-series, (e.g., GEE), or group-based trajectory models
- `CMA_sliding_window(CMA.to.apply="CMA9", data, ...)`



Dealing with Polypharmacy

- calculation of one single adherence value
- two-step process
  - create treatment groups
  - aggregate treatment groups into single adherence value

Treatment groups

- treatment-switches vs. two-drug regimens
- decide which medications can be used interchangeably
- e.g. based on ATC codes

Aggregation methods

- CMA for periods with ANY treatment available
- CMA for periods with ALL treatments available
- Average of CMAs for individual treatments, unweighted
- Average of CMAs for individual treatments, weighted by treatment episode (DPPR)
- Dichotomized: CMA for individual treatments larger than cutoff

4. Reporting

- describe data preparation choices
- justify choice of functions
- report any sensitivity analyses
- share the analysis code (and anonymized dataset, if possible)
- use RMarkdown to embed code and R plots in your reports

Take home messages

- Data Preparation & Exploration are essential for meaningful estimation of adherence
- Meaningful Adherence estimation requires clear operationalization of the reported measure
- AdhereR provides functions to prepare, analyze, and visualize EHD
- AdhereR functions are flexible, transparent, and ensure reproducibility

Practical session(s)

- interactive online-tutorial with example data (for beginners)
- commented R script to use within R Studio (for advanced R users)
- R-Markdown document with explanations and code examples for reference