# 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

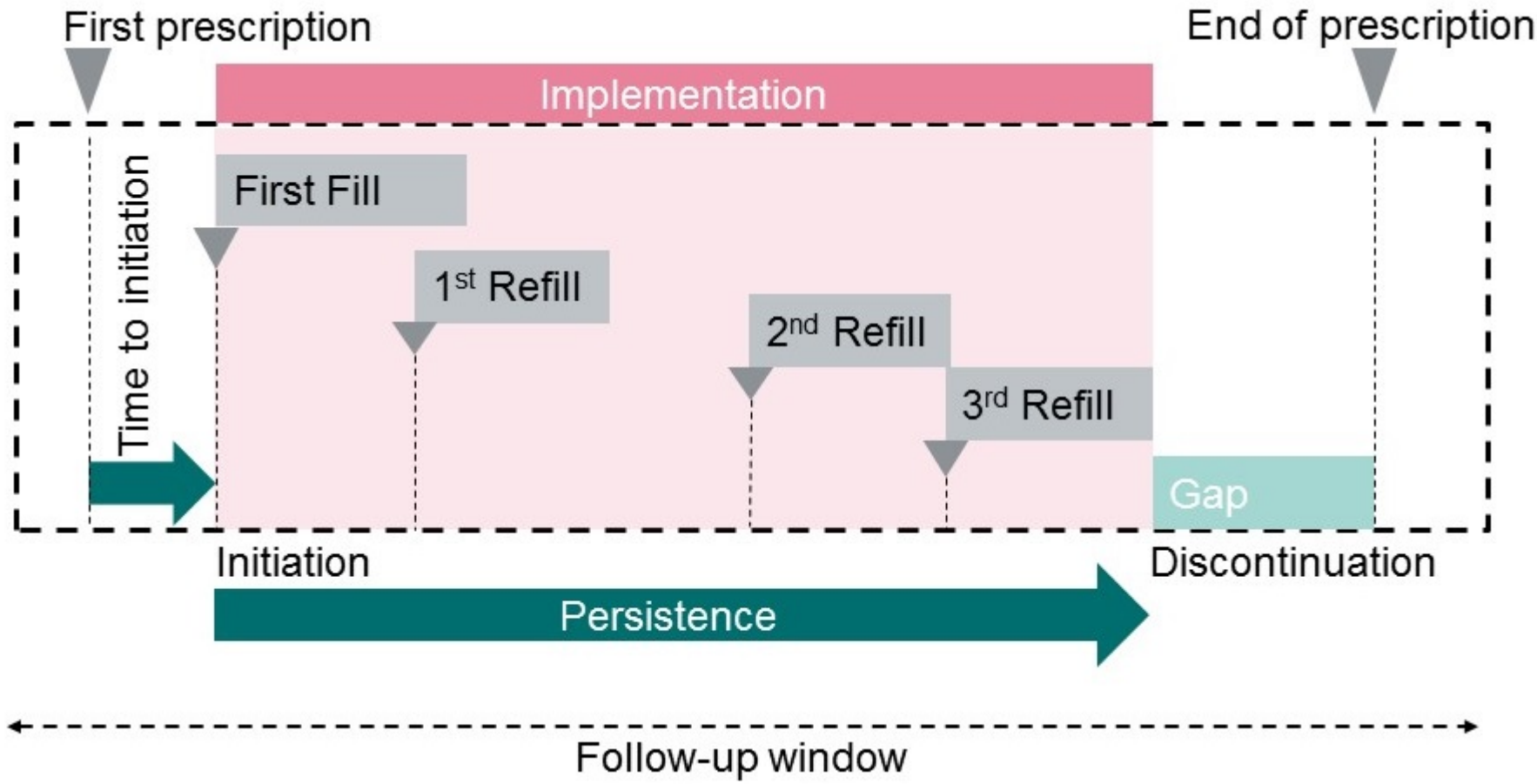
# Definitions: Data source

- *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

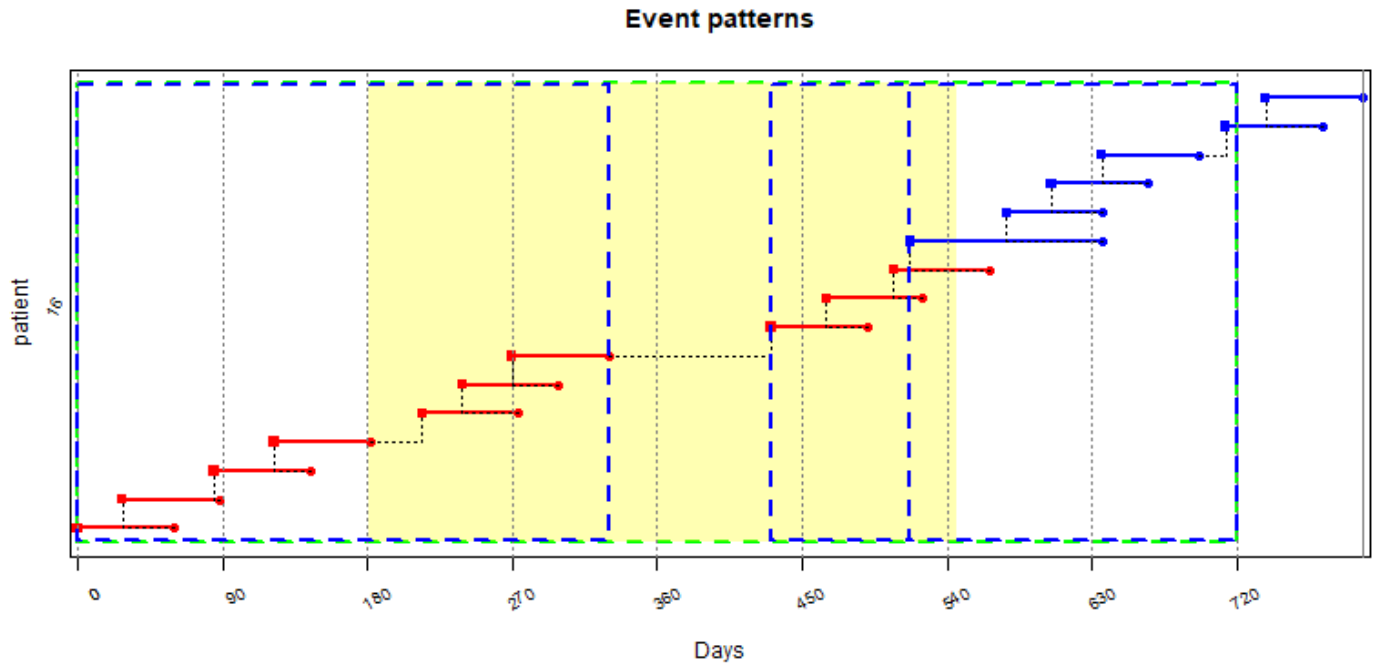
# ABC Taxonomy for EHD




ABC taxonomy figure adapted for EHD

# Definitions: Time frames

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



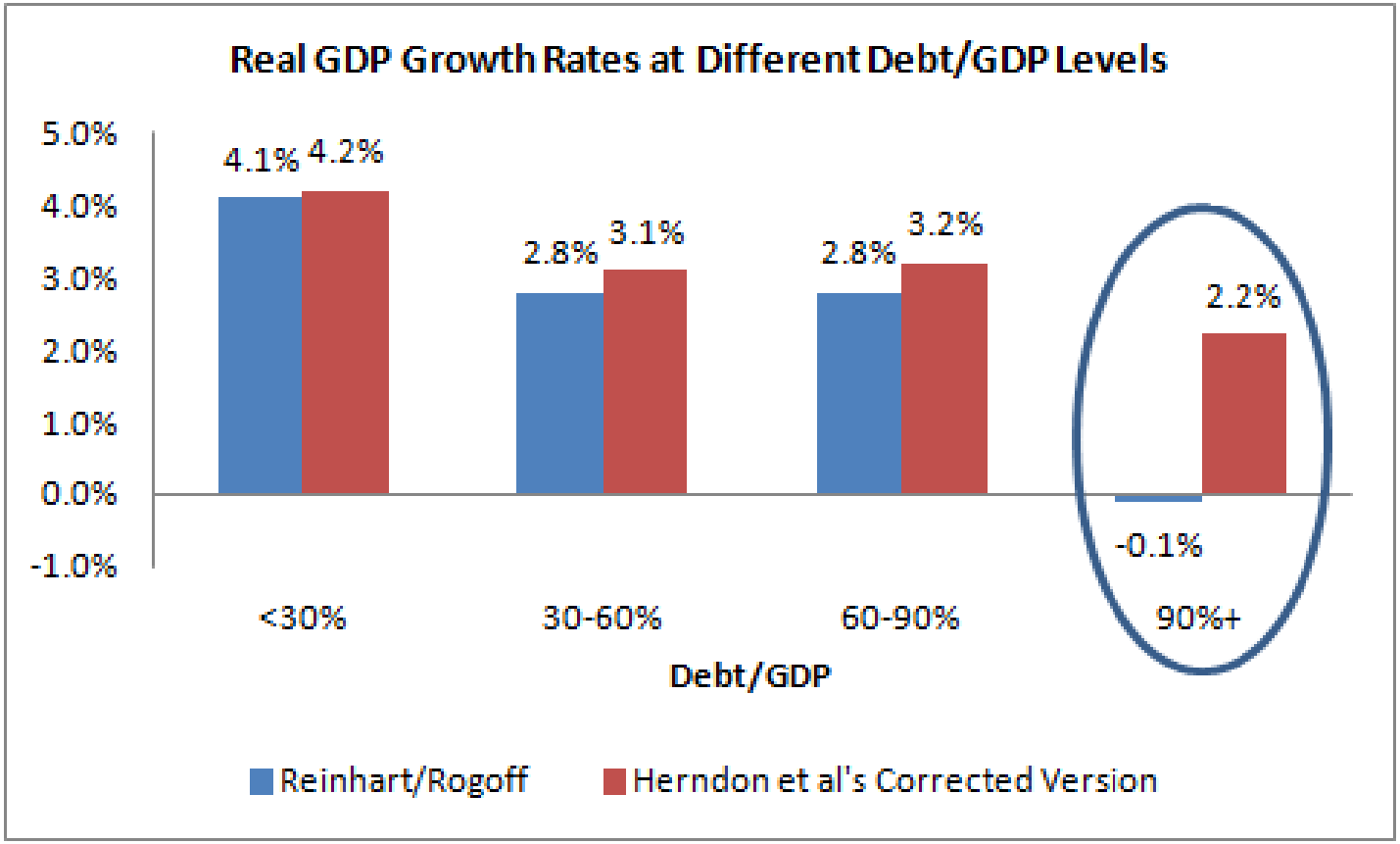
# Working with AdhereR

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



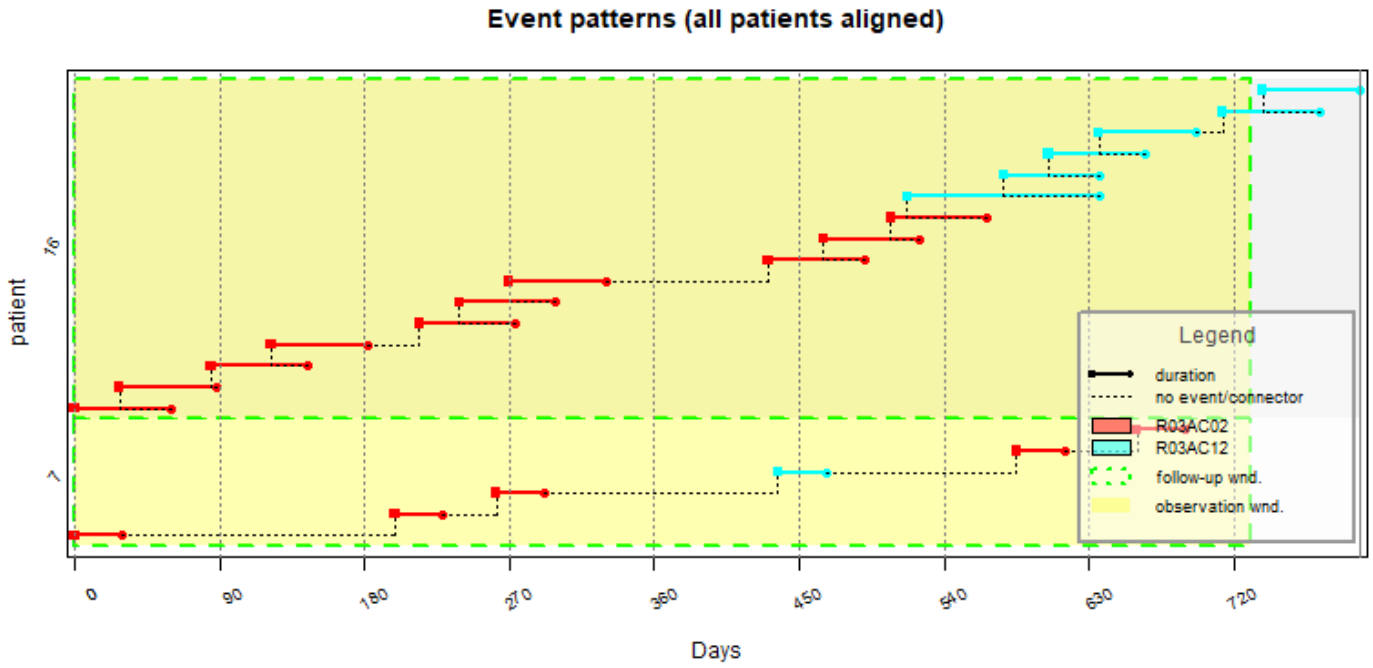

Herndon, T., Ash, M., & Pollin, R. (2014). Cambridge journal of economics, 38(2), 257-279.

# 1. Data preparation

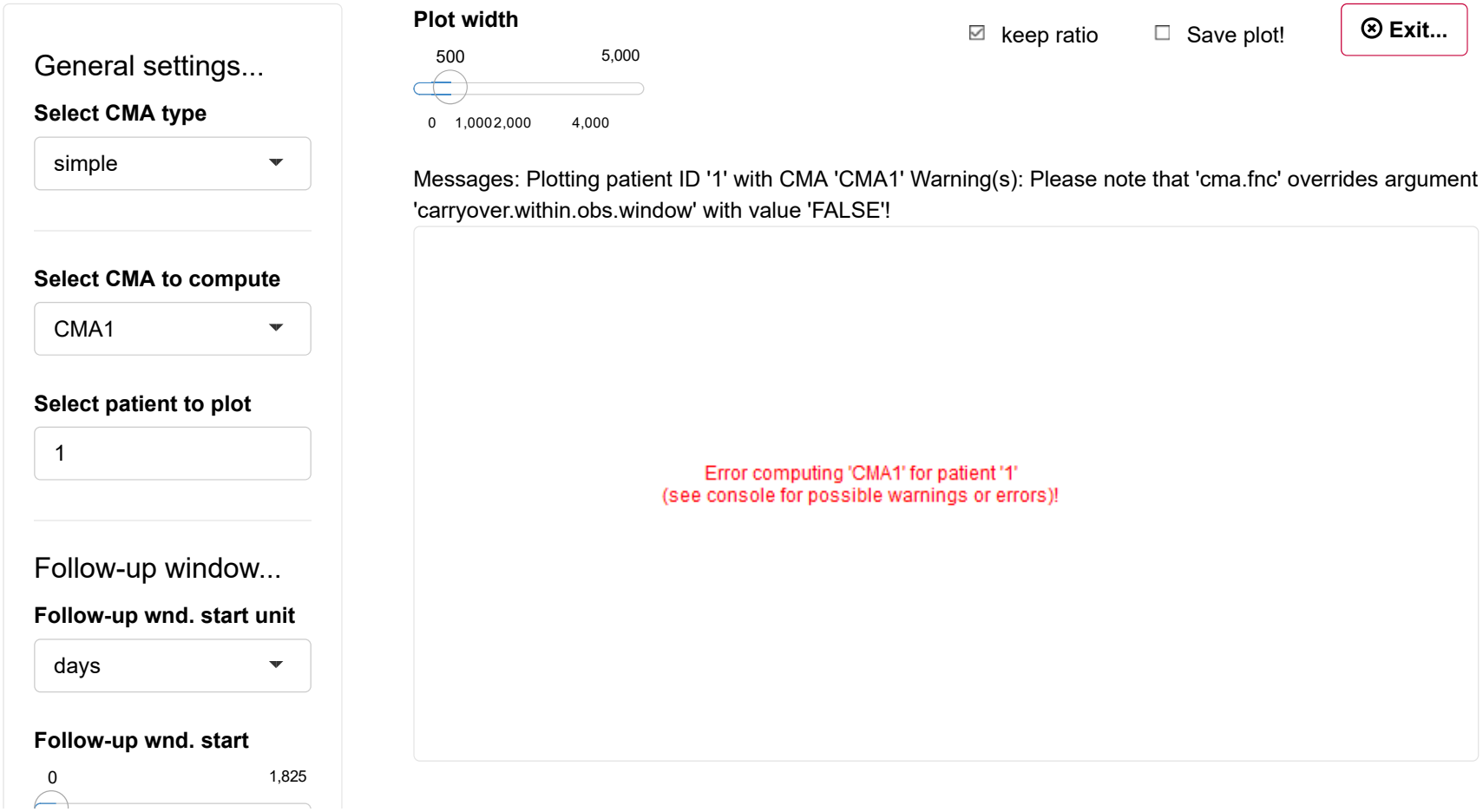
- selecting medication events applicable to the research question
- coding medication type depending on clinical considerations
- calculate medication event durations (if necessary)
- check plausible values and correcting any deviations
- handle missing data
- see Huang, Yunyu, Jaco Voorham, und Flora 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).

# 2. Data exploration/Visualization

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



# Interactive Plotting



# 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")
```

```
## Warning in CMA0(data = data, ID.colname = ID.colname, event.date.colname = event.date.
```

# 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

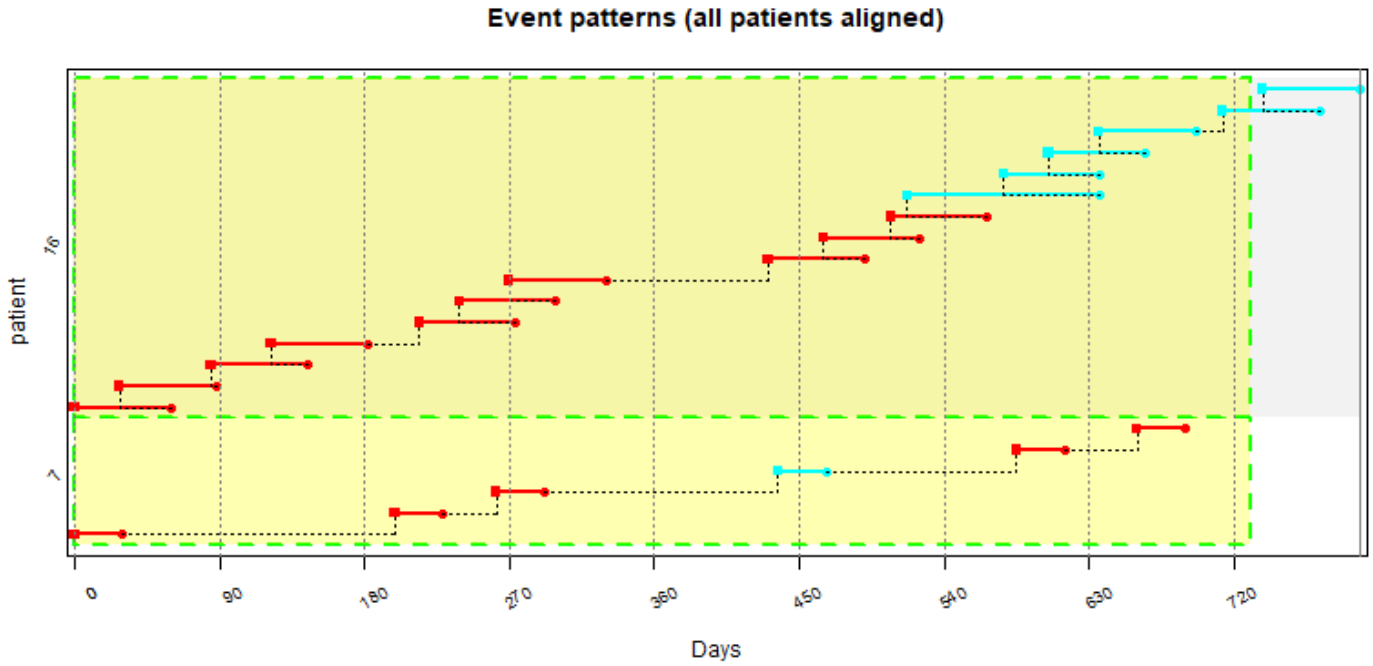
# Time to initiation

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

```
## Warning in time_to_initiation(presc.data = prescription_episodes[grepl("^R03AC", : Dis
```

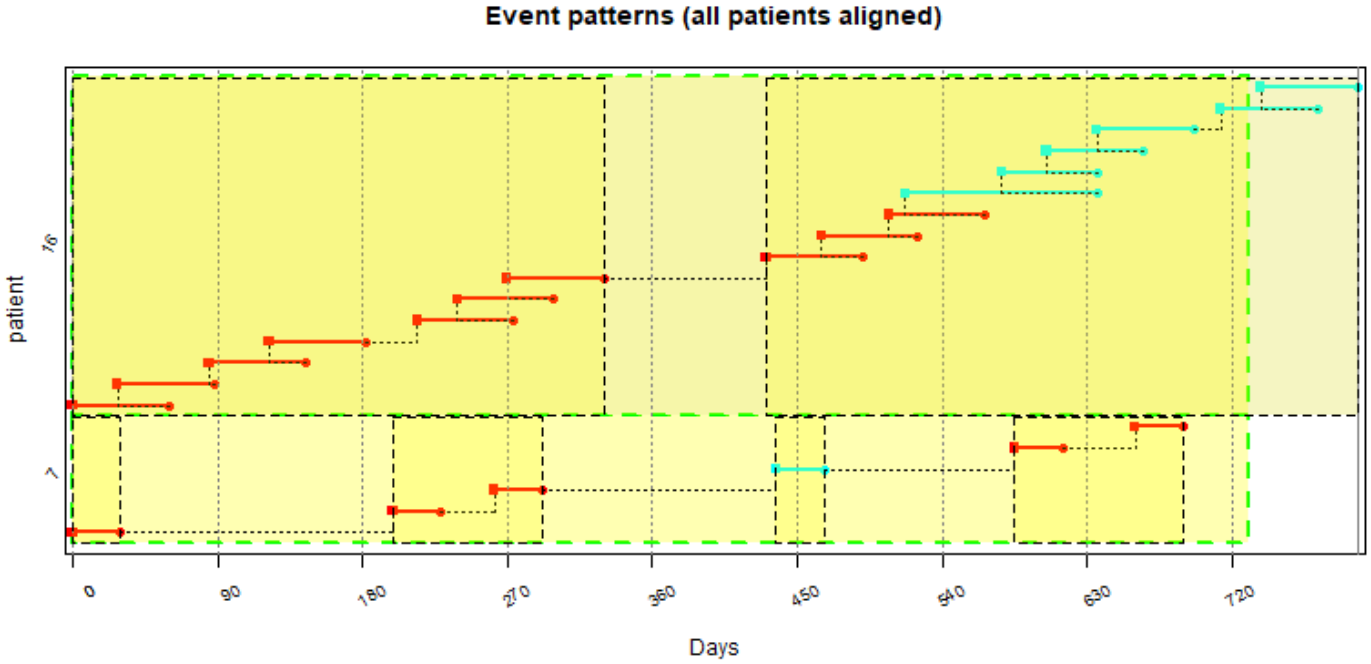
# Persistence

- 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, ...)`

**Error:** undefined columns selected

# Longitudinal analysis

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

**Error:** arguments imply differing number of rows: 1, 8

# Dealing with Polypharmacy

- calculation of one single adherence value: Continuous Aggregated Polypharmacy Score (CAPS)
- Process with 4 components:
  - Grouping of related medication classes into treatment groups
  - Prepare data (adjust observation window, apply carryover, cover special periods, etc.)
  - Aggregate across treatment groups
  - Summarize over time

# Treatment groups

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

((example visualization))

# Aggregation methods

- Periods with ANY treatment available
- Periods with ALL treatments available
- Average of CMAs for individual treatments
- Average of all treatments available per intervall
- Dichotomized: CMA for individual treatments larger than cutoff

((Examples))

# Function CMA_polypharmacy

((show function & example))

# 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