SUPPLEMENTAL MATERIAL
SUPPLEMENTAL METHODS

Overall Life Expectancy Calculations for Systolic Blood Pressure Intervention Trial (SPRINT) Participants

Our approach allows an estimate overall life expectancy for each SPRINT participant (Figure S1). However, the flexible parametric survival models were developed specifically for SPRINT participants (Tables S1 and S2) and are not necessarily generalizable to other populations. We describe the steps required to calculate overall life expectancy and provide an example applying them to a 55-year-old female with the characteristics shown in Table S3. We calculate the estimated survival for the first example SPRINT participant (Table S4) and present a second example SPRINT participant (a 70-year-old male, Tables S3 and S4) for comparison.

The following steps are used to calculate life expectancy for each SPRINT participant (corresponding to Stages 2-4 in Figure S1):

1. Calculate the probability of surviving each year of follow up during the in-trial period (Formula S1 and Table S1)
2. Calculate the survival probability for each year of follow up during post-trial period, conditioned on surviving the in-trial period (Formula S2 and Table S2)
3. Combine the in- and post-trial period survival probabilities and calculate life expectancy as the area under the overall survival probability curve

**Step 1: Calculate the probability of surviving each year of follow up during the in-trial period**

In Step 1, we first modeled in-trial survival in SPRINT participants using a time-based flexible parametric survival model.
Formula S1. Probability of surviving at a given year of follow up during the in-trial period.

\[ S(t | x_i) = \exp \left( -\exp \left( \gamma_0 + \gamma_1 z_1 + \ldots + \gamma_{K-1} z_{K-1} + x_i \beta \right) \right) \]

where:

\[ \gamma_0 + \gamma_1 z_1 + \ldots + \gamma_{K-1} z_{K-1} \]

is the log baseline cumulative hazard function estimated using restricted cubic splines of log(time) with K knots; the knot locations were at 25th, 50th, and 75th percentiles of the distribution of uncensored log event times.

The restricted cubic spline variables \( z_j \) are calculated as follows:

\[ z_1 = x \]

\[ z_j = (x - k_j)^3 - \phi_j (x - k_1)^3 - (1 - \phi_j) (x - k_K)^3 \quad j = 2, ..., K - 1 \]

\[ \phi_j = (k_K - k_j)/(k_K - k_1) \]

\( x_i \) is the covariate matrix

\( \beta \) is the beta coefficients from the model based on the in-trial period (Table S2)

To calculate the probability of survival at one year of follow up during the in-trial period in our 55-year-old female example SPRINT participant:

- Calculate the log baseline cumulative hazard (i.e., \( \gamma_0 + \gamma_1 z_1 + \ldots + \gamma_{K-1} z_{K-1} \)) at time \( t = 1 \) year and the 25th, 50th, and 75th percentiles of the distribution of uncensored log event times, (Table S1):
  - Constant = -11.2238
  - Parameter 1 of the restricted cubic spline = 0
  - Parameter 1 beta coefficient = 0.9355
  - Parameter 2 of the restricted cubic spline = -4.48
  - Parameter 2 beta coefficient = -0.1033

\[ S(Year \ 1 | x_i) = \exp \left( -\exp \left( -11.2238 + 0.9355 \times 0 + -0.1033 \times -4.48 + x_i \beta \right) \right) \]
\[ S(Year \ 1|x_i) = \exp (-\exp (-10.7610 + x_i\beta)) \]

- Calculate the model coefficients multiplied by the individual’s characteristics \((x_i\beta)\) (Tables S1 and S3)

\[ S(Year \ 1|x_i) = \exp (-\exp (-10.7610 + 4.7262)) = 0.998 \]

**Step 2: Calculate the survival probability for each year of follow up during post-trial period, conditioned on surviving the in-trial period**

In Step 2, we first modeled post-trial survival in SPRINT-eligible National Heart, Lung, and Blood Institute Pooled Cohorts Study (NHLBI-PCS) participants using an age-based flexible parametric survival model. We then applied the model estimates back to SPRINT participants to estimate their post-trial survival.

Formula S2. Probability of surviving at a given year of follow up during the post-trial period, conditioned on surviving the in-trial period.

\[
(1) \quad S(Age|x_i) = \exp (-\exp (\gamma_0 + \gamma_1z_1 + ... + \gamma_{K-1}z_{K-1} + x_i\beta))
\]

\[
(2) \quad S(t|x_i) = \frac{S(Age|x_i)}{S(Age \ at \ year \ 4|x_i)} \times S(Year \ 4|x_i)
\]

where:

\(\gamma_0 + \gamma_1z_1 + ... + \gamma_{K-1}z_{K-1}\) is the log baseline cumulative hazard function estimated using restricted cubic splines of log(age) with K knots; the knot locations were at 25\(^{th}\), 50\(^{th}\), and 75\(^{th}\) percentiles of the distribution of uncensored log event times.

The restricted cubic spline variables \(z_j\) are calculated as follows:

\[
z_1 = x
\]

\[
z_j = (x - k_j)^3 - \phi_j(x - k_1)^3 - (1 - \phi_j)(x - k_K)^3 \quad j = 2, ..., K - 1
\]

\[
\phi_j = (k_K - k_j)/(k_K - k_1)
\]
\( x_i \) is the covariate matrix

\( \beta \) is the beta coefficients from the model based on the post-trial period (Table S3)

Using the same process outlined in Step 1, we can calculate the probability of survival at age 65 years (or 10 years from SPRINT baseline) for our 55-year-old female case example using a combination of the age-based post-trial survival and in-trial time-based formulas.

\[
S(\text{Year 10}|x_i) = \frac{S(\text{Age 65 years}|x_i)}{S(\text{Age 59 years}|x_i)} \times S(\text{Year 4}|x_i) = 0.950
\]

**Step 3: Combine the in- and post-trial period survival probabilities and calculate life expectancy as the area under the overall survival probability curve**

Next, we combine the predicted in-trial survival probabilities from Step 1 and post-trial survival probabilities from Step 2 to obtain the overall survival curve for each SPRINT participant with standard treatment. Finally, the predicted life expectancy for each participant is calculated as the area under the individual’s survival curve (Table S4). For the intensive arm, we applied the observed hazards ratio from SPRINT, and assumed it was constant over the lifetime.

When we calculated the area under the survival curve for our 55-year-old female case example, we estimate she would survive 28.5 years from baseline (age 83.5 years) in the standard arm compared to 30.6 years (age 85.6 years) in the intensive arm. For the second case example, the 70-year-old male, we calculated that he would survive 16.1 years from baseline (age 86.1 years) in the standard arm and 18.0 years (age 88.0 years) in the intensive arm.
Table S1. Flexible Parametric Survival Model for the In-Trial Period.

| Covariate                                           | Beta Coefficient |
|-----------------------------------------------------|------------------|
| Intervention (REF Control)                          | -0.2562          |
| Baseline age (years)                                | 0.0704           |
| Female                                              | -0.3843          |
| Race (REF White)                                    |                  |
| Black                                               | 0.3678           |
| Hispanic                                            | 0.1339           |
| Other                                               | 0.4332           |
| Body mass index (kg/m$^2$)                          | 0.0061           |
| Smoking status (REF Never)                          |                  |
| Former                                              | 0.3413           |
| Current                                             | 1.2444           |
| Systolic blood pressure                             | 0.0105           |
| Diastolic blood pressure                            | 0.0015           |
| Low-density lipoprotein cholesterol                 | -0.0038          |
| High-density lipoprotein cholesterol                | -0.0012          |
| eGFR                                                | -0.0124          |
| History of coronary heart disease                   | 0.3957           |
| Restricted cubic splines for baseline cumulative hazard (with knots placed at ln(t) = -3.50, 0.87, and 1.38) | |
| 1st spline parameter                                | 0.9355           |
| 2nd spline parameter                                | -0.1033          |
| Constant                                            | -11.2238         |

eGFR – estimated glomerular filtration rate.
Table S2. Flexible Parametric Survival Model for the Post-Trial Period.

| Covariate                                                                 | Beta Coefficient |
|---------------------------------------------------------------------------|------------------|
| Female                                                                    | -0.3338          |
| Race (REF White)                                                          |                  |
| Black                                                                     | 0.0818           |
| Hispanic                                                                  | -0.6716          |
| Other                                                                     | -0.7158          |
| Body mass index (kg/m²)                                                  | 0.0120           |
| Smoking status (REF Never)                                                |                  |
| Former                                                                    | 0.2038           |
| Current                                                                   | 0.9518           |
| Systolic blood pressure                                                  | 0.0048           |
| Diastolic blood pressure                                                 | 0.0061           |
| Low-density lipoprotein cholesterol                                      | 0.0003           |
| High-density lipoprotein cholesterol                                     | 0.0004           |
| eGFR                                                                      | -0.0042          |
| History of coronary heart disease                                        | 0.3105           |
| Restricted cubic splines for baseline cumulative hazard (with knots placed at ln(age) = 3.99, 4.43, and 4.68) |      |
| 1st spline parameter                                                     | 5.9999           |
| 2nd spline parameter                                                     | -22.0180         |
| Constant                                                                 | -29.2969         |

eGFR – estimated glomerular filtration rate.
Table S3. Baseline Characteristics of Two Hypothetical SPRINT Participants.

| Baseline Characteristics                        | Example SPRINT Participant #1 | Example SPRINT Participant #2 |
|-------------------------------------------------|------------------------------|------------------------------|
| Age (years)                                      | 55                           | 70                           |
| Sex                                              | Female                        | Male                         |
| Race                                             | White                         | White                        |
| Body mass index (kg/m²)                          | 32                            | 35                           |
| Smoking status                                   | Former                        | Never                        |
| Systolic blood pressure (mm Hg)                  | 145                           | 150                          |
| Diastolic blood pressure (mm Hg)                 | 85                            | 90                           |
| Low-density lipoprotein cholesterol (mg/dL)      | 102                           | 140                          |
| High-density lipoprotein cholesterol (mg/dL)     | 55                            | 40                           |
| eGFR                                             | 72                            | 55                           |
| History of coronary heart disease                | Yes                           | No                           |

eGFR – estimated glomerular filtration rate.
Table S4. Estimated Survival Probability in Two Hypothetical SPRINT Participants.

| Year of Follow Up | Age | Probability of Survival | Probability of Survival |
|-------------------|-----|-------------------------|-------------------------|
|                   |     | Standard Arm            | Intensive Arm*          |
| Example SPRINT Participant #1 |     |                         |                         |
| 0                 | 55  | 100.0%                  | 100.0%                  |
| 1                 | 56  | 99.8%                   | 99.8%                   |
| ...               |     |                         |                         |
| 4 (end of in-trial period) | 59  | 98.1%                   | 98.5%                   |
| ...               |     |                         |                         |
| 10                | 65  | 95.0%                   | 96.3%                   |
| ...               |     |                         |                         |
| 40                | 95  | 7.8%                    | 15.6%                   |
| Estimated survival (years) |     | 28.5                   | 30.6                   |
| Example SPRINT Participant #2 |     |                         |                         |
| 0                 | 70  | 100.0%                  | 100.0%                  |
| 1                 | 71  | 99.4%                   | 99.6%                   |
| ...               |     |                         |                         |
| 4 (end of in-trial period) | 74  | 95.5%                   | 96.5%                   |
| ...               |     |                         |                         |
| 10                | 80  | 79.6%                   | 84.5%                   |
| ...               |     |                         |                         |
| 40                | 110 | <0.001%                 | <0.001%                 |
| Estimated survival (years) |     | 16.1                   | 18.0                   |

*Assuming a constant treatment effect for the intensive arm (hazards ratio = 0.73) during the post-trial period.

SPRINT – Systolic Blood Pressure Intervention Trial.

Notes: The table shows the probability of survival calculated at selected years of follow up, the corresponding ages, and estimated survival for two hypothetical SPRINT participants. To estimate overall survival, the probability of survival is calculated for each year of follow up as described above in the Supplemental Methods. These are used to create the survival curve for the SPRINT participant and the estimated survival is calculated as the area under the survival curve.
Table S5. Baseline Characteristics of SPRINT Participants Who Were Included vs. Excluded in the Analysis Due to Missing Covariate Data.

| Characteristics                          | Overall SPRINT (N=9,361) | Included (N=8,584) | Excluded (N=777) | P-value (Included vs. Excluded) |
|-----------------------------------------|--------------------------|--------------------|------------------|-------------------------------|
| **Demographics**                        |                          |                    |                  |                               |
| Age (Year)                              | 67.9 ± 9.4               | 67.9 ± 9.4         | 68.2 ± 9.3       | 0.29                          |
| 50-59                                    | 21.1                     | 21.1               | 20.7             |                               |
| 60-69                                    | 36.4                     | 36.5               | 34.9             |                               |
| 70-79                                    | 30.1                     | 30.0               | 32.0             |                               |
| ≥80                                      | 12.3                     | 12.3               | 12.4             |                               |
| Female                                   | 35.6                     | 35.5               | 36.9             | 0.41                          |
| Race                                     |                          |                    |                  | <0.001                        |
| White                                    | 57.7                     | 57.6               | 59.3             |                               |
| Black                                    | 29.9                     | 29.6               | 33.2             |                               |
| Hispanic                                 | 10.5                     | 10.9               | 6.0              |                               |
| Other                                    | 1.8                      | 1.9                | 1.4              |                               |
| **Clinical Characteristics**             |                          |                    |                  |                               |
| Current Smoker                           | 13.2                     | 13.1               | 15.2             | <0.001                        |
| BMI (kg/m²)                              | 29.9 ± 5.8               | 29.9 ± 5.8         | 29.8 ± 5.8       | 0.94                          |
| Systolic Blood Pressure (mm Hg)          | 139.7 ± 15.6             | 139.7 ± 15.6       | 139.0 ± 15.4     | 0.24                          |
| Diastolic Blood Pressure (mm Hg)         | 78.1 ± 11.9              | 78.2 ± 12.0        | 77.5 ± 11.7      | 0.14                          |
| Antihypertensive medication use          | 90.9                     | 90.9               | 91.1             | 0.83                          |
| Low-density Lipoprotein Cholesterol (mg/dL) | 112.5 ± 35.0             | 112.5 ± 35.0       | 112.2 ± 36.8     | 0.94                          |
| High-density Lipoprotein Cholesterol (mg/dL) | 52.8 ± 14.4              | 53.0 ± 14.3        | 44.9 ± 15.0      | <0.001                        |
| Estimated Glomerular Filtration Rate (mL/min/1.73 m²) | 71.8 ± 20.6              | 71.9 ± 20.5        | 69.9 ± 21.8      | 0.01                          |
| 10-year Framingham Risk Score (%)        | 24.8 ± 12.5              | 24.7 ± 12.3        | 26.8 ± 14.5      | <0.001                        |
| **High Cardiovascular Disease Risk Criteria** |                          |                    |                  |                               |
| Characteristics                                      | Overall SPRINT (N=9,361) | Included (N=8,584) | Excluded (N=777) | P-value (Included vs. Excluded) |
|-----------------------------------------------------|--------------------------|--------------------|------------------|-------------------------------|
| Clinical coronary heart disease                     | 20.1                     | 19.9               | 21.4             | 0.34                          |
| Estimated glomerular filtration rate 20-59 mL/min/1.73 m² | 28.1                     | 27.9               | 30.5             | <0.001                        |
| 10-year Framingham risk score ≥15%                   | 75.9                     | 76.2               | 71.9             | <0.001                        |
| Age ≥75 years                                       | 28.2                     | 28.2               | 27.9             | 0.88                          |

* Values are mean ± SD or % base on non-missing data.
Figure S1. Overview of Approach to Estimate Life Expectancy in SPRINT Participants.

**Stage 1** – Use propensity score to weight NHLBI-PCS participants to resemble SPRINT participants

**Stage 2** – Estimate in-trial survival (years 1-4) using SPRINT data (time-based model)

**Stage 3** – Estimate post-trial survival (>4 years) using NHLBI-PCS data (age-based model)

**Stage 4** – Combine in-trial & post-trial survival; Estimate total survival for SPRINT participants

NHLBI-PCS – National Heart, Lung, and Blood Institute Pooled Cohort Study; SPRINT – Systolic Blood Pressure Intervention Trial.
Figure S2. Distribution of Systolic Blood Pressure Before and After Propensity Score Weighting.

NHLBI-PCS – National Heart, Lung, and Blood Institute Pooled Cohort Study. SPRINT – Systolic Blood Pressure Intervention Trial.

Note: The figure shows the distribution of systolic blood pressure before and after propensity score weighting. The SPRINT inclusion criteria were a systolic blood pressure between 130 and 180 mm Hg. We strictly applied this criterion in the NHLBI-PCS population. However, SPRINT participants were allowed to be outside this range if, with adjustments to their blood pressure lowering medications, they were expected to be within the range.
Figure S3. SPRINT Observed vs. Predicted In-trial Survival Using Flexible Parametric and Gompertz Survival Models.

FPsm – Flexible parametric survival model; Gompertz – Gompertz regression model; KM – Kaplan-Meier Curve; SPRINT – Systolic Blood Pressure Intervention Trial.

Note: The figure shows the overall survival from randomization over four years observed in SPRINT (KM) and that predicted in SPRINT participants by the multivariable FPSM and Gompertz regression models. The shaded regions represent the 95% confidence intervals.
Figure S4. SPRINT Observed vs. Predicted In-trial Survival.

FPSM – flexible parametric survival model; KM – Kaplan-Meier Curve; NHLBI-PCS – National Heart, Lung, and Blood Institute Pooled Cohorts Study; SPRINT – Systolic Blood Pressure Intervention Trial.

Note: The figure shows the survival observed and predicted for SPRINT participants during the in-trial period (0-4 years). Each of the parametric survival models was adjusted for the same variables (i.e., age, sex, race, body mass index, smoking status, systolic blood pressure, diastolic blood pressure, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and estimated glomerular filtration rate). Model fit was best with the Gompertz model (AIC 3417.2) with only a slightly lower AIC than the FPSM (AIC 3419.2), Weibull (AIC 3423.0), and generalized gamma (AIC 3423.3).
Figure S5. Predicted Overall Survival in SPRINT Participants Compared to NHLBI-PCS Participants.

FPSM – flexible parametric survival model, KM – Kaplan-Meier, NHLBI-PCS – National Heart, Lung, and Blood Institute Pooled Cohorts Study, SPRINT – Systolic Blood Pressure Intervention Trial.

Notes: The figure shows the predicted overall survival for SPRINT participants using the FPSM estimates derived by combining: (1) the in-trial period (0-4 years) estimates from FPSM of SPRINT participants and (2) the post-trial period (>4 years) estimates from applying to SPRINT participants the baseline hazards and coefficients of FPSM in National Heart, Lung, and Blood Institute Pooled Cohorts Study participants propensity-score weighted to resemble SPRINT participants. These are compared to the overall survival observed in SPRINT-eligible NHLBI-PCS participants weighted to resemble SPRINT participants.
Figure S6. Predicted Survival in SPRINT Participants.

FPSM – flexible parametric survival model; SPRINT – Systolic Blood Pressure Intervention Trial.

Note: The figure shows the survival predicted for SPRINT participants. The FPSM estimates derived by combining: (1) the in-trial period (0-4 years) estimates from FPSM of SPRINT participants and (2) the post-trial period (>4 years) estimates from applying to SPRINT participants the baseline hazards and coefficients of FPSM in National Heart, Lung, and Blood Institute Pooled Cohorts Study participants propensity-score weighted to resemble SPRINT participants. The other parametric models (i.e., Gompertz, Weibull, and generalized gamma) show the extrapolations when based on only the SPRINT observed trial data.
Note: The figure shows the survival predicted for SPRINT participants when extrapolating survival estimates derived from a flexible parametric survival model based on only the SPRINT observed trial data.

Mean (standard deviation) life expectancy was 25.6 (6.9) in the intensive arm and 23.7 (7.0) in the standard arm.