Code:

- Section 2.1 & Appendix F.1: Bivariate normality of surrogate and true effect sizes
  - Code: Bivariate_Check.R
  - Data: Bivariate Normal Check.csv
  - Figures: Figure 7
  - Results: "the Henze-Zirkler test failed to reject the null hypothesis of bivariate normality for 22 of the 30 pairs ($p>0.05$)," and "average effect sizes are indeed close to 0 in practice"
- Section 3.2:
  - Code: regions_tte.R
  - Figures: Figure 2
  - Results: an example of regions where Type C comparative statics behave differently
- Section 3.3: Numerical simulation
  - Code: numericalSimulations.R
  - Helper code: Type1Type2SurvivalFunc_discounting.R
  - Data: params_comp_stats_plot_int.csv
  - Figures: Figure 3
  - Results: Identification of 2 regions where our trial design provides the most benefit compared to the best-performing single-endpoint design
- Section 3.3: Scatterplot of study-level vs. individual level correlations for different true and surrogate outcome pairs
  - Code: IPD_surrogate_correlations.R
  - Data: IPD_surrogate_correlations.csv
  - Figures: Figure 4
  - Results: identifying which surrogate/true outcome pairs fall into our areas of special interest (second to last paragraph of section).
- Section 4.1
  - Code: summaryTable.R
  - Data: MBCinfo.csv, OS_HR.csv, PFS_HR.csv, TTP_HR.csv
  - Tables: Table 4.1
- Section 4: Main simulation from Kaplan-Meier curves
  - Code: mainSim.R
  - Helper code: Parameterizing_prior_Simulation.R
  - Data: MBC data (folder)
  - Figures: Figure 5, Figure 6
  - Tables: Table 4.3, Table 4.2 (first 3 and last 10 entries)
  - Results: Values in section 4.1 for $\sigma_{0S}, \sigma_{0T}, \rho_0$, and optimal trial design parameters (from helper code). All results in section 4.3
- Appendix E: expected successes
  - Code: expectedSuccess.R
  - Results: Results in E.2 Numerical Simulations
- Appendix F.2:
  - Code: Plot_MBCtrialInfo_OverTime.R
  - Data: OS_HR.csv
  - Figures: Figure 8

    - Results: All results in appendix F.2
- Appendix G: robustness checks
    - Code: misspecificationSensitivityAnalysis.R
    - Figures: Figure 9, Figure 10
    - Results: All results in appendix G

Data dictionary:

- Bivariate Normal Check.csv
  Compiled from scraping data from 30 meta-analyses for different diseases with time-to-event outcomes.
  - Paper: id for meta-analysis it comes from (first 4 letters of first author's last name + mmyy of publication)
  - Disease: disease this trial is looking to treat
  - TRUE: which true outcome measured by the trial
  - Surrogate: which surrogate outcome measured by the trial
  - Trial: Trial name/id
  - Patients Treatment: treatment group size
  - Patients Control: control group size
  - HR Surrogate: the hazard ratio measured for the surrogate outcome
  - CI Surrogate: confidence interval for HR Surrogate
  - HR True: the hazard ratio measured for the true outcome
  - CI True: confidence interval for HR True
- IPD_surrogate_correlations.csv
  Compiled from scraping data from meta-analyses for different diseases with time-to-event outcomes. To collect these papers, we searched PubMed for meta-analyses of surrogate time-to-event endpoints and wound up with 80 papers. Some of these papers contain multiple surrogate endpoints for the same disease.
  - Paper: id for meta-analysis paper data pulled from (first 4 letters of first author's last name + mmyy of publication)
  - Disease: disease analyzed
  - Surrogate: surrogate outcome
  - End Outcome: true outcome of interest
  - Numerical Relationship to OS (Rho_I): reported individual level correlation (if included)
  - Rho_I 95% CI: reported confidence interval for individual level correlation (if included)
  - Treatment Effect Correlation (Rho_0): reported study level correlation (if included)
  - Rho_0 95% CI: reported confidence interval for study level correlation (if included)
  - Notes: any additional concerns
- params_comp_stats_plot_int.csv
  Set of different parameters we want to test for our numerical simulations. Includes blank columns to be filled out during the simulation runs.
  - rho0: study-level correlation for this simulation
  - rhoI: individual-level correlation for this simulation
  - s0S: study-level surrogate effect size variance for this simulation
  - s0T: study-level true effect size variance for this simulation
  - lCT: control arm's exponential distribution rate for true outcome
  - cw: cost of waiting ($/month)
  - All other variables are place-holders for the output of running a clinical trial
- MBC data:

All data is pulled manually from repository of 1,865 studies of MBC drug therapies collected by Silberholz et al. (2019),which is publicly available at http://www.cancertrials.info

- KM curves
  - .png files: one for each Kaplan Meier curve found in the papers in the MBC repository. Labeled as "paper id"_"outcome".png
  - .xml files: one for each arm in every Kaplan Meier curve .png file. Labeled as "paper id"_"outcome"_"arm id".xml
- MBC_data_final.csv:
  Information collected for each arm of each trial in MBC repository
  - Unique_ID: "id of paper this arm comes from"_"arm specific id"
  - Arm.Name: short description of trial arm
  - Randomized: whether or not this was a randomized trial
  - KM_Curves: Yes/No, whether this paper contained KM curves for this arm
  - N_Patient: number of patients in this arm of the trial
  - OS: median overall survival for this arm of this trial
  - OS_Comp: OS hazard ratio and confidence interval for this trial (if recorded in paper; only recorded in one arm per trial)
  - OS_pval: p-value for hazard ratio (if recorded in paper; only recorded in one arm per trial)
  - OS_events: total number of overall survival events seen in this trial arm (if recorded in paper)
  - OS_KM: file name for xml file of extracted overall survival KM curve for this treatment arm
  - OS_Note: anything else deemed important by RAs
  - TTP: median time-to-progression for this arm of this trial
  - TTP_Comp: TTP hazard ratio and confidence interval for this trial (if recorded in paper; only recorded in one arm per trial)
  - TTP_pval: p-value for hazard ratio (if recorded in paper; only recorded in one arm per trial)
  - TTP_events: total number of time-to-progression events seen in this trial arm (if recorded in paper)
  - TTP_KM: file name for xml file of extracted time-to-progression KM curve for this treatment arm
  - TTP_Note: anything else deemed potentially important by RAs
  - PFS: median progression-free survival for this arm of this trial
  - PFS_Comp: PFS hazard ratio and confidence interval for this trial (if recorded in paper; only recorded in one arm per trial)
  - PFS_pval: p-value for hazard ratio (if recorded in paper; only recorded in one arm per trial)
  - PFS_events: total number of progression-free survival events seen in this trial arm (if recorded in paper)
  - PFS_KM: file name for xml file of extracted progression-free survival KM curve for this treatment arm
  - PFS_Note: anything else deemed important by RAs

- MBC_phase.csv
  Additional information about each arm of each trial in the MBC repository
  - Unique_ID: “id of paper this arm comes from”_”arm specific id”
  - Phase: I/II, II, or III indicating whether this is a phase I/II trial, a phase II trial, or a phase III trial
  - Arm_Type: control or experiment, denoting whether this is the control or experiment arm

- MBCinfo.csv
  Data is pulled manually from each arm of the 89 trials which are used to create the 93 randomized comparisons in our simulation. These trials can be found in the repository of studies of MBC drug therapies collected by Silberholz et al. (2019).
  - Unique_ID: identification for paper and study arm
  - ECOG_0: proportion of patients with level 0 ECOG performance status (Eastern Cooperative Oncology Group (ECOG) performance status measures patient level of functioning on a scale from 0 (active) to 5 (dead))
  - ECOG_1: proportion of patients with level 1 ECOG performance status
  - ECOG_2: proportion of patients with level 2 ECOG performance status
  - ECOG_3: proportion of patients with level 3 ECOG performance status
  - ECOG_4: proportion of patients with level 4 ECOG performance status
  - N_Patient: number of patients in this arm of this study
  - Pub_Year: year trial was published
  - FRAC_MALE: fraction of participants in study arm who were male
  - AGE_MED: median age of participant in study arm
  - Prop_Visceral: proportion of patients with visceral disease (particularly severe MBC spread to internal organs)
  - OS: median overall survival reported in this arm
  - PFS: median progression free survival reported in this arm
  - Arm.Name: id for treatment given in this arm
  - Title: title of the published study for this trial
  - Arm_Type: experiment/control to delineate whether this arm was the experiment or control arm
  - Rand_Group: for multi-arm trials, there are multiple randomized comparisons; this column delineates which arms were compared to one another.

- OS_HR
  Data is pulled manually from the subset of studies from the repository of studies of MBC drug therapies collected by Silberholz et al. (2019) that contain estimates of overall survival hazard ratios.
  - IDexp: id for experimental arm
  - IDctl: id for control arm
  - rcode: identification number for paper
  - effect: HR effect size estimate for overall survival from paper
  - effectSD: standard deviation for effect size estimate

- PFS_HR
  Data is pulled manually from the subset of studies from the repository of studies of MBC drug therapies collected by Silberholz et al. (2019) that contain estimates of progression free survival hazard ratios.

    - IDexp: id for experimental arm
    - IDctl: id for control arm
    - rcode: identification number for paper
    - effect: HR effect size estimate for progression free survival from paper
    - effectSD: standard deviation for effect size estimate
- TTP_HR
  Data is pulled manually from the subset of studies from the repository of studies of MBC drug therapies collected by Silberholz et al. (2019) that contain estimates of time to progression hazard ratios.
    - IDexp: id for experimental arm
    - IDctl: id for control arm
    - rcode: identification number for paper
    - effect: HR effect size estimate for time to progression from paper
    - effectSD: standard deviation for effect size estimate