Day 2, Lecture 3

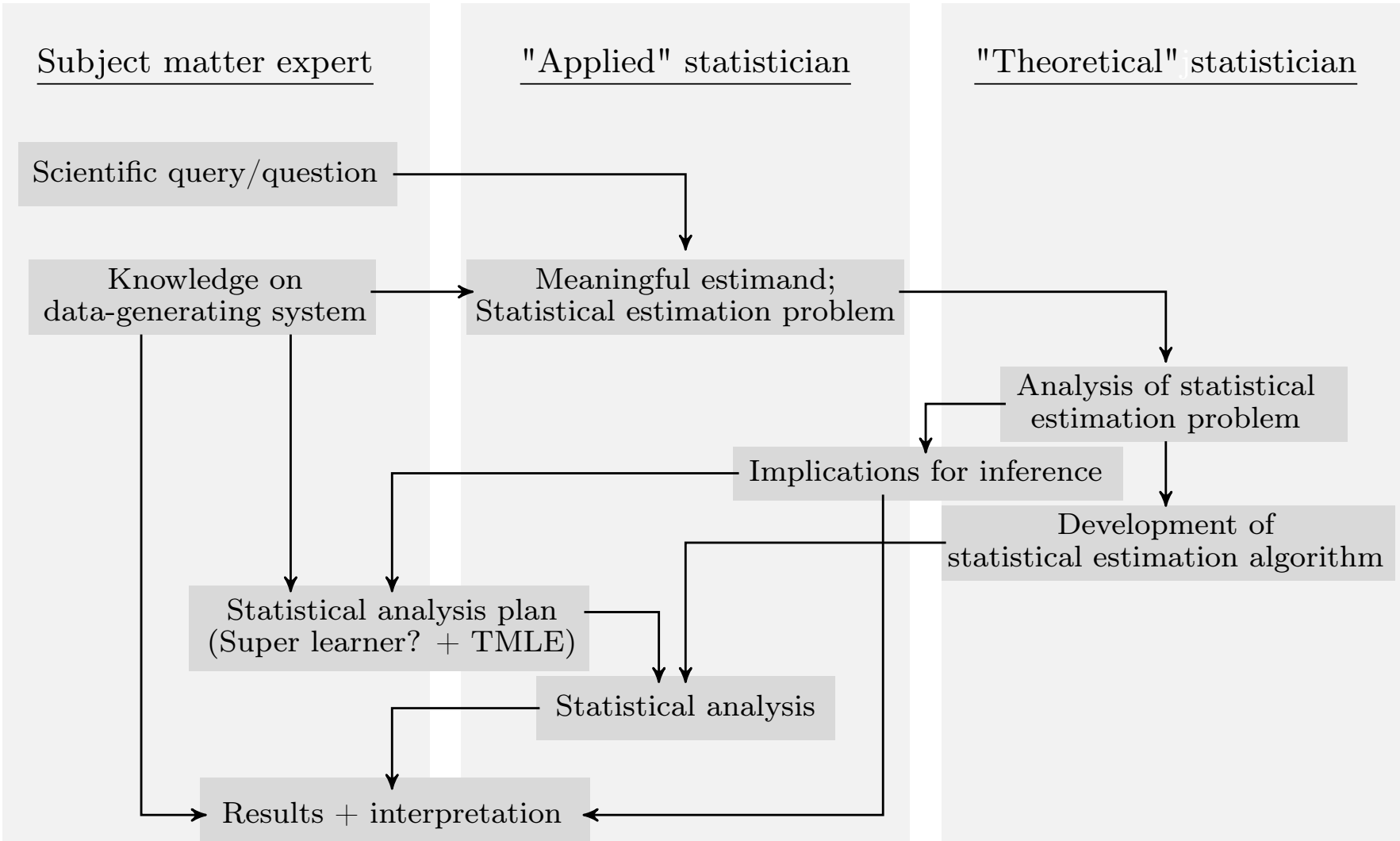
# Time-varying treatments and outcomes

# More general data settings

In this lecture, our goal is to:

1. Identify and discuss challenges and opportunities in time-varying settings, with presence of time-varying treatments, right-censoring and death.
2. Exemplify the use of counterfactuals and dynamic treatment regimes to avoid common biases in the analysis of observational data, highlighting the role of causal inference tools in defining meaningful target parameters.

# Targeted learning framework



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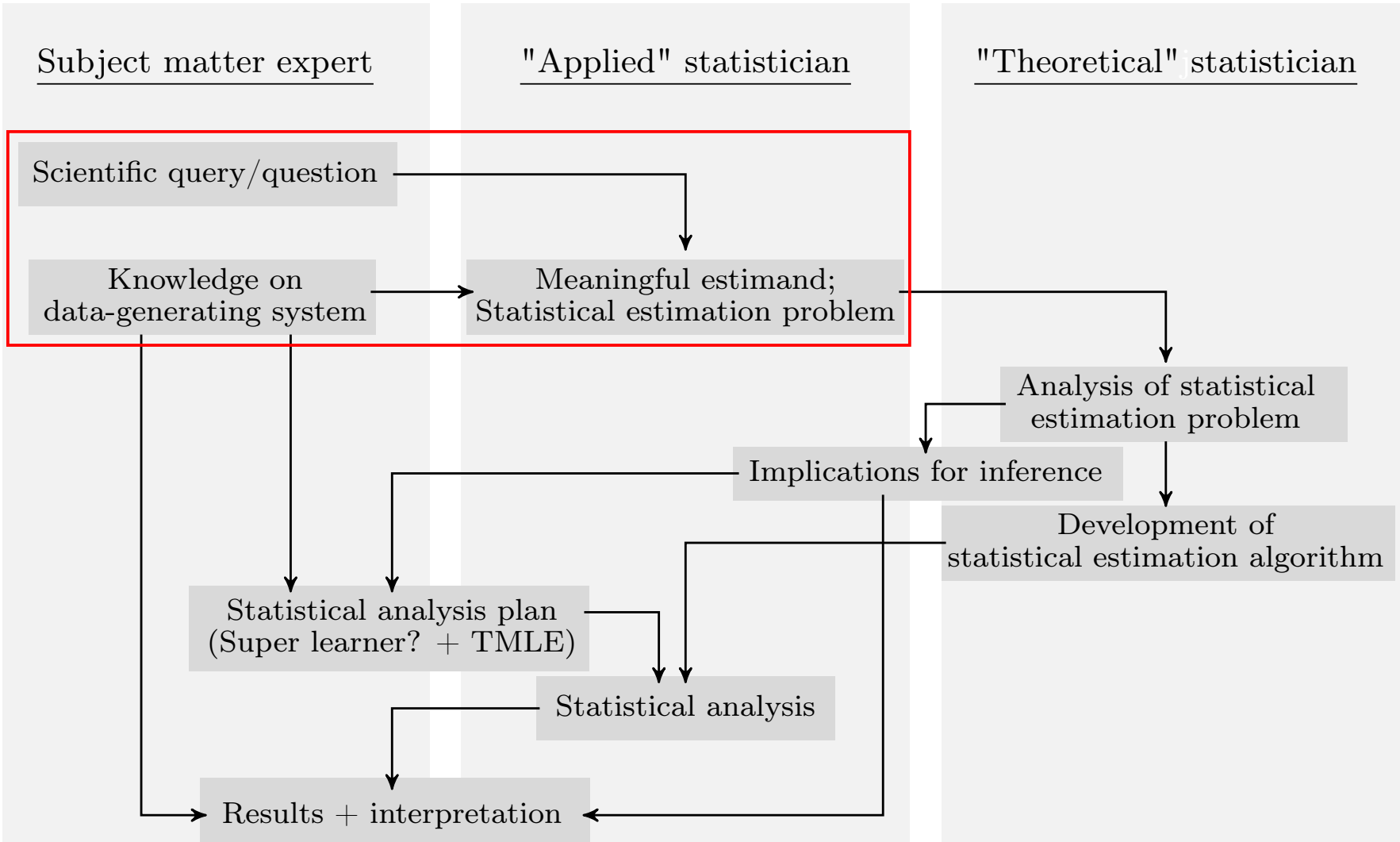

# More general data settings

**Data structure considered so far:**

- $O = (X, A, Y) \in \mathbb{R}^d \times \{0, 1\} \times \{0, 1\}$
- Covariates $X$ are measured before treatment decision $A$ is made
- After treatment decision $A$, the outcome $Y$ is observed

# More general data settings

Longitudinal data structure:

- $O = (X_0, A_0, \ldots, Y_k, D_k, C_k, X_k, A_k, \ldots, Y_K)$
- Outcome process $Y_k$, death status $D_k$, censoring status $C_k$
- Covariates $\bar{X}_K = (X_0, X_1, \ldots, X_K)$ change over time
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# More general data settings

The data setting $O = (X, A, Y)$ may fit many problem settings

- point treatment such as planned cesarian section, or a surgery
- intention-to-treat analysis, e.g., of randomized trials

Right-censoring and death (due to other causes)

- play a big role in medical research
- sometimes in settings with point treatment

The general longitudinal data setting may involve

- treatments changing during follow-up
- right-censoring, time-to-event outcome, competing risks

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**Presence of competing risk events** No one can experience the outcome event of interest if they already died.

**Treatment discontinuation/switching** Subjects may discontinue, never take their assigned treatment, or they could start a different treatment as well.

# More general data settings

These are different types of complications. How we handle them is reflected in our

- formulation of causal parameter;
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This is relevant in observational studies as well as in randomized controlled trials.

# More general data settings

***From day 1***

To answer a causal question, we ideally want to know

Scenario 1 What would have happened to a subject had they been exposed?

Scenario 2 What would have happened to the same subject had they not been exposed?

We imagine a model with two outcomes for each subject:

- a variable $Y^1$ corresponding to scenario 1, and
- a variable $Y^0$ corresponding to scenario 2

= the "counterfactuals" (aka potential outcomes).

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# Time-to-event data settings

1. link between counterfactuals and the concept of "uncensored" event times
2. benefits of counterfactual reasoning (under additional treatment interventions)

# Time-to-event settings

In a "classical" event history (survival) analysis setting:

- $T \in \mathbb{R}_+$ time to event
- we only observe $\tilde{T} = \min(T, C)$, where $C \in \mathbb{R}_+$ is the time to right-censoring, as well as $\tilde{\Delta} = 1\{T \leq C\}$

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So this is really a counterfactual as well.

. . . there is a close link between handling right-censoring and imposing certain treatment interventions.

. . . basically, right-censoring can be viewed as just another time-varying treatment.

# Time-to-event settings

## Observed data with baseline treatment:

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- variables $T^1$ if a subject was assigned treatment, and
- variables $T^0$ if a subject was assigned no treatment

in the absence of censoring.

# Time-to-event settings

Target parameter can be defined for example as an absolute risk difference:

$$\begin{aligned}\Psi(P) &= \mathbb{E}_P[T^1 \leq \tau] - \mathbb{E}_P[T^0 \leq \tau] \\ &\stackrel{*}{=} \mathbb{E}_P[\mathbb{E}_P[T \leq \tau \mid A = 1, X] - \mathbb{E}_P[T \leq \tau \mid A = 0, X]]\end{aligned}$$

The equality $\stackrel{*}{=}$ follows under causal identifiability assumptions.[1]

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This is a meaningful causal parameter.

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# Time-to-event settings

Hazard ratios $\lambda(t \mid A = 1)/\lambda(t \mid A = 0)$, where

$$\lambda(t \mid A = a) = \lim_{h \to 0} \frac{1}{h} P(T \in [t, t + h) \mid T \geq t, A = a),$$

on the other hand:

- suffer interpretational difficulties due to a built-in selection bias from conditioning on different surviving groups.[2]

  [ representing a weighted average of potentially time-varying period-specific hazard ratios, which again may be time-varying due the selection bias. ]

- cannot be interpreted as a causal contrast (despite historically prevalent use in medical research).

[2] Hernán, M. A. (2010). The hazards of hazard ratios. Epidemiology (Cambridge, Mass.), 21(1), 13.

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A competing risk is an event that can happen to subjects/patients, after which the outcome of interest cannot happen.

Whenever the outcome of interest is not all-cause mortality (such as discharge from ICU), there can be competing risks.

A competing risk event is not a right-censoring event. We are not (rarely?) interested in reporting the treatment effect *in the absence of death*.

# Time-to-event settings

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- $T \in \mathbb{R}_+$ time to event, $\Delta = \{1, 2\}$ indicator of event or death
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We define our target parameter for example as an absolute risk difference:

$$\begin{aligned}\Psi(P) &= \mathbb{E}_P[T^1 \leq \tau, \Delta^1 = 1] - \mathbb{E}_P[T^0 \leq \tau, \Delta^0 = 0] \\ &\stackrel{*}{=} \mathbb{E}_P[\mathbb{E}_P[T \leq \tau, \Delta = 1 \mid A = 1] - \mathbb{E}_P[T \leq \tau, \Delta = 0 \mid A = 0]]\end{aligned}$$

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# Time-varying treatments

1. dynamic treatment interventions
2. importance of being clear about what effect is targeted
3. longitudinal framework handling right-censoring with no new ideas (just as another time-varying treatment process)

# Time-varying treatments

General data structure:[3]

$$O = (X_0, A_0, \ldots, Y_k, D_k, C_k, X_k, A_k, \ldots, Y_K)$$

- Outcome process $Y_k$, death status $D_k$, censoring status $C_k$
- ~~Covariates $\bar{X}_K = (X_0, X_1, \ldots, X_K)$ change over time~~
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./figures/fig-time-long-general.pdf

# More general data settings

## This could for example be data from an RCT setting

- $X_0$ are baseline covariates (age, sex, disease/medical history, ...)
- $A_0$ tells us the randomization arm (treatment/placebo)

  ⋮

- $Y_k$ is the status of a primary outcome at the $k$th follow-up visit
- $D_k$ is the survival status (competing risk) at the $k$th follow-up visit
- $C_k$ is the censoring status at the $k$th follow-up visit
- $X_k$ are covariates measured at the $k$th follow-up visit
- $A_k$ is the treatment decision made at the $k$th follow-up visit (adherence to randomization arm)

  ⋮

- Final outcome status $Y_K$

# More general data settings

## Observational data settings

- when data is not randomized (i.e., observational), the discrete time-grid may be a bit artificial.[4]
- but otherwise the difference between observational and experimental (randomized) settings mostly consists in the randomized treatment decision at baseline.

[4] any analysis involves data modeling choices to make it fit this structure.

# Time-varying treatments

Counterfactual outcomes

$$Y_k^{A_0=a_0^*, A_1=a_1^*, \ldots, A_k=a_k^*}, \qquad \text{for,} \quad a_0^*, \ldots, a_K^* \in \{0, 1\}$$

= defined by a sequence of treatment decision rules that we choose.

also called:

- hypothetical treatment interventions
- hypothetical treatment strategies
- hypothetical treatment regimes

# Time-varying treatments

"Static" regimes/interventions/strategies:

- an intervention that sets a specific (deterministic) value for treatment decisions at each time-point.

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- in causal inference literature, "dynamic" is used to refer specifically to interventions depending on (past) covariates,
- but in other (survival) contexts, "dynamic" is used to indicate that the interventions are applied over time.

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- in causal inference literature, "dynamic" is used to refer specifically to interventions depending on (past) covariates,
- but in other (survival) contexts, "dynamic" is used to indicate that the interventions are applied over time.

However, the latter definition of "dynamic" also fits into the former, since interventions are always *only* applied to subjects while alive and at risk. (This is hidden in the notation).

# Time-varying treatments

OBS: usually we further impose "no censoring"

Counterfactual outcomes

$$Y_k^{A_0=a_0^*, A_1=a_1^*, \ldots, A_k=a_k^*, C_0=0, C_1=0, \ldots, C_k=0},$$

for $a_0^*, \ldots, a_K^* \in \{0, 1\}$

Note that:

- if $Y_k = 1\{\tilde{T} \leq t_k, \tilde{\Delta} = 1\}$,
- then $Y_k^{C_0=0, C_1=0, \ldots, C_K=0} = 1\{T \leq t_k, \Delta = 1\}$.

This is an example of a static intervention.

# Time-varying treatments

## Continued treatment and never treated:

- $Y_K^{A_0=1,A_1=1,\ldots,A_k=1}$ = outcome if treated throughout follow-up
- $Y_K^{A_0=0,A_0=0,\ldots,A_k=0}$ = outcome if untreated throughout follow-up

The risk difference

$$\Psi(P) = \mathbb{E}_P[Y_K^{A_0=1,A_1=1,\ldots,A_K=1}] - \mathbb{E}_P[Y_K^{A_0=0,A_0=0,\ldots,A_K=0}]$$

is the effect of being treated versus untreated throughout follow-up.

# Time-varying treatments

## Intention-to-treat (ITT):

- $Y_K^{A_0=1}$ = outcome if assigned to treatment arm
- $Y_K^{A_0=0}$ = outcome if assigned to placebo arm

The risk difference

$$\Psi(P) = \mathbb{E}_P[Y_K^{A_0=1}] - \mathbb{E}_P[Y_K^{A_0=0}]$$

is the effect of being assigned to the treatment versus the placebo arm.

# Hernán et al., 2008

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## Background for the paper:

- An RCT found **greater** risk of coronary heart disease (CHD) in women assigned to hormon therapy than those assigned to placebo.
- Earlier observational studies had found **reduced** risk of CHD among hormon users.

The difference has been explained as due to unobserved confounding.

Conclusion: *Cannot use observational data for causal inference?*

# Hernán et al., 2008

The **RCT results** were based on an intention-to-treat[5] (ITT) analysis

- trial participants were randomized to hormone treatment initiation or placebo at baseline

[5] Subjects are analyzed irrespective of their actual adherence to their assigned randomization arm.

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- trial participants were randomized to hormone treatment initiation or placebo at baseline

Whereas the **observational analyses** were based on a comparison of two groups:

- "Current users"
- "Never users"

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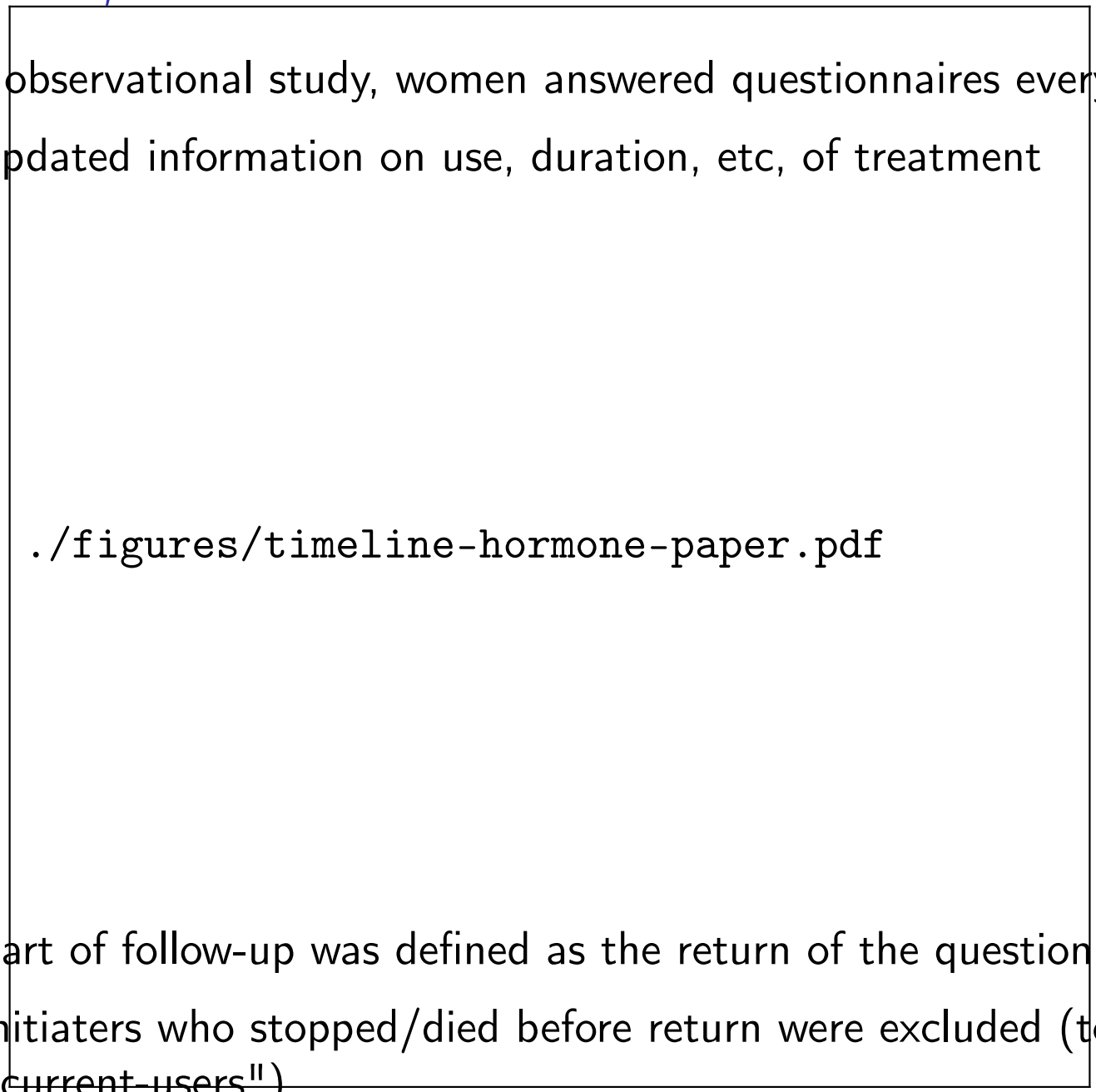
# Hernán et al., 2008

- In the observational study, women answered questionnaires every two years
  - updated information on use, duration, etc, of treatment

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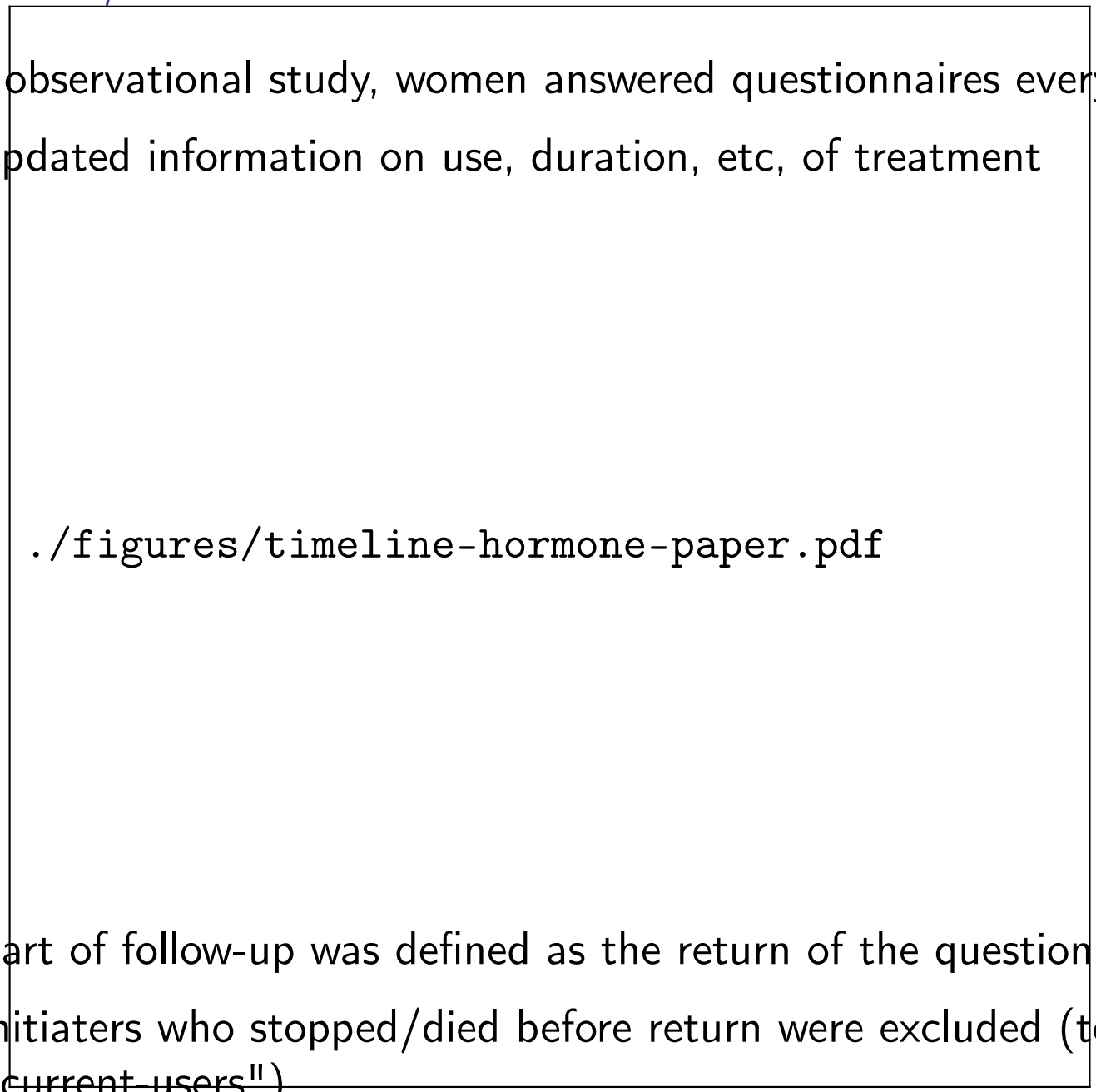


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# Hernán et al., 2008

Hernán et al. reanalyze the observational data and show in their paper that:

1. When using the current user design (including the selection bias), the result of a **beneficial** effect from earlier observational studies was reproduced.
2. *When imitating the analysis of the randomized trial*, targeting the ITT effect, the result that the treatment has a **harmful** effect was reproduced.

The discrepancy found in the previous analyses had nothing to do with confounding.

Many such biases can be avoided by explicitly defining a "target experiment", and corresponding counterfactuals.

# Hernán et al., 2008

The current user strategy does not allow us to answer a causal question

1. The inclusion criterion is defined after initiation of the treatment strategy.
2. The current user strategy changes over the follow-up;
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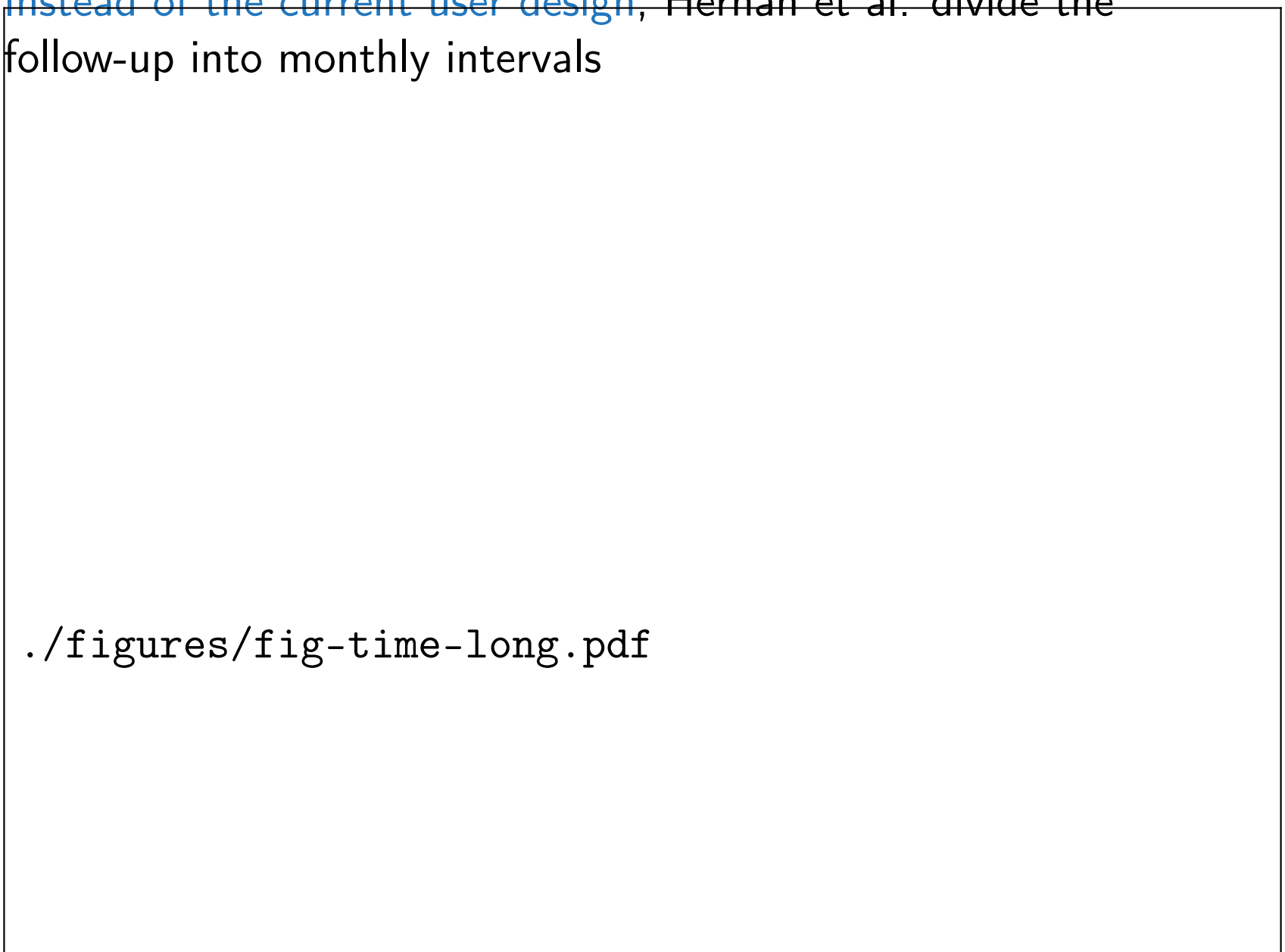
The current user strategy is an attempt to estimate the effect of treatment *usage* (contrary to initiation)?

- Most appropriate summary measure would be the adherence-adjusted effect (comparing 'always treated' to 'never treated')?

# Hernán et al., 2008

~~Instead of the current user design~~, ~~Hernán et al. divide the~~ follow-up into monthly intervals



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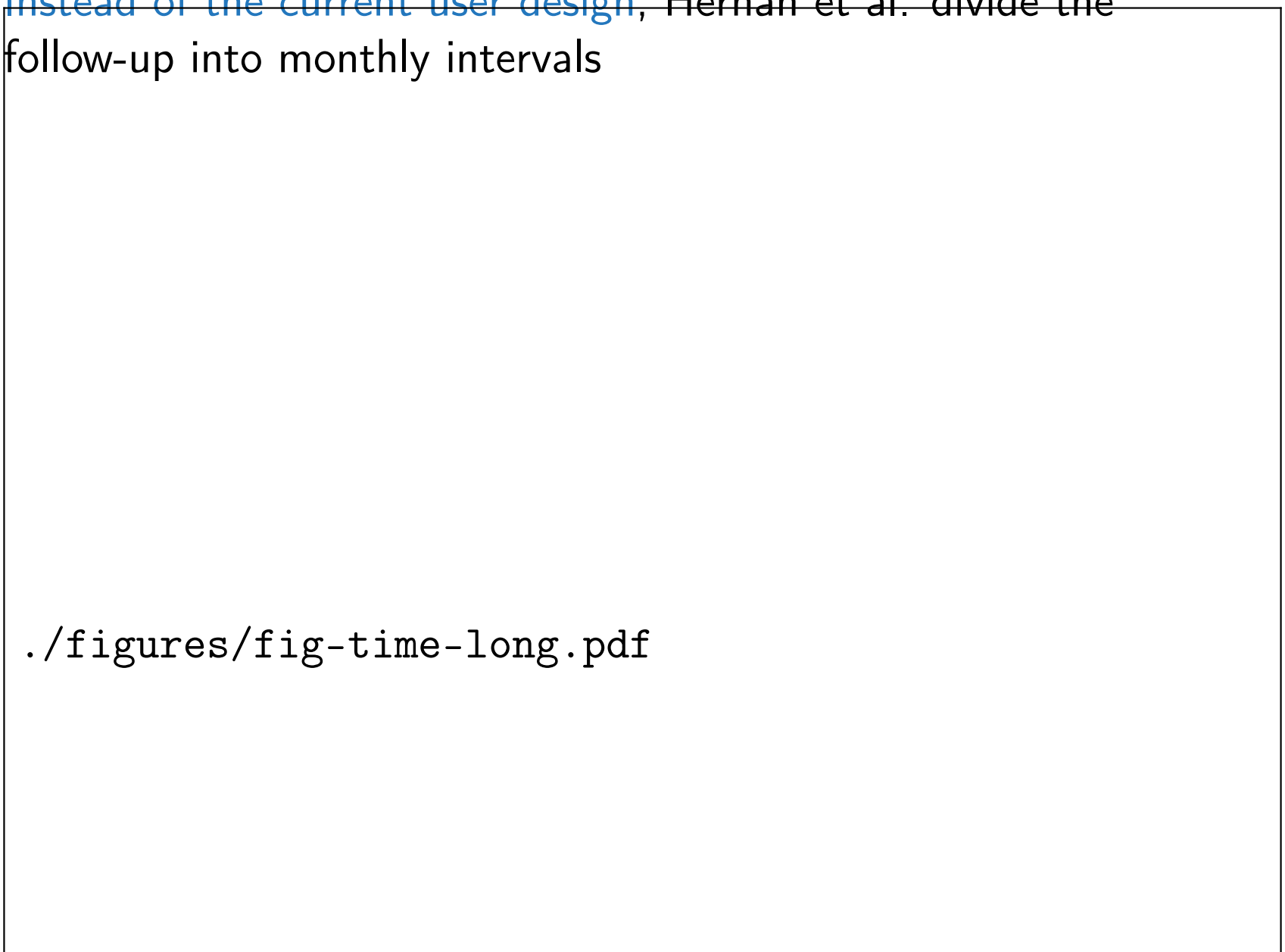

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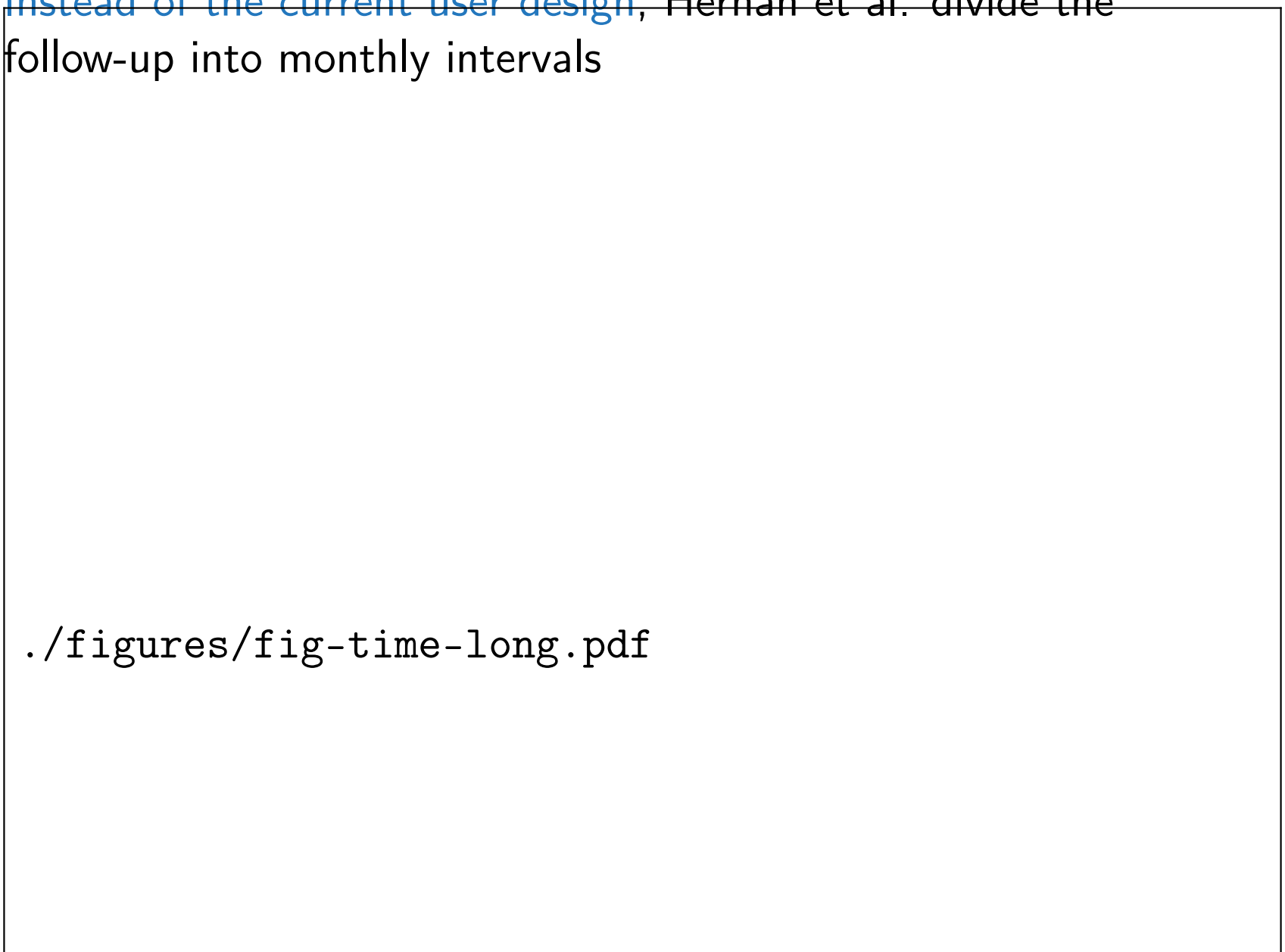

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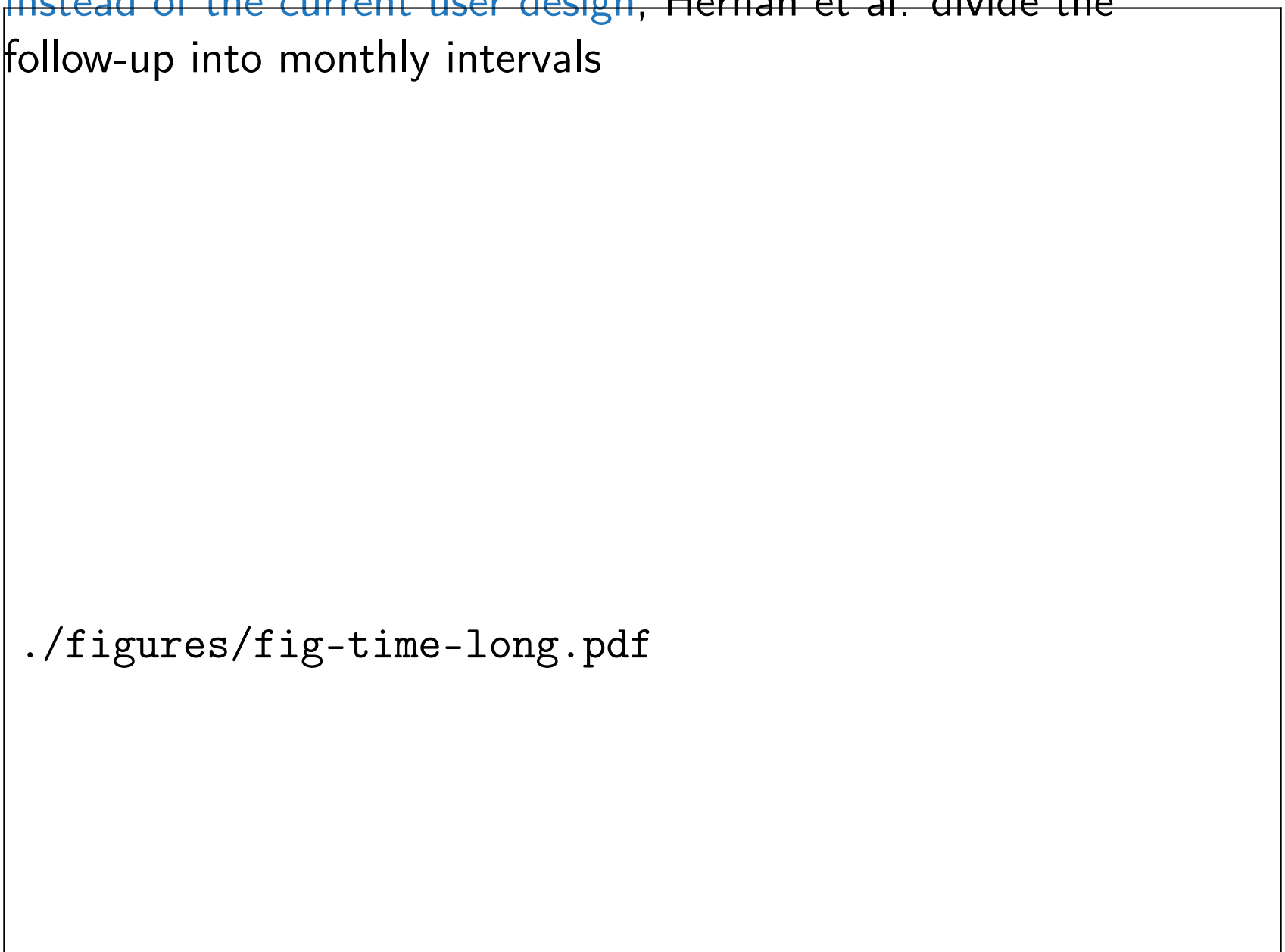

# Hernán et al., 2008

1. When using the current user design, the result of a **beneficial** effect from earlier observational studies (due to selection bias) was reproduced.
2. When imitating the analysis of the randomized trial, targeting the ITT effect, the result that the treatment has a **harmful** effect was reproduced.

# Hernán et al., 2008

1. When using the current user design, the result of a **beneficial** effect from earlier observational studies (due to selection bias) was reproduced.
2. When imitating the analysis of the randomized trial, targeting the ITT effect, the result that the treatment has a **harmful** effect was reproduced.
3. A **larger harmful** effect was found when targeting the effect of 'continued exposure', i.e., the adherence-adjusted effect.

# Practical 2: Simulating longitudinal data

As part of the exercise we will —

1. Simulate (simple) longitudinal data with time-varying treatment and covariates;
2. Approximate the true effect of different longitudinal interventions by simulating counterfactuals.
3. Illustrate various issues in interpreting hazard ratios.
4. Illustrate the benefits of targeting dynamic effects in survival settings.

The exercise is described in detail in: **day3-practical2.pdf**.