

## Supplement to “CITIES: Clinical Trials With Intercurrent Events Simulator”

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### 1 Supplementary Material

To access the Shiny application, simply use the following link (<https://hakeemwahabapp.shinyapps.io/cities/>) where the default settings are set to the ones used in Section 2. The file `app.R` contains all the script used for the R shiny app. Although all CITIES outputs are in color, they appear as greyscale in this manuscript for the purposes of publication. The CITIES packages is available on CRAN (<https://cran.r-project.org/web/packages/cities/index.html>). A vignette (`CITIES_demo.Rmd`) is provided to replicate all output in this manuscript, and an additional example for custom covariates and covariances. Further, all code is publicly available on github (<https://github.com/hakeemwahab/cities>).

For the custom covariates and covariances example in the Rshiny app, users can use the attached csv file “`custom_covariate_3arm.csv`” for the custom covariates and “`custom_covariance.csv`” for the custom covariances (for all arms). The former is a csv containing 2 continuous covariates simulated from a standard normal and one binary covariate sampled from a bernoulli with probability 0.5 per subject with column names specified, while the latter contains a 5×5 covariance matrix without any column and row names. Note that users can have different custom covariances for each arm as well. For this example, you need to specify the following:

1. a vector of length 5 for the “Time Indices”, e.g. 0, 12, 24, 48, 55.
2. a total of 300 subjects across all arms for the “Arms” input, e.g. 150, 50, 100 for arms 1, 2, and 3 respectively.
3. the “Baseline Covariate Coefficients” should all be of length 3 since we have 3 columns or covariates in the supplied covariance csv file, e.g. 1.25, 1.25, 1 for all arms.

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4. the "Means" should all be of length 5, and all have the same initial baseline value. For a 3-arm example, you could supply "0, 0, 0, 0, 0" for arm 1, and "0, 0.2, 0.4, 0.6, 0.8" for arms 2 and 3 respectively.

## 1.1 Diabetes Clinical Trial Figures

CITIES	Mean Treatment Response Settings	LoE & EE	Admin & AE	Average Treatment Effects
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**No. of Datasets**

**Reference Group**

**Threshold (leave empty if not binary)**

**Time Indices**

**Treatment Policy:**

**Upload Custom Covariance?**

☐ Yes

☒ No

**Upload Custom Covariates?**

☐ Yes

☒ No

Add Arm Remove Arm

**Size**

**Arm 1**

**Arm 2**

**Stdev**

**Arm 1**

**Arm 2**

**Baseline Covariate Coefficients**

**Arm 1 (Only 2 values)**

**Arm 2 (Only 2 values)**

**Mean**

**Arm 1**

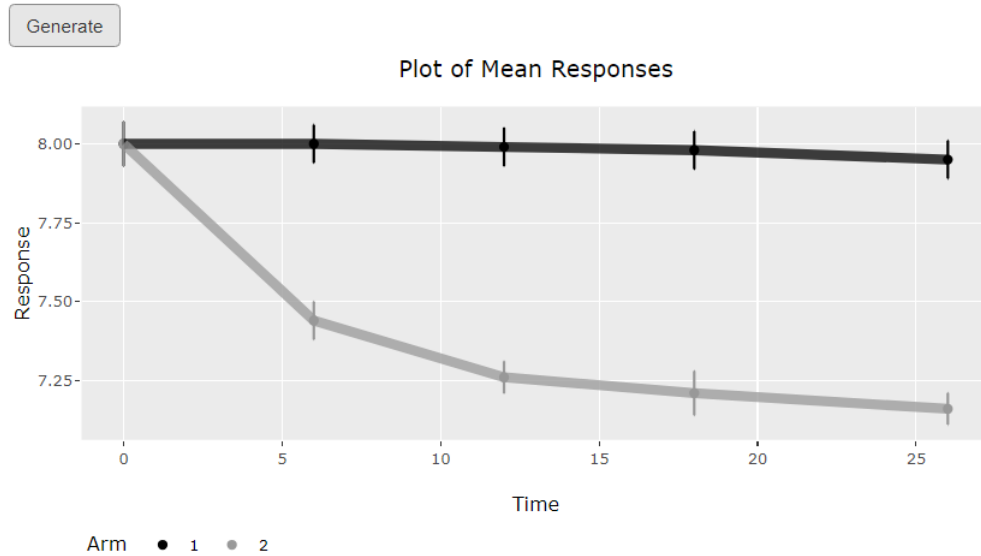
**Arm 2**

**AR(k)**

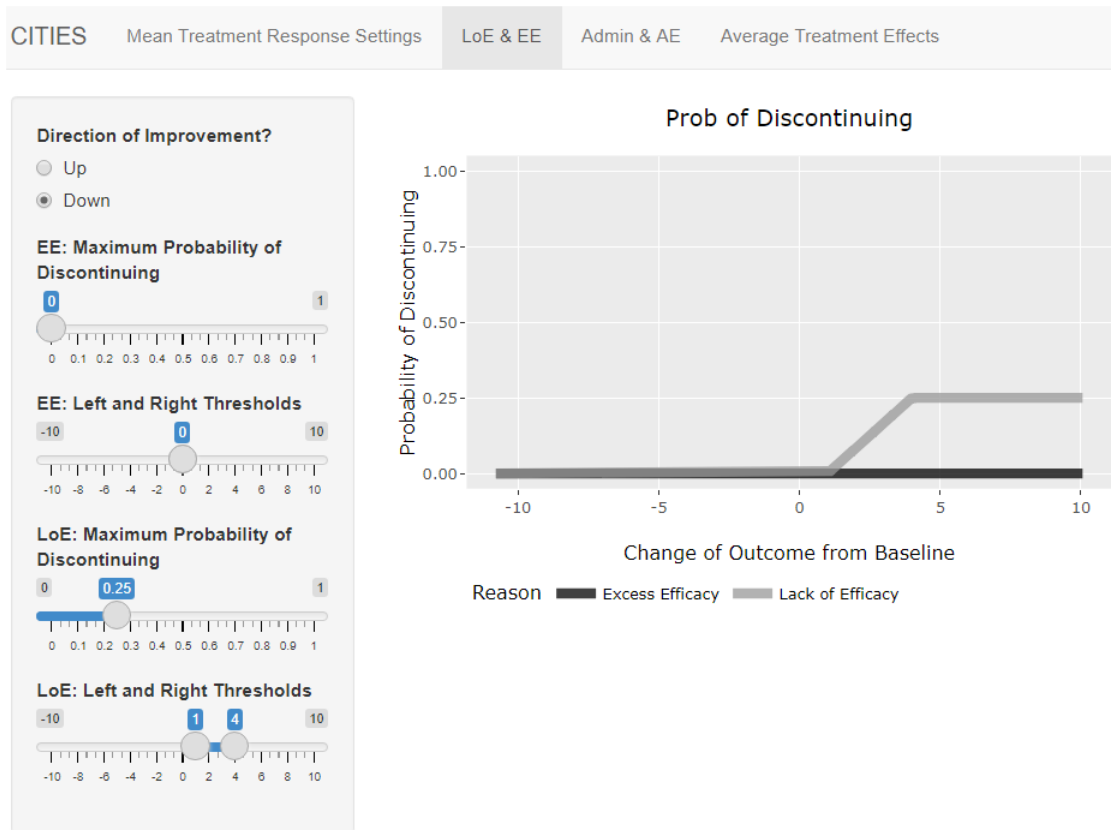
**Arm 1**

**Arm 2**

**Figure S1** The Mean Treatment Response Settings tab in CITIES for the Diabetes case study.



**Figure S2** The Mean Treatment Response Settings Profile in CITIES for the Diabetes case study.



**Figure S3** The LoE & EE tab in CITIES for the Diabetes case study.



Figure S4   The Admin & AE tab in CITIES for the Diabetes case study.

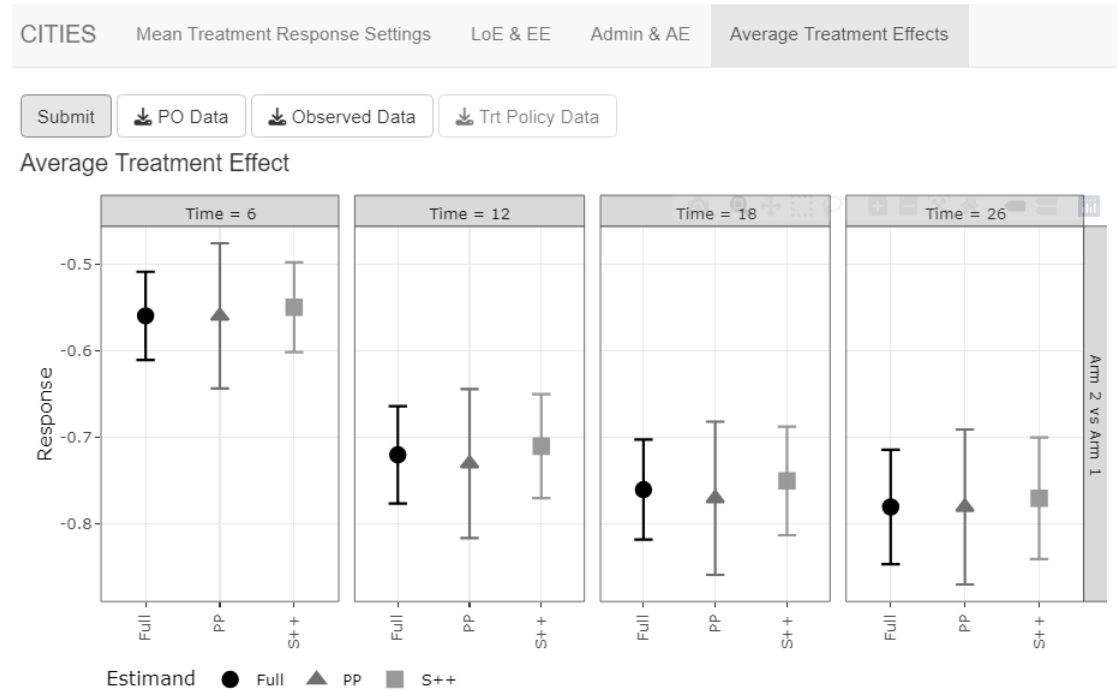
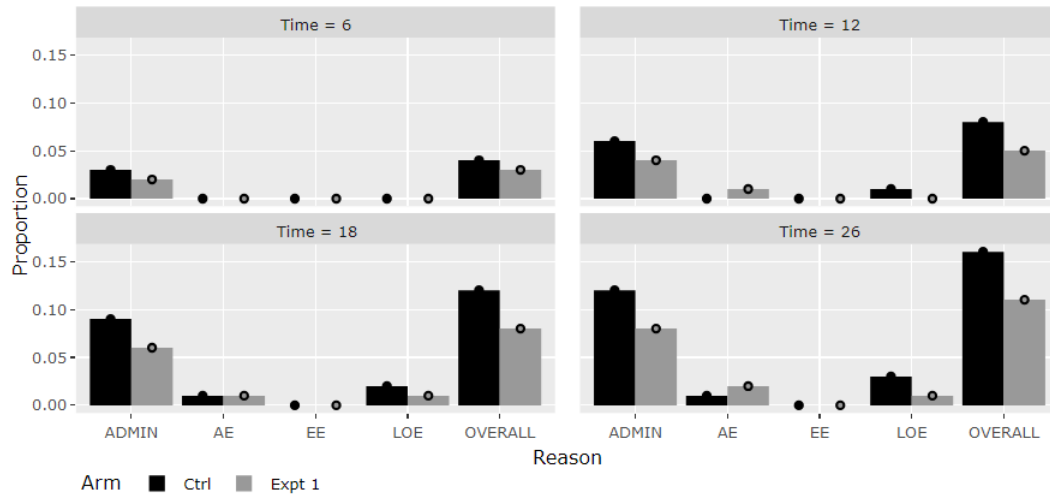


Figure S5   Treatment effect profiles for the three estimands in CITIES for the Diabetes case study. Note that the "Trt Policy Data" is greyed out, since the Treatment Policy options were not elected in Figure S1.

## Cumulative Proportion Discontinued



**Figure S6** Percentages of treatment discontinuations, and the corresponding ICEs in CITIES for the Diabetes case study.

1.2 Alzheimer’s Clinical Trial Figures

CITIES

Mean Treatment Response Settings

LoE & EE

Admin & AE

Average Treatment Effects

No. of Datasets

100

Reference Group

1

Threshold (leave empty if not binary)

Time Indices

0,12,24,36,52,64,76

Treatment Policy:

Nothing selected

Upload Custom Covariance?

Yes

No

Upload Custom Covariates?

Yes

No

Add Arm

Remove Arm

Size

Arm 1

126

Arm 2

131

Stdev

Arm 1

10

Arm 2

10

Baseline Covariate Coefficients

Arm 1 (Only 2 values)

NA

Arm 2 (Only 2 values)

NA

Mean

Arm 1

106, 105.87, 104.81, 102.85, 99.31, 97.67, 95.97

Arm 2

106, 106.35, 106.06, 105.29, 102.98, 101.09, 99.17

AR(k)

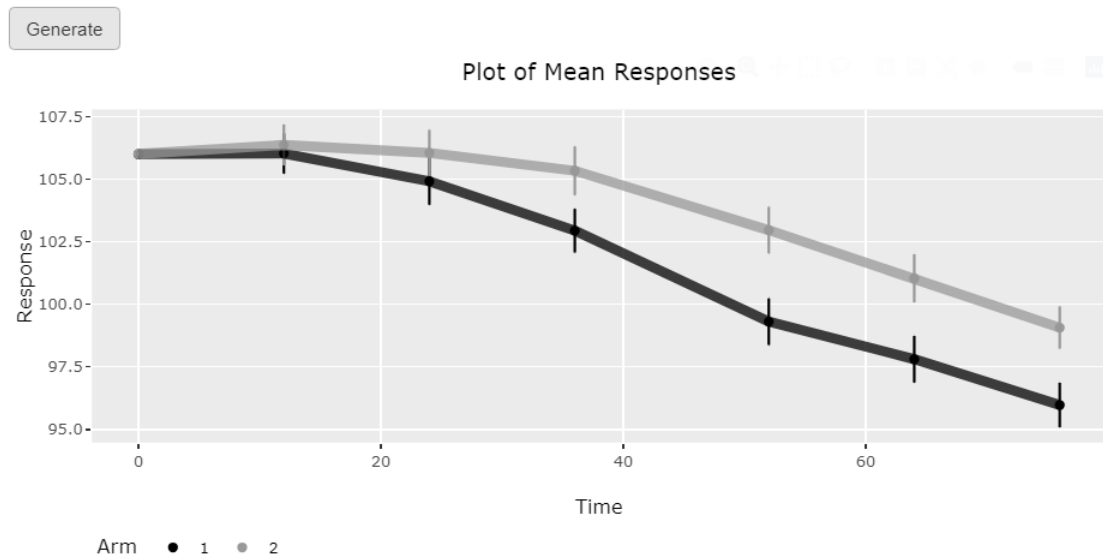
Arm 1

0.5

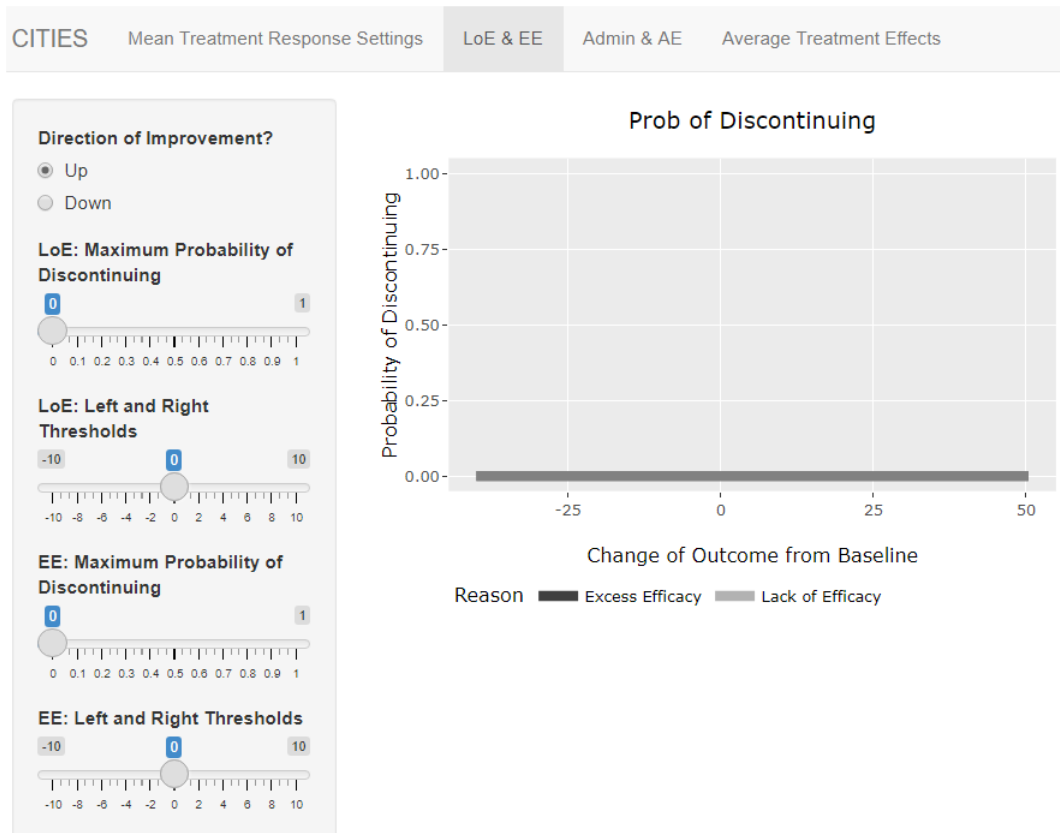
Arm 2

0.5

Figure S7 The Mean Treatment Response Settings tab in CITIES for the Alzheimer’s case study.



**Figure S8** The Mean Treatment Response Settings Profile in CITIES for the Alzheimer's case study.



**Figure S9** The LoE & EE tab in CITIES for the Alzheimer's case study.



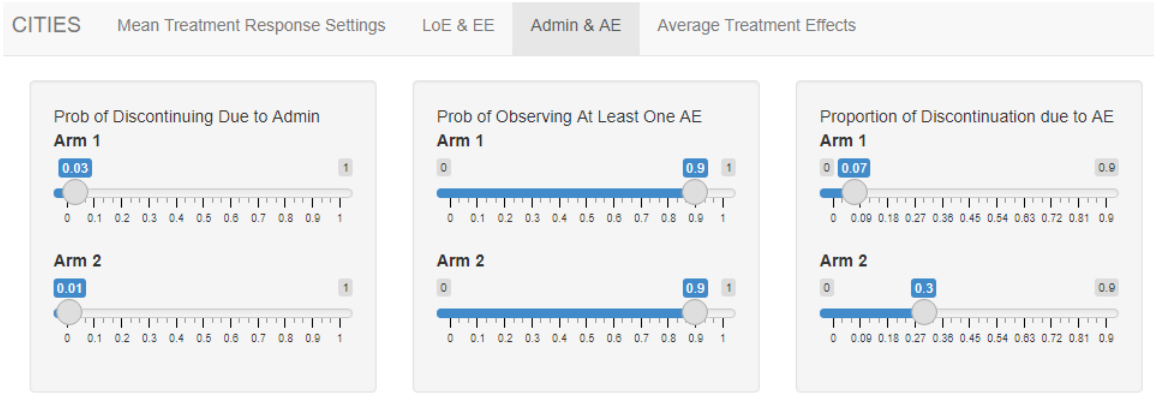


Figure S10 The Admin & AE tab in CITIES for the Alzheimer’s case study.

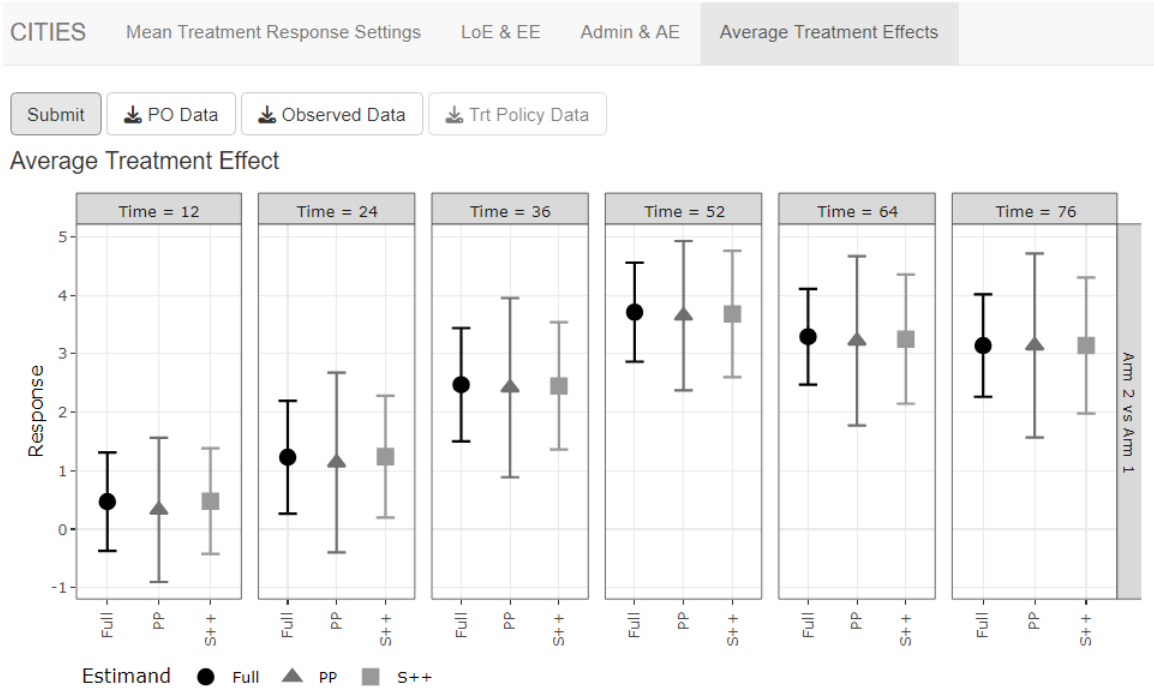
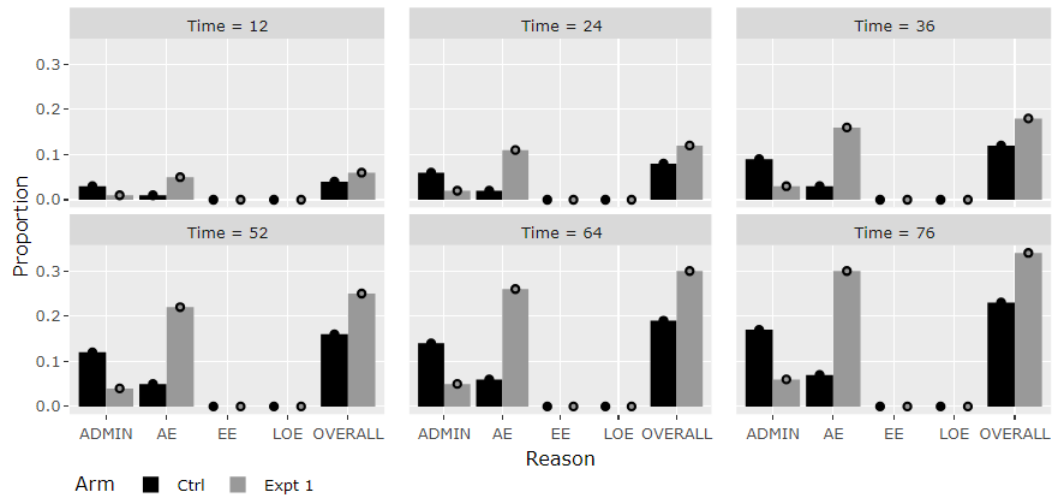


Figure S11 Treatment effect profiles for the three estimands in CITIES for the Alzheimer’s case study. Note that the ”Trt Policy Data” is greyed out, since the Treatment Policy options were not elected in Figure S7.

## Cumulative Proportion Discontinued



**Figure S12** Percentages of treatment discontinuations, and the corresponding ICEs in CITIES for the Alzheimer's case study.