

## Supplementary Online Content

Williamson JD, Supiano MA, Applegate WB, et al, for the SPRINT Study Research Group. Intensive vs standard blood pressure control and cardiovascular disease outcomes in adults aged  $\geq 75$  years: a randomized clinical trial. *JAMA*. doi:10.1001/jama.2016.7050

### **Trial protocol**

This supplementary material has been provided by the authors to give readers additional information about their work.

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# **Systolic Blood Pressure Intervention Trial (SPRINT)**

**Protocol Version 5.0**

**October 15, 2015**

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63 **SPRINT Protocol**  
64 **Executive Summary**

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67 **SPECIAL UPDATE TO PROTOCOL VERSION 5.0:**

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69 ***On August 4, 2015, the SPRINT Data and Safety Monitoring Board (DSMB)***  
70 ***recommended unmasking trial investigators and notifying participants of the lower***  
71 ***rate of cardiovascular outcomes and total mortality in the intensive arm. The board***  
72 ***also recommended developing a transition plan for collecting additional outcome data***  
73 ***and for managing study participants' blood pressure. In addition, the DSMB***  
74 ***recommended promptly modifying the protocol to reflect the changes required by this***  
75 ***early finding of benefit in the intensive arm of the trial.***

76

77 ***The NHLBI accepted the DSMB recommendations on August 20, 2015, and asked the***  
78 ***SPRINT Steering Committee to rapidly implement these recommendations, including***  
79 ***notifying SPRINT staff and study participants. These notifications occurred during the***  
80 ***week of September 8-11, 2015, with the goal of informing staff of this news in advance***  
81 ***of the participants receiving their letters. Participant letters were mailed on***  
82 ***September 8, 2015.***

83

84 ***This protocol modification incorporates changes required for discontinuing the blood***  
85 ***pressure intervention (see Chapter 4) and outlines the measurements that will be***  
86 ***taken at closeout visits (see Chapter 5). The goals are to continue ensuring participant***  
87 ***safety while collecting additional outcome data and conducting an orderly trial***  
88 ***closeout.***

89

90

91 The Systolic Blood Pressure Intervention Trial (SPRINT) is a 2-arm, multicenter,  
92 randomized clinical trial designed to test whether a treatment program aimed at reducing  
93 systolic blood pressure (SBP) to a lower goal than currently recommended will reduce  
94 cardiovascular disease (CVD) risk. About 9250 participants with SBP  $\geq$  130 mm Hg and  
95 at least one additional CVD risk factor will be recruited at approximately 90 clinics within  
96 5 clinical center networks (CCNs) over a 2-year period, and will be followed for 4-6  
97 years. Approximately 4300 participants will have chronic kidney disease (CKD), and  
98 3250 will be aged 75 or older. The primary outcome is the first occurrence of a  
99 myocardial infarction (MI), acute coronary syndrome (ACS), stroke, heart failure (HF), or  
100 CVD death. Secondary outcomes include all-cause mortality, decline in renal function or  
101 development of end stage renal disease (ESRD), dementia, decline in cognitive function,  
102 and small vessel cerebral ischemic disease.

103

104 **Design**

105

106 SPRINT will randomize about 9250 participants aged  $\geq$  50 years with SBP  $\geq$ 130 mm Hg  
107 and at least one additional CVD risk factor. The trial will compare the effects of  
108 randomization to a treatment program of an intensive SBP goal with randomization to a  
109 treatment program of a standard goal. Target SBP goals are  $<$ 120 vs  $<$ 140 mm Hg,

110 respectively, to create a minimum mean difference of 10 mm Hg between the two  
111 randomized groups. The primary endpoint is incident CVD events identified over a  
112 follow-up period of up to six years. The primary hypothesis is that CVD event rates will  
113 be lower in the intensive arm. Both the number of randomizations and the length of  
114 follow-up may differ from these targets depending on how observed values of  
115 parameters differ from estimates used to design the study. Secondary hypotheses  
116 include whether the lower SBP goal reduces CVD event rates and progression of renal  
117 disease in people with CKD, whether the lower SBP goal reduces progression of CVD  
118 event rates in people aged 75 or older, the impact of treatment strategy on health-related  
119 quality of life (HRQL), and the relative cost-effectiveness of the two strategies.  
120 Investigation of relevant genetic pathways and other genetic analyses will also be  
121 conducted. The sample size of the trial will be enriched by including 4300 persons with  
122 CKD (estimated GFR 20-59 ml/min/1.73 m<sup>2</sup>) to permit assessment of treatment effect on  
123 CVD in this subgroup, as well as on measures of progression of kidney disease. The  
124 trial will also include 3250 participants who are 75 years old or older. The SPRINT  
125 Memory and cognition IN Decreased hypertension (SPRINT MIND study) will test  
126 whether the lower SBP goal influences the rate of incident dementia and mild cognitive  
127 impairment, global and domain-specific cognitive function, and small vessel ischemic  
128 disease. The sample sizes for each of the three components of the MIND study are  
129 different. Incident dementia will be determined in all participants. The rate of non-  
130 dementia related cognitive decline in important domains of cognition will be measured in  
131 2800 persons representative of all SPRINT participants and from these 2800 persons  
132 the magnetic resonance imaging (MRI) study will involve a sub-set of 640 participants.

133

#### 134 Patient population

135

136 Although epidemiologic evidence strongly suggests that lowering SBP will reduce CVD  
137 risk in nearly all adults, for practical and public health reasons the hypothesis is most  
138 efficiently studied in persons with an elevated risk of CVD. Thus, the trial will recruit  
139 persons 50 years or older with SBP  $\geq$ 130 mm Hg and at least one additional CVD risk  
140 factor. Three groups will be excluded – patients with diabetes, patients with polycystic  
141 kidney disease (PKD), and patients who have had a stroke – because they are the target  
142 groups of completed or ongoing trials that are testing a lower BP goal. SPRINT will  
143 focus on three high risk groups: patients with clinical CVD other than stroke, patients  
144 with chronic kidney disease (estimated glomerular filtration rate [eGFR] 20-59  
145 mL/min/1.73 m<sup>2</sup>), and patients who have a Framingham Risk Score (FRS) of  $\geq$ 15%. A  
146 large subgroup will be participants who are 75 years old or older. This trial is expected  
147 to enroll 50% women and 40% who are members of minority groups (African Americans,  
148 Hispanics, Native Americans, and Asians)

149

#### 150 Sample size and power

151

152 Based on the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack  
153 Trial (ALLHAT) event rates adjusted downward approximately 50% for temporal changes  
154 in CVD risk factors and improved therapy, a sample size of 9250 provides approximately  
155 90% power to detect a 20% effect on the primary composite endpoint of CVD mortality  
156 and non-fatal MI, ACS, stroke, and heart failure. The annual event rate used in this  
157 calculation was 2.2%. Recruitment of a subgroup of 4300 participants with CKD  
158 provides 80% power to detect a 20% effect on the same CVD composite endpoint. The  
159 probable dementia component of the MIND study will provide 80% power to detect a  
160 15% reduction in the incidence of dementia, 2800 SPRINT-MIND participants will

161 provide ample power to detect a 20% reduction in the rate of decline in cognitive function  
162 between the two arms (more intensive vs. less intensive blood pressure control). In  
163 addition, MRI testing to detect differences in small vessel ischemic disease and total  
164 brain volume will provide 80% and 90% power, respectively, between the two strategy  
165 groups in SPRINT.

166  
167 Other secondary outcomes

168  
169 Several additional secondary outcomes will be examined, such as markers of renal  
170 function in non-CKD participants, co-morbidities, quality of life, and cost-effectiveness.  
171 Adverse events (e.g., postural hypotension, including falls) and biochemical changes will  
172 be measured and analyzed by randomized arm.

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# Chapter 1 – Introduction and Background

## 1. Background

### 1.1 Hypertension, public health and the need for a clinical trial testing a lower SBP target.

Elevated blood pressure (BP) is an important public health concern. It is highly prevalent, the prevalence may be increasing, and it is a risk factor for several adverse health outcomes, especially coronary heart disease, stroke, heart failure, chronic kidney disease, and decline in cognitive function. Given the high prevalence and severity of adverse outcomes, even small improvements in the treatment of elevated BP would result in widespread benefit. The benefit of lowering SBP to around 140 mm Hg is well-accepted, but patients treated to this level of BP are still at increased risk of BP-related adverse outcomes. Observational studies document a progressive increase in risk as BP rises above 115/75 mm Hg. Such epidemiologic evidence suggests there may be substantial benefit to targeting treatment to a SBP <120 mm Hg instead of <140 mm Hg. In contrast, targeting to <120 mm Hg may be harmful or unnecessarily costly and burdensome with limited expectation of benefit. Apart from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, which was restricted to participants with diabetes mellitus, no clinical trial has been conducted to test the hypothesis that more intensive reduction in SBP to <120 mm Hg is beneficial compared to the current recommendation of a goal SBP <140 mm Hg. At present, the results from clinical trials that have addressed related hypotheses are ambiguous. A definitive clinical trial testing whether lowering SBP below 120 mm Hg is better than lowering SBP below 140 mm Hg in non-diabetic hypertensive patients is needed, and this has been designated by an NIH Expert Panel as the most important hypothesis to test regarding the prevention of hypertension-related complications (2007).

#### 1.1.1 Prevalence of hypertension

Approximately 1 billion people worldwide have hypertension (HTN) (Kearney and others, 2005). HTN is highly prevalent in the adult population of the US, especially among those aged  $\geq 60$  years. Two-thirds of those over age 60 have HTN, and the prevalence has increased in recent decades (Chobanian and others, 2003; Cutler and others, 2008; Hajjar and Kotchen, 2003; Ong and others, 2007; World Health Organization, 2002). By age 50 years, isolated systolic hypertension (ISH) is the most common form of HTN, and is associated with greatest risk of target organ damage and adverse health outcomes (Franklin, 1999; Franklin and others, 2001).

#### 1.1.2 Hypertension as a cardiovascular risk factor

The importance of BP, especially SBP, as an independent risk factor for coronary events, stroke, chronic heart failure (CHF), and ESRD is well documented (Vasan and others, 2001; Collins and others, 1990; Macmahon and others, 1990; Sacco and others, 2001; Jackson, 2000; Staessen and others, 1997; Hsu and others, 2005; Chobanian and others, 2003; Gillum, 1991; Prospective Studies Collaboration, 2002; Levy and others, 1996). There is also substantial epidemiologic and clinical trial evidence supporting a role for hypertension therapy in reducing risk for age-related dementia, including vascular dementia and Alzheimer's dementia (Forette and others, 1998; Luchsinger and

228 Mayeux, 2004;Reitz and others, 2007;Skoog and Gustafson, 2003;Skoog and others,  
229 2005;Skoog and Gustafson, 2006;Tzourio and others, 2003). Clinical trial data have  
230 shown reductions in CVD outcomes, including incident stroke (35% to 40%), MI (15% to  
231 25%), and CHF (up to 50%) (Chobanian and others, 2003;Psaty and others, 1997;Neal,  
232 Macmahon, and Chapman, 2000). However, optimal targets for BP lowering are not  
233 established.

234

### 235 **1.1.3 Support for current target**

236

237 In addition to the Seventh Report of the Joint National Committee on Prevention,  
238 Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) (Chobanian and  
239 others, 2003), most recent practice guidelines recommend a target SBP <140 mm Hg in  
240 persons with established uncomplicated hypertension (Campbell and others,  
241 2009;Mancia and others, 2007;Mancia and others, 2009;National Collaborating Centre  
242 for Chronic Conditions, 2006;National Heart Foundation of Australia (National Blood  
243 Pressure and Vascular Disease Advisory Committee), 2009;Whitworth, 2003). The  
244 benefits of lowering high BP in reducing CV morbidity and mortality are well-established  
245 (Cutler, MacMahon, and Furberg, 1989;Psaty and others, 1997). A meta-analysis  
246 evaluating the treatment efficacy of hypertension therapy in adults over age 60, from  
247 three major trials from different countries (Liu and others, 1998;SHEP, 1991;Staessen  
248 and others, 1997) found that lowering SBP significantly reduced all-cause and CVD  
249 mortality by 17% and 25% respectively, and all CVD end-points by 32% (Staessen and  
250 others, 1999;Staessen, Wang, and Thijs, 2001), though both treatment goals and the  
251 achieved SBP were >140 mm Hg.

252

### 253 **1.1.4 Risk of SBP above normal but below current target**

254

255 The World Health Organization estimates that about two-thirds of the cerebrovascular  
256 disease burden and one-half of the coronary heart disease (CHD) burden on a  
257 worldwide basis is attributable to SBP >115 mm Hg (World Health Organization, 2002).  
258 Further, SBP > 115 mm Hg has been estimated to account for 7.6 million premature  
259 deaths (13.5% of the global total), 92 million disability-adjusted life years (6.0% of the  
260 global total), 54% of stroke, and 47% of ischemic heart disease. About half of this  
261 burden is in persons with a SBP<145 mm Hg (Lawes, Vander, and Rodgers, 2008).  
262 The JNC-7 defined pre-hypertension based on the evidence that SBP values between  
263 120 and 139 mm Hg and diastolic blood pressure (DBP) values between 80 and 89 mm  
264 Hg are associated with increased cardiovascular (CV) risk. Although the risk of a BP  
265 between 120/80 and 139/89 mm Hg is not as pronounced as that associated with a BP  
266 above 140/90 mm Hg (Chobanian and others, 2003), 36% of the adult US population  
267 had a BP within this range in the 2007-2008 National Health and Nutrition Examination  
268 Survey (Wang and Wang, 2004).

269

270 Strong evidence from large population-based longitudinal observational studies indicates  
271 that, regardless of other cardiovascular risk factors, SBP levels of about 115 mm Hg in  
272 adults over the age of 40 years are associated with lower CVD event rates, including  
273 death and slower progression of subclinical CVD (Lewington and others, 2002;Sipahi  
274 and others, 2006) compared to higher SBPs. In the Framingham Heart Study (FHS), the  
275 risk of CVD following 10 years of follow-up among persons with SBP 130-139 mm Hg  
276 and/or DBP 85-89 mm Hg and SBP 120-129 mm Hg and/or diastolic blood pressure  
277 (DBP) 80-84 mm Hg was significantly higher when compared to their counterparts with  
278 SBP <120 mm Hg and DBP <80 mm Hg (Vasan and others, 2001). Experience in the



279 Atherosclerosis Risk in Communities (ARIC) and Women's Health Initiative (WHI)  
280 studies also showed that individuals with SBP of 120-139 mm Hg and/or DBP of 80-89  
281 mm Hg had an increased risk of CV events, relative to persons with SBP <120 mm Hg  
282 (Hsia and others, 2007;Kshirsagar and others, 2006). A large meta-analysis of data  
283 from 61 population-based longitudinal epidemiological studies showed a strong  
284 continuous graded relationship between SBP and CVD death risk for all age deciles  
285 between 40-89 years, independent of other CVD risk factors, beginning at SBP levels of  
286 about 115 mm Hg (Lewington and others, 2002). For those aged 40-69 years, there was  
287 an approximate doubling in the rates of death from stroke, ischemic heart disease and  
288 other vascular causes with each increase of 20 mm Hg in usual (that is, long-term  
289 average) SBP.

290

### 291 **1.1.5 Evidence for possible benefit of lower target on CV outcomes**

292

293 Clinical trial evidence of benefit from achieving SBP levels that approach the current  
294 recommended goal of <140 mm Hg with pharmacologic treatment is strong, but a trial  
295 specifically designed to test lowering the SBP treatment goal below the 140 mm Hg  
296 level, the ACCORD trial, found no clear evidence of benefit. The ACCORD trial tested  
297 the research question of whether a therapeutic strategy aimed at reducing SBP to <120  
298 mm Hg was more effective in reducing CVD events than a strategy aimed at SBP <140  
299 mm Hg in participants who had diabetes and were at increased risk for CVD events.  
300 ACCORD found a non-significant reduction in CV events in the intensively treated group,  
301 though a lower than expected event rate contributed to an inability to exclude a clinically  
302 meaningful effect (The ACCORD Study Group, 2010). The lack of overall benefit was  
303 generally consistent across a variety of subgroups. This is in contrast to prior  
304 experience of improved outcomes with more compared to less intensive BP reduction in  
305 the diabetic participants in the United Kingdom Prospective Diabetes Study (UKPDS)  
306 and in the diabetic subgroups in the Hypertension Optimal Treatment trial (HOT),  
307 Systolic Hypertension in the Elderly Program (SHEP) and Systolic Hypertension in  
308 Europe trial (Syst-Eur). Importantly, none of these trials tested the same level of  
309 intensity of BP reduction or the low BP goal employed in ACCORD. Consistent with  
310 previous trials, ACCORD did find a large reduction in the incidence of stroke in the  
311 intensively treated group, and though the incidence of serious adverse effects was  
312 significantly greater in the intensive treatment group, adverse events occurred with  
313 relatively low frequency overall.

314

315 Results from overall or subgroup analyses of other CV outcome trials are mixed, with  
316 some providing support for the benefit of a lower BP goal but others not providing such  
317 evidence. In addition, supportive data from other trials have generally been based on  
318 analyses of achieved BP rather than pre-defined treatment goals. For example, the  
319 Hypertension Detection and Follow-up Program (HDFP) showed reductions in mortality  
320 (17%) and CVD mortality (19%) in participants randomized to Stepped Care treatment of  
321 hypertension compared with Referred Care. Participants in the Stepped Care arm  
322 averaged 159 mm Hg at baseline and achieved SBP levels of 130 mm Hg at 4 years and  
323 140 mm Hg at 5 years of follow-up (Abernethy and others, 1986;HDFP, 1979b;HDFP,  
324 1979a;HDFP, 1982). In the Heart Outcomes Prevention Evaluation (HOPE) study, the  
325 use of ramipril in high-risk patients lowered SBP by 3-4 mm Hg from a baseline mean of  
326 139 mm Hg compared to placebo and reduced the composite CVD endpoint that  
327 included CVD death (26%), MI (20%), stroke (32%), revascularization (15%), and CHF  
328 (23%) (Yusuf and others, 2000). In the European Trial on Reduction of Cardiac Events  
329 with Perindopril in Stable Coronary Artery Disease (EUROPA), use of perindopril (vs.

330 placebo) resulted in a 5/2 mm Hg reduction in BP (from a mean baseline value of 137/82  
331 mm Hg) and a 20% reduction in CVD events (Fox, 2003). The perindopril protection  
332 against recurrent stroke study (PROGRESS) showed a significant reduction in stroke  
333 and major vascular events associated with a 9/4 mm Hg reduction in BP from a baseline  
334 mean of 147/86 mm Hg (PROGRESS Collaborative Group, 2001). More importantly, in  
335 a pre-specified subgroup analysis, those receiving 2 drugs (perindopril plus indapamide)  
336 had greater reductions in BP (12/5 mm Hg) and risk (43%) compared with placebo  
337 versus those on perindopril alone compared with placebo (5/3 mm Hg and 5%),  
338 supporting the hypothesis that lower BP is better. There were similar reductions in the  
339 risk of stroke in hypertensive and non-hypertensive subgroups (all  $p < 0.01$ ). Finally, in  
340 the Comparison of Amlodipine vs. Enalapril to limit Occurrences of Thrombosis trial  
341 (CAMELOT), a placebo-controlled trial of patients with heart disease and DBP  $< 100$  mm  
342 Hg (mean 129/78 mm Hg), amlodipine decreased BP by 4.8/2.5 mm Hg and CVD events  
343 by 31% (hazard ratio [HR], 0.69; 95% CI, 0.54-0.88); whereas enalapril lowered BP by  
344 4.9/2.4 mm Hg but did not decrease events (HR, 0.85; 95%CI 0.67-1.07) (Nissen and  
345 others, 2004).

346  
347 Other trials have not supported the hypothesis of benefit from a lower SBP target. In the  
348 HOT study, there were no differences in CVD events between groups randomized to  
349 target DBPs of  $\leq 90$  mm Hg vs  $\leq 85$  mm Hg vs  $\leq 80$  mm Hg in the entire cohort of 18,790  
350 hypertensive participants; the average on-treatment SBP levels were 140 mm Hg and  
351 144 mm Hg, respectively, in the  $\leq 80$  and  $\leq 90$  mm Hg target groups (Hansson and  
352 others, 1998). Only a post hoc analysis of the diabetic subgroup ( $n=1,501$ ) showed that  
353 major CVD events were reduced by 51% ( $p=0.005$ ) in those randomized to the lower BP  
354 goal. The average on-treatment SBP levels were 140 mm Hg and 144 mm Hg in the  
355  $\leq 80$  and  $\leq 90$  mm Hg target groups, respectively (Hansson and others, 1998). Likewise,  
356 there was no special benefit in those with an achieved SBP of 130 mm Hg vs. 134 mm  
357 Hg in the Prevention of Events with Angiotensin Converting Enzyme (PEACE) trial,  
358 which compared trandolapril treatment to placebo in persons with stable coronary artery  
359 disease (Braunwald and others, 2004). In the aggregate, these trials had only modest  
360 net reductions in SBP (4-6 mm Hg), though ACCORD and other trials have shown that a  
361 much larger reduction (14 mm Hg difference in SBP between the two arms) can be  
362 achieved.

363  
364 The ACCORD BP results provide a strong rationale for testing the potential benefits of  
365 intensive BP lowering. (i) The confidence interval around ACCORD's non-significant  
366 effect does not exclude benefit in the range of 20% to 25% reduction in the rate of CV  
367 events. Effects of that magnitude would be of considerable importance to public health.  
368 (ii) Serious adverse effects were significantly more frequent in the intensive treatment  
369 group, but occurred with low frequency overall. (iii) People without diabetes, who are  
370 probably less prone to microvascular disease but were excluded from ACCORD, may  
371 benefit from more intensive BP lowering. (iv) ACCORD excluded people with serum  
372 creatinine levels  $> 1.5$  mg/dL, which are prevalent in the US population and associated  
373 with high CV risk. (v) The glycemia arm of the ACCORD trial was stopped early because  
374 of an excess in total mortality and the possibility of interaction between these two  
375 interventions is still under investigation. The safety and benefit of intensive BP reduction  
376 in patients  $> \text{age } 75$  remain to be tested. Thus, it is imperative that the potential benefits  
377 and harms of intense SBP-lowering be examined definitively in this and other high-risk  
378 populations, e.g. those with chronic kidney disease (CKD) or underlying CVD.  
379

### 1.1.6 Possible harm from treatment of SBP to <120 mm Hg

There are a number of reasons for requiring recommendations to lower SBP treatment goals be based on definitive trial evidence. Treating to lower BP levels with medications could be harmful. For example, one proposed mechanism that has some support in post hoc analyses of clinical trials (Cruickshank and others, 1987; Cruickshank, 2000; Somes, Shorr, and Pahor, 1999), known as the “J-curve” hypothesis, states that lowering DBP too much may decrease coronary artery perfusion and increase the risk of CVD events in patients with coronary artery disease (CAD). In post-hoc observational analyses of clinical trial experience, the level of DBP below which risk increased has varied by trial, sometimes being as high as <85 mm Hg (Cruickshank and others, 1987). In corresponding analyses of SHEP participants, the higher risk was reported with DBP <55-60 mm Hg during treatment (Somes and others, 1999).

Further, if treatment has little or no benefit, adding drugs is a waste of patients’ and payers’ resources and time. For example, in a cost-effectiveness analysis of the HOT trial, which overall did not show a significant benefit for lower DBP goals, the cost-effectiveness ratios, expressed as cost per year of life gained, were most favorable for the DBP ≤90 mm Hg target group (\$4262) and for added aspirin treatment (\$12,710) (HOT, 1998). In the moderately intensive treatment (DBP ≤85 mm Hg) group, the cost-effectiveness ratio escalated to \$86,360; with intensive treatment (DBP ≤80 mm Hg), costs further increased to \$658,370 per year of life gained. Only treatment to a DBP target of 90 mm Hg and co-administering aspirin were considered highly cost effective; intensive BP lowering down to 80 mm Hg was clearly very costly.

A third reason for not recommending lower SBP goals without definitive clinical trial evidence relates to the increased number of drugs required to achieve these goals. For example, in the African American Study of Kidney disease and hypertension (AASK) trial, the intensive BP goal (achieved SBP = 128 mm Hg) group required an average of 3.04 drug classes compared with 2.39 in the conventional BP goal group (Wright, Jr. and others, 2002a) and in the ACCORD BP trial experience >3 drug classes were required for the intensive SBP goal group to achieve a SBP average of 119 mm Hg, compared with 2 classes in the standard SBP goal group with a mean SBP achieved of 134 mm Hg (The ACCORD Study Group, 2010). In addition to being more costly and having greater potential for drug-related adverse events, even 1-2 more medications per day may contribute to reduced adherence to other evidence-based drug treatment (e.g., statins or aspirin). Patients may choose to not take medications without more evidence for safety and benefit. In addition to being more costly, burdensome, and potentially risky, a 20-mm Hg lower SBP goal (and/or a 10 mm Hg lower DBP goal) would likely mean that up to 70-80 million Americans now considered “prehypertensive” may require drug therapy for a condition that has not been proven to be benefited by treatment (Greenlund, Croft, and Mensah, 2004).

Finally, all medications carry an intrinsic risk of side effects which may adversely affect clinical outcomes and quality of life, and lead to drug interactions, especially in older persons who may need to take a variety of medications.

### 1.1.7 Conclusion

If the SPRINT results are positive and support a SBP goal <120 mm Hg, and this is fully applied in practice a large number of major CVD could be prevented each year, in the

431 U.S. alone. If the results are negative and SPRINT is sufficiently powered and well-  
432 conducted, then recommendations for SBP goal in the treatment of most hypertensive  
433 patients, including those with stage 3 CKD and pre-existing CVD, would 1) allow for a  
434 redoubled focus on achieving a SBP goal of <140 mm Hg, and 2) abrogate the need for  
435 the additional effort and cost of achieving a lower SBP goal than currently recommended  
436 for most patients with elevated BP. If none of the major outcomes show harm from  
437 lowering to <120, and if any of the outcomes are positive, SPRINT may make a  
438 substantial contribution to public health.

439

## 440 **1.2 SPRINT's target patient population**

441

442 Although epidemiologic evidence strongly suggests that lowering SBP will reduce CVD  
443 risk in nearly all adults, for practical and public health reasons the hypothesis is most  
444 efficiently studied in high-risk individuals. A high risk population stands to benefit most in  
445 the sense that a greater number of events may be prevented per treated individual.  
446 Furthermore, results in a diverse high risk population will likely generalize to lower risk  
447 populations, at least in terms of relative risk reduction. Thus, the SPRINT trial will recruit  
448 patients 50 years or older with SBP  $\geq 130$  mm Hg who either have or are at high risk for  
449 CVD. SPRINT will focus on three high risk groups: individuals with clinical CVD other  
450 than stroke, individuals with CKD (estimated glomerular filtration rate [eGFR] 20-59  
451 ml/min/1.73 m<sup>2</sup>), and individuals without clinical CVD who have high estimated CVD risk  
452 based on factors such as smoking, low levels of HDL, high levels of LDL or age. Three  
453 other groups will be excluded: patients with diabetes, patients with polycystic kidney  
454 disease (PKD), and patients who have had a stroke. Patients with diabetes have been  
455 studied in the ACCORD trial; patients with prior stroke and PKD are part of other  
456 ongoing trials.

457

### 458 **1.2.1 Chronic Kidney Disease (CKD)**

459

460 An important and under-studied high-risk group for CVD is the population with CKD  
461 (Coca and others, 2006). In the U.S., the number of persons with Stage 3 CKD (eGFR  
462 between 30 and 60 ml/min/1.73 m<sup>2</sup>) has recently been estimated to be 7.7% of the adult  
463 population, or 15.5 million (Coresh and others, 2007). Patients with prevalent CVD have  
464 a high prevalence of CKD, with reported ranges of 30-60% (Keeley and others,  
465 2003;Levey and others, 1998;Shlipak and others, 2002).

466

467 Individuals with CKD are at high risk for CVD events (Shlipak and others, 2009;Go and  
468 others, 2004;Rahman and others, 2006;Weiner and others, 2004;Foster and others,  
469 2007;McCullough and others, 2007;Rashidi and others, 2008;Fried and others, 2009). A  
470 meta-analysis of reported data from prospective studies in Western populations  
471 demonstrated that people with an eGFR of <60 ml/min/1.73m<sup>2</sup> have a relative risk of 1.4  
472 for CVD, compared to those with an eGFR of  $\geq 60$  ml/min/1.73m<sup>2</sup> (Di Angelantonio and  
473 others, 2007). The relative risk increases as eGFR declines (Go and others, 2004).  
474 Pooled data from the ARIC and CHS cohorts demonstrated that participants with CKD  
475 were also at increased risk for stroke (Weiner and others, 2007), and CKD was a risk  
476 factor for CVD and all-cause mortality independent of traditional CVD risk factors  
477 (Weiner and others, 2004). In ALLHAT, despite exclusion criteria designed to exclude  
478 participants with significant GFR impairment, about 18% of participants had an eGFR  
479 30-60 ml/min/1.73m<sup>2</sup>. In that CKD subgroup, CHD was 38% higher and combined CVD  
480 35% higher than in those with an eGFR >90 ml/min/1.73m<sup>2</sup> (Rahman and others, 2006).

481 The effect of BP control on the development of CVD in the CKD population is far less  
482 clear (Berl and others, 2005).

483 A strategy of treating to a lower BP goal may reduce the progression of kidney disease.  
484 The risk of CKD increases progressively beginning with pre-HTN levels of BP through  
485 the various stages of HTN (Haroun and others, 2003). Several observational studies  
486 have suggested that achievement of lower BP is associated with lower risk of adverse  
487 kidney outcomes (Bakris and others, 2000;Klag and others, 1996;Schaeffner and others,  
488 2008). However, two randomized clinical trials, AASK and the Modification of Diet in  
489 Renal Disease Study (MDRD) that examined lower-than-usual BP goals failed to show  
490 an overall significant beneficial long-term effect of lower BP on decline in kidney function  
491 (Klahr and others, 1994;Wright, Jr. and others, 2002b) Both studies enrolled participants  
492 with non-diabetic CKD and randomized them to a mean arterial pressure (MAP) goal of  
493 <92 mm Hg (corresponding to <125/75 mm Hg) or a MAP goal of <107 mm Hg  
494 (corresponding to <140/90 mm Hg). The AASK trial compared two BP goals based on  
495 MAP (102-107 vs. <92 mm Hg) in 1094 African Americans with hypertensive kidney  
496 disease; the achieved difference of 128/78 vs. 141/85 did not reduce the progression of  
497 CKD (Wright, Jr. and others, 2002b). However, subgroup analyses of long-term (up to  
498 10 years) post trial follow-up suggested the possibility of benefit in participants with  
499 baseline urinary protein excretion equivalent to >300 mg/day who were randomized to  
500 the lower goal (Appel and others, 2008). Among 585 non-diabetic participants with  
501 Stage 3/4 CKD in MDRD, 24% had PKD and only 53 were African American (Klahr and  
502 others, 1994). Mean baseline proteinuria was 2.2 g/d, and a beneficial effect of the  
503 lower BP goal on GFR was observed in the subgroup with urinary protein > 1 g/d  
504 (Peterson and others, 1995;Sarnak and others, 2005). In addition to the inherent  
505 problems associated with subgroup analysis, major caveats of these results from the  
506 MDRD Study were that the number of patients in the heavy proteinuric subgroups was  
507 small and the results were confounded by the use of angiotensin converting enzyme  
508 (ACE) inhibitors. Together, these studies fail to show convincing renoprotective effects  
509 for the lower BP goal; however their results have led to clinical recommendations that  
510 patients with high levels of proteinuria should have blood pressure goals below 140/90  
511 mm Hg. They were not adequately powered to consider CVD outcomes. Nonetheless,  
512 they successfully demonstrated the feasibility of achieving significant separation in BP in  
513 large cohorts with advanced CKD. Given the rapid increase in the prevalence of CKD,  
514 the effects of aggressively lowering BP on the risks of CVD and CKD progression need  
515 to be clarified in a sample that appropriately mirrors the U.S. population with CKD  
516 (Sarnak and others, 2003).

517

### 518 **1.2.2 SENIOR participants and SPRINT-MIND**

519

520 Including a large subgroup of participants aged 75+ will provide data on whether  
521 intensive BP treatment will reduce CVD and renal events in the elderly. Both the  
522 Treatment of Hypertension in Patients over 80 Years of Age (HYVET) (Beckett and  
523 others, 2008) and the SHEP (SHEP, 1991) trials found that a SBP delta of 15 and 11  
524 mm Hg, respectively, between treated and placebo groups resulted in >30% reduction in  
525 stroke, HF, and overall CVD events in the treated groups. Unlike HYVET and SHEP,  
526 which had SBP levels of about 150 and 143 mm Hg at the end of the trials, SPRINT will  
527 have a substantially lower SBP target of <120 mm Hg in the intensive treatment group, a  
528 goal which has never been tested in the elderly. No previous large scale trial has  
529 examined the impact of treating SBP in the elderly to <120 mm Hg versus <140 mm Hg.

530

531 Importantly, the elderly pose an additional question as to the safety of intensive SBP  
532 lowering in a population with known wider pulse pressures and a risk of excessively low  
533 DBP with intensive SBP treatment. In addition to concerns about hypotension, syncope,  
534 and falls, there may be a point of maximal benefit beyond which lowering BP could be  
535 detrimental in the elderly. This is a specific concern related to very low DBP, which  
536 could compromise coronary blood flow. The SPRINT-Senior cohort will allow us to more  
537 precisely assess the safety of the lower SBP goal.

538  
539 The SPRINT Senior cohort also provides a critically important the main body of  
540 participants for SPRINT-MIND. Dementia is a leading cause of placement into nursing  
541 homes and assisted living facilities (guero-Torres and others, 2001;Guralnik and others,  
542 1997;Magsi and Malloy, 2005;National Institute on Aging, 2000). Dementia affects 24  
543 million individuals globally and 4.5 million persons in the US, a number that is expected  
544 to double by 2040 (Ferri and others, 2005;Plassman and others, 2007). Both dementia  
545 and a precursor, mild cognitive impairment (MCI), are highly prevalent among adults  
546 over age 70, with estimates running between 15-20% and 40-50% respectively in  
547 persons over age 80. In addition, there is evidence that MCI is also highly prevalent in  
548 persons above age 60 with CKD. Notably, approximately 15% of persons with MCI  
549 progress to dementia each year (Petersen, 2000), accruing substantial negative societal  
550 impact, and threatening the quality of life of its victims, their families and other  
551 caregivers. Proven strategies for prevention and delay of cognitive decline and  
552 dementia are lacking, and there is a clear need for clinical trials testing promising  
553 preventive interventions. Even a moderately effective strategy could have tremendous  
554 benefits, with a 5-year delay in onset of dementia estimated to decrease the number of  
555 cases of incident dementia by about 50% after several decades (Brookmeyer and  
556 others, 2002).

557  
558 Cognitive impairment can have multiple etiologies and vascular risk factors are  
559 implicated in a large proportion of dementias including neurodegenerative dementias like  
560 Alzheimer's type (Qiu, Winblad, and Fratiglioni, 2005c). With this strong link to CVD risk  
561 plus several observational studies suggesting that the ideal SBP to lower CVD risk may  
562 be below 120 mm Hg (Chobanian and others, 2003) it is possible that targeting intensive  
563 blood pressure control intensive blood pressure control may have substantial  
564 implications for preserving brain function.

565  
566 Substantial epidemiologic evidence identifies hypertension as a risk factor for dementia.  
567 Longitudinal observational studies have yielded mixed results, depending on the age at  
568 which blood pressure is measured, the impact and duration of treatment, duration of  
569 hypertension, and level of BP control (Birns and others, 2006;Qiu, Winblad, and  
570 Fratiglioni, 2005). Midlife hypertension appears to increase the risk of all-cause  
571 dementia in large prospective cohort studies (Freitag and others, 2006;Kivipelto and  
572 others, 2001b). However, lower SBP in older adults has been associated with  
573 subsequent development of dementia (Nilsson and others, 2007). Clinical trials of  
574 antihypertensive treatment have also provided conflicting experience regarding the  
575 impact of treatment of hypertension on the risk of cognitive impairment and dementia in  
576 older people (Guo and others, 1999; Hajjar and others, 2005; Veld and others, 2001).  
577 Four large randomized, placebo-controlled studies have investigated the effects of  
578 antihypertensive agents on the incidence of dementia. The Syst-Eur (Staessen and  
579 others, 1997) and the Perindopril Protection Against Recurrent Stroke Study  
580 (PROGRESS) studies (Tzourio and others, 2003) found that more aggressive  
581 antihypertensive treatment reduced the rate of small vessel ischemic disease (also the

582 primary outcome of SPRINT MIND MRI), a risk factor for dementia (Dufouil and others,  
583 2009), as well as reducing dementia incidence by 50% compared to placebo. In contrast,  
584 the Study on Cognition and Prognosis in the Elderly (SCOPE) and SHEP trials (SHEP,  
585 1991) found no significant difference in incidence of dementia between the active  
586 treatment and placebo groups, although differential missing data for the placebo vs.  
587 treatment groups may explain the SHEP findings (Di Bari and others, 2001). More  
588 recently, the HYVET-COG, a BP lowering trial in people age  $\geq 80$ , was powered to detect  
589 a 33% reduction in adjudicated incident dementia (Peters 2008). The trial was stopped  
590 prior to its planned date of completion due to significant reductions in stroke and all-  
591 cause mortality in the intervention group. It yielded a 14% non-significant reduction in  
592 incident dementia. One reason for the non-significant result was a loss of power due to  
593 the unexpectedly early conclusion of follow-up, resulting in a relatively short, two-year  
594 period of follow-up. One possible explanation for the ambiguous relationships described  
595 between hypertension, hypertension treatment and preservation of cognitive function is  
596 that the cognitive measures included in most of these trials have not been sensitive  
597 enough to detect early, but clinically important, cognitive changes in a cohort with intact  
598 general cognitive function at baseline. Studies using more sensitive neuropsychological  
599 tests, such as the testing proposed for SPRINT-MIND, have shown the strongest  
600 relationships (Elias and others, 1993;Kivipelto and others, 2001a;Kivipelto and others,  
601 2001c;Knopman and others, 2001).

602  
603 Hypertension is the primary risk factor for small vessel ischemic disease and cortical  
604 white matter abnormalities (Basile and others, 2006;Kuller and others, 2010;Liao and  
605 others, 1996;Longstreth, Jr. and others, 1996). Chronic kidney disease is also  
606 associated with white matter abnormalities (Ikram and others, 2008), thus the SPRINT  
607 population is at high risk for significant white matter changes. Longitudinal studies  
608 document that hypertension-associated white matter abnormalities are an independent  
609 risk factor for cognitive decline and dementia (Verdelho and others, 2007;Vermeer and  
610 others, 2003), lower extremity functional abnormalities (Rosano and others, 2005), and  
611 clinical stroke (DeBette and others, 2010). However, there is limited evidence that better  
612 control of BP slows the progression of white matter lesions in the brain (Dufouil and  
613 others, 2005). Recently reported results from the Women's Health Initiative Memory  
614 Study (WHIMS) indicate that white matter volume (detected by MRI) is associated with  
615 baseline BP, even after adjustment for treatment, other CVD risk factors, and age (Coker  
616 L.H. and others, 2008). Although the beneficial effects of treating hypertension on CVD,  
617 such as stroke have been shown (Collins and others, 1990), it is not known whether  
618 intensive lowering of SBP as proposed in SPRINT will provide reduction in the risk for  
619 developing white matter disease and brain volume loss.

## 620 621 SUMMARY

622  
623 Higher than optimal BP is the leading cause of disability adjusted life-years lost on a  
624 global basis, and more intensive control of SBP than is currently recommended may  
625 contribute to reductions in stroke, heart failure, coronary heart disease, chronic kidney  
626 disease, and dementia. This potential benefit must be weighed against potential risks,  
627 including complications resulting from low coronary, cerebral, and renal perfusion  
628 pressure and the medications themselves. Definitive evidence from a well designed and  
629 conducted trial should form the foundation for pertinent recommendations and  
630 healthcare policies.

631  
632  
633

## Chapter 2 – Overview of Trial Design

The SPRINT randomized controlled clinical trial will examine the effect of a high BP treatment strategy aimed at reducing SBP to a lower goal than is currently recommended. The primary objective is to determine whether randomization to this intensive strategy is more effective than a standard strategy in reducing the incidence of serious cardiovascular disease events. Other important study objectives are to assess the impact of more intensive SBP reduction on renal function, incidence of probable dementia, quality of life, cost-effectiveness, cognitive function and small vessel ischemic disease.

The study cohort will include approximately 9250 people aged  $\geq 50$  years with SBP  $\geq 130$  mm Hg. SPRINT will focus on three high risk groups: patients with clinical CVD other than stroke, patients with chronic kidney disease (estimated glomerular filtration rate (eGFR) 20 -59 mL/min/1.73 m<sup>2</sup>), and patients who have a Framingham Risk Score (FRS) of  $\geq 15\%$ . Participants will be recruited over a 2-year period at approximately 80 to 100 clinics in 5 clinical center networks (CCNs) and will be followed for up to 6 years. Both the number of randomizations and the length of follow-up may differ from these targets depending on how observed values of parameters differ from estimates used to design the study. Approximately 4300 SPRINT participants will have CKD, and 3250 will be age 75 or older. Chapter 3 presents the eligibility criteria for the trial.

Participants will be stratified by clinic and randomly assigned to either the intensive or standard SBP lowering strategy. Chapter 4 and 5 provides a general description of the intervention.

The primary outcome will be a composite end-point consisting of the first occurrence of a myocardial infarction (MI, by electrocardiogram (ECG) or hospitalization), stroke, heart failure, non-MI acute coronary syndrome, or CVD death. Study outcomes are described in Chapters 6, 7 and 9.

The sample size for SPRINT is estimated to provide 90% power to detect a 20% relative decrease in the rate of the composite primary outcome in participants randomized to the more intensive SBP lowering strategy. Sample size estimation is described further in Chapter 10.

The major objectives of the SPRINT trial are as follows:

### 2.1 Primary Hypothesis

In people aged  $\geq 50$  years with SBP  $\geq 130$  mm Hg and either a history of CVD, eGFR between 20 and 59, or a Framingham Risk Score (FRS) indicating 10-year CVD risk of  $\geq 15\%$ , does a therapeutic strategy that targets a SBP of  $< 120$  mm Hg reduce the rate of CVD events compared to a strategy that targets a SBP of  $< 140$  mm Hg? This hypothesis will be tested using a composite outcome including

- cardiovascular death,
- myocardial infarction,
- stroke,
- heart failure, and
- non-MI acute coronary syndrome



684 ascertained over a follow-up period of up to 6 years. Interim monitoring for overall trial  
685 efficacy will be based on the accrued rate of this primary outcome. The anticipated event  
686 rate for this outcome is 2.2%/year.

687

## 688 **2.2 Subgroup Hypotheses**

689

690 SPRINT will examine intervention effects in a number of subgroups; these are presented  
691 in greater detail in Chapter 10. Two subgroups are of particular interest due their  
692 connection to possible biological mechanisms affecting the primary outcome:

693

- 694 1. participants with and without CKD (eGFR <60 ml/min/1.73m<sup>2</sup>) at baseline,
- 695 2. participants < or ≥ 75 years at baseline.

696

697 Consistency of the effects for the intervention on the primary outcome will also be  
698 examined in subgroups defined by gender, race/ethnicity (black vs. non-black), presence  
699 of clinical CVD at baseline (i.e., primary and secondary prevention participants) and  
700 tertiles of baseline systolic BP.

701

702 Subgroup analyses for secondary outcomes are described in Chapter 10.

703

## 704 **2.3 Secondary Hypotheses**

705

706 SPRINT prespecifies two types of secondary hypotheses. The first type will address  
707 secondary outcomes in analyses designed to support and confirm the primary analysis.  
708 These will include components of the primary composite outcome, total mortality, and a  
709 composite of the primary composite with total mortality (CVD-free survival). The other  
710 type addresses two areas of non-cardiovascular clinical effects: renal and cognitive  
711 outcomes.

712

### 713 **2.3.1 Objectives for renal outcomes and the CKD subgroup**

714

- 715 1. For the CKD subgroup, we will determine whether the intensive intervention arm  
716 experiences a lower rate of a composite of renal outcomes composed of:
  - 717 • ESRD or
  - 718 • A 50% decline from baseline eGFR
- 719 2. For the non-CKD subgroup, we will determine whether the intensive intervention arm  
720 experiences a lower rate of progression to CKD, defined as
  - 721 • ESRD or
  - 722 • 30% decrease from baseline eGFR and an end value of <60 ml/min/1.73M<sup>2</sup>

724

### 725 **2.3.2 SPRINT MIND Hypotheses**

726

- 727 1. All-cause Dementia. The incidence of all-cause dementia will be lower in SPRINT  
728 participants assigned to the intensive SBP treatment arm compared to their  
729 counterparts assigned to the standard SBP treatment arm.
- 730 2. Cognitive Decline. The combined rate of decline in all domains of cognition will be  
731 slower in the intensive SBP treatment arm compared to the standard SBP treatment  
732

733 arm. This hypothesis will be tested in a randomly selected subset of 2800  
734 participants enrolled in SPRINT.

735

736 3. MRI Brain Changes. The volume small vessel ischemic disease (SVI) will be lower  
737 in SPRINT participants assigned to the intensive SBP treatment arm compared to  
738 their counterparts assigned to the standard SBP treatment arm. A sub-hypothesis is  
739 that total brain volume will also be greater (thus less atrophy) in the intensively  
740 treated group. The MRI sub-study will be conducted in 640 participants chosen from  
741 the 2800 selected to receive regular extensive cognitive assessment.

742

743

744

745

## Chapter 3 – Participant Selection

### 3.1 Eligibility Criteria

The objective of setting inclusion/exclusion criteria is to identify a trial population that will ensure adequate event rates for statistical power, provide maximum generalizability, and maximize safety. Inclusion/exclusion criteria were made as simple as possible to ensure standard implementation across all SPRINT study sites. Specifically, the SPRINT eligibility criteria were developed to facilitate the identification and inclusion of a trial population at high risk for the major trial endpoints, including CVD, CKD, cognitive decline, and dementia. Hence, the trial population is comprised of individuals in three major classes: those with existing CVD, existing CKD, or an elevated estimated risk for CVD disease based on age and other risk factors.

Implementation of these inclusion and exclusion criteria and related recruitment strategies will be accomplished to meet several goals with respect to composition of the study population. The overall goal for recruitment is 9,250 participants, although the final number of randomizations may be between 8,500 and 10,000. For the target of 9,250 participants, we will strive to include approximately 4300 (46%) with chronic kidney disease (eGFR 20 -59 ml/min/1.73m<sup>2</sup>), expected to be divided approximately evenly below and above 45 ml/min/1.73m<sup>2</sup>, and approximately 3250 (35%) who are at least 75 years old. In addition, we will strive to include 50% women, 40% minorities, and 40% with clinical or subclinical cardiovascular disease. Among these goals there is an implicit hierarchy based on study hypotheses and design considerations: first, attain the overall sample size, to preserve power for the main hypothesis of SPRINT; second, reach the required sample sizes for formal sub-group hypotheses among participants with CKD and among seniors; and third, ensure a sufficiently diverse study population so that results are broadly applicable to the affected U.S. population. We will monitor these goals on an ongoing basis and the Recruitment, Retention, and Adherence Subcommittee and the Steering Committee will evaluate recruitment strategies and implement corrective actions.

#### a) Inclusion Criteria

1. At least 50 years old
2. Systolic blood pressure
  - SBP: 130 – 180 mm Hg on 0 or 1 medication
  - SBP: 130 – 170 mm Hg on up to 2 medications
  - SBP: 130 – 160 mm Hg on up to 3 medications
  - SBP: 130 – 150 mm Hg on up to 4 medications
3. There are no diastolic blood pressure (DBP) inclusion criteria, since risk is more related to SBP than DBP in the age and risk population anticipated for SPRINT. If a screenee is otherwise eligible for SPRINT but presents with a treated BP and/or number of medications that fall outside the SPRINT inclusion criteria, BP-lowering medications may be adjusted prior to the randomization visit to determine whether, with such adjustments, the screenee will meet eligibility criteria for SPRINT. A screenee who presents on no BP medications should have documentation of SBP

795 ≥130 mm Hg on 2 visits within 3 months prior to the randomization visit in order to be  
796 eligible for the trial.

797

798 4. Risk (one or more of the following):

799 a) Presence of clinical\* or subclinical\*\* cardiovascular disease other than stroke

800 b) CKD, defined as eGFR 20 – 59 ml/min/1.73m<sup>2</sup> based on the 4-variable  
801 Modification of Diet in Renal Disease (MDRD) equation and latest lab value,  
802 within the past 6 months. (If the serum creatinine is unstable within the last 6  
803 months, enrollment into SPRINT could be delayed until the serum creatinine  
804 has been stabilized and the eGFR is still within the allowed range.)

805 c) Framingham Risk Score for 10-year CVD risk ≥ 15% based on laboratory  
806 work done within the past 12 months for lipids

807 d) Age ≥ 75 years.

808

809 5. Clinical CVD (other than stroke)

810 a) Previous myocardial infarction (MI), percutaneous coronary intervention  
811 (PCI), coronary artery bypass grafting (CABG), carotid endarterectomy  
812 (CE), carotid stenting

813 b) Peripheral artery disease (PAD) with revascularization

814 c) Acute coronary syndrome with or without resting ECG change, ECG  
815 changes on a graded exercise test (GXT), or positive cardiac imaging  
816 study

817 d) At least a 50% diameter stenosis of a coronary, carotid, or lower extremity  
818 artery

819 e) Abdominal aortic aneurysm (AAA) ≥5 cm with or without repair

820

821 6. Subclinical CVD

822 a) Coronary artery calcium score ≥ 400 Agatston units within the past 2  
823 years.

824 b) Ankle brachial index (ABI) ≤0.90 within the past 2 years.

825 c) Left ventricular hypertrophy (LVH) by ECG (based on computer reading),  
826 echocardiogram report, or other cardiac imaging procedure report within  
827 the past 2 years.

828

## 829 **b) Exclusion Criteria**

830

831 1. An indication for a specific BP lowering medication (e.g., beta-blocker following  
832 acute myocardial infarction) that the person is not taking and the person has not  
833 been documented to be intolerant of the medication class. (If a screenee has a non-  
834 hypertension indication for a BP-lowering medication (e.g., beta-blocker post-MI,  
835 renin angiotensin system (RAS) blocker for CVD prevention, or alpha blocker for  
836 benign prostatic hypertrophy (BPH)), the screenee should be on the appropriate  
837 dose of such medication before assessing whether he/she meets the SPRINT  
838 inclusion criteria. If the investigator believes that a potential participant has such an  
839 indication but is not receiving appropriate treatment, he/she should encourage the  
840 potential participant's primary care provider to consider placing the patient on the  
841 appropriate therapy prior to proceeding with the screening process.)

842 2. Known secondary cause of hypertension that causes concern regarding safety of  
843 the protocol.

844 3. One minute standing SBP < 110 mm Hg. Not applicable if unable to stand due to  
845 wheelchair use.

- 846 4. Proteinuria in the following ranges (based on a measurement within the past 6  
847 months)  
848 (a) 24 hour urinary protein excretion  $\geq 1$  g/day, or  
849 (b) If measurement (a) is not available, then 24 hour urinary albumin excretion  $\geq$   
850 600 mg/day, or  
851 (c) If measurements (a) or (b) are not available, then spot urine protein/creatinine  
852 ratio  $\geq 1$  g/g creatinine, or  
853 (d) If measurements (a), (b), or (c) are not available, then spot urine  
854 albumin/creatinine ratio  $\geq 600$  mg/g creatinine, or  
855 (e) If measurements (a), (b), (c), or (d) are not available, then urine dipstick  $\geq 2+$   
856 protein
- 857 5. Arm circumference too large or small to allow accurate blood pressure  
858 measurement with available devices
- 859 6. Diabetes mellitus. Participants taking medications for diabetes at any time in the  
860 last 12 months are excluded. Participants are also excluded if there is  
861 documentation of: FPG at or above 126 mg/dL, A1C  $\geq 6.5$  percent, a two-hour value  
862 in an OGTT (2-h PG) at or above 200 mg/dL or a random plasma glucose  
863 concentration  $\geq 200$  mg/dL. The diagnosis of diabetes must be confirmed on a  
864 subsequent day by repeat measurement, repeating the same test for confirmation.  
865 However, if two different tests (e.g., FPG and A1C) are available and are  
866 concordant for the diagnosis of diabetes, additional testing is not needed. If two  
867 different tests are discordant, the test that is diagnostic of diabetes should be  
868 repeated to confirm the diagnosis.
- 869 7. History of stroke (not CE or stenting)
- 870 8. Diagnosis of polycystic kidney disease
- 871 9. Glomerulonephritis treated with or likely to be treated with immunosuppressive  
872 therapy
- 873 10. eGFR  $< 20$  ml/min /1.73m<sup>2</sup> or end-stage renal disease (ESRD)
- 874 11. Cardiovascular event or procedure (as defined above as clinical CVD for study  
875 entry) or hospitalization for unstable angina within last 3 months
- 876 12. Symptomatic heart failure within the past 6 months or left ventricular ejection  
877 fraction (by any method)  $< 35\%$
- 878 13. A medical condition likely to limit survival to less than 3 years, or a cancer  
879 diagnosed and treated within the past two years that, in the judgment of clinical  
880 study staff, would compromise a participant's ability to comply with the protocol and  
881 complete the trial. Exceptions to the exclusion for diagnosed cancer would include,  
882 for example, non-melanoma skin cancer, early-stage prostate cancer, localized  
883 breast cancer.
- 884 14. Any factors judged by the clinic team to be likely to limit adherence to interventions.  
885 For example,  
886 (a) Active alcohol or substance abuse within the last 12 months  
887 (b) Plans to move outside the clinic catchment area in the next 2 years without  
888 the ability to transfer to another SPRINT site, or plans to be out of the study  
889 area for more than 3 months in the year following enrollment.  
890 (c) Significant history of poor compliance with medications or attendance at clinic  
891 visits  
892 (d) Significant concerns about participation in the study from spouse, significant  
893 other, or family members  
894 (e) Lack of support from primary health care provider

- 895 (f) Residence too far from the study clinic site such that transportation is a  
896 barrier including persons who require transportation assistance provided by  
897 the SPRINT clinic funds for screening or randomization visits  
898 (g) Residence in a nursing home. Persons residing in an assisted living or  
899 retirement community are eligible if they meet the other criteria.  
900 (h) Clinical diagnosis of dementia, treatment with medications for dementia, or in  
901 the judgment of the clinician cognitively unable to follow the protocol  
902 (i) Other medical, psychiatric, or behavioral factors that in the judgment of the  
903 Principal Investigator may interfere with study participation or the ability to  
904 follow the intervention protocol  
905 15. Failure to obtain informed consent from participant  
906 16. Currently participating in another clinical trial (intervention study). Note: Patient must  
907 wait until the completion of his/her activities or the completion of the other trial  
908 before being screened for SPRINT.  
909 17. Living in the same household as an already randomized SPRINT participant  
910 18. Any organ transplant  
911 19. Unintentional weight loss > 10% in last 6 months  
912 20. Pregnancy, currently trying to become pregnant, or of child-bearing potential and  
913 not using birth control

914

### 915 **c) Additional Criteria**

#### 916 I. SENIOR

917

918 Whereas there are no eligibility criteria specific to the SENIOR subgroup other than age,  
919 the general eligibility criteria were influenced by consideration of factors of importance to  
920 the inclusion of older participants in SPRINT, including cognitive status, orthostasis,  
921 transportation, and site of residence (e.g., nursing home). The goal is to assemble a  
922 representative population of older patients for whom intensive BP lowering is reasonable  
923 to consider from a medical perspective. This goal is motivated by the perspective that  
924 there may be some older persons with advanced frailty and/or multiple comorbid  
925 conditions whose health is so poor that it would not be reasonable to attempt to treat  
926 SBP as intensively as needed to control SBP to less than 120 mm Hg.

927

#### 928 II. Participants with CKD

929

930 For the purposes of SPRINT, qualifying CKD is defined by eGFR, determined during the  
931 6 months prior to randomization, between 20 and 59 ml/min/1.73m<sup>2</sup>, inclusive, based on  
932 the 4-variable MDRD equation. Patients with significant proteinuria, defined as a 24-  
933 hour urine protein excretion exceeding 1 gram, or rough equivalents thereof (see  
934 Exclusion Criterion 4 above), will be excluded from SPRINT based on evidence from  
935 previous trials suggesting that intensive BP lowering therapy may be beneficial with  
936 respect to slowing the progression of CKD. The vast majority of participants with CKD  
937 so defined will likely be at high risk for CVD. An estimated 82.3% of those who qualify  
938 with eGFR between 45 and 59 ml/min/1.73m<sup>2</sup> will have a Framingham Risk Score for  
939 CVD exceeding 15% over 10 years, and an estimated 71.2% have a Framingham Risk  
940 Score for CVD exceeding 20% over 10 years; hence, these participants will contribute  
941 substantially to the overall event rate and provide the basis for informative subgroup  
942 analyses.

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III. MIND

Dementia Screening - All individuals will receive dementia screening at baseline and every 2 years following baseline. Individuals who have been previously diagnosed with dementia by their physicians are excluded from SPRINT and SPRINT MIND.

Comprehensive Cognitive Assessment substudy – A subset of 2800 participants enrolled in SPRINT will also be assigned to undergo more extensive cognitive assessment to evaluate the impact of the intervention on decline in overall and domain-specific cognitive function that does not meet criteria for dementia. With limited exceptions, all clinics will enroll participants into this 2800 subset, and this subgroup is expected to be representative of all randomized participants, including the important CKD and SENIOR participants.

IV. MIND MRI

Individuals who enroll in the Comprehensive Cognitive Assessment substudy at a clinic within sufficient proximity to a SPRINT MIND MRI center, generally defined as within a 2 to 3 hour driving radius, are eligible to enroll in the MIND MRI Study. The MIND MRI Study will have a recruitment goal of approximately 640 participants. Standard safety-related exclusions pertaining to the ability to have a magnetic resonance imaging procedure performed will be applied.

**Recruitment and risk implications of inclusion and exclusion criteria**

As shown in Table 3.1, according to analyses of the National Health and Nutrition Examination Survey (NHANES) data for 1999-2004, approximately 6% of the US population meets the basic eligibility criteria related to age and SBP, and are free of diabetes and previous stroke. Among that group, approximately 70% meet the risk criteria described above. The vast majority of these individuals have an estimated 10-year risk of CVD exceeding 20% and the population average 10-year risk for CVD is approximately 28%. (Note that the use of the FRS in this manner likely underestimates the risk of those individuals with existing CHD and stage 3 CKD.) This analysis provides evidence that the recruitment pool will be large enough to enable us to recruit successfully and to generalize our ultimate results to a reasonably large proportion of the US population.

Table 3.1. Distribution of 10-year risk of CVD in NHANES participants who met basic SPRINT eligibility criteria

Criteria	% of US Population meeting basic eligibility criteria (age, SBP, no DM or stroke)	% of those meeting basic eligibility requirements who meet risk criteria	10-year CVD Risk Distribution (%)				Mean 10-yr CVD risk (%)
			5-10%	10-15%	15-20%	20+%	
CHD or Stage 3 CKD or FR $\geq$ 15%	6.7	70.3	1.3	3.2	24.3	71.1	28.6

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In additional analyses of the NHANES potentially eligible pool, 16.3% had stage 3 CKD (3.6% had eGFR < 45ml/min/1.73m<sup>2</sup>), 15.6% had a history of CVD, 34.6% were 75 years old or older, 8.1% were African Americans, and 49.8% were women. Stage 3a

989 CKD, defined as eGFR 45-59 ml/min/1.73m<sup>2</sup>, but a urine albumin-to-creatinine (ACR) ≤  
 990 10 mg/g, comprised 6.1% of the eligible pool. These analyses, shown in Table 3.2,  
 991 provide evidence to support our recruitment targets for participants with CKD, in the  
 992 SENIOR population, minorities and women.

993

994 Table 3.2. Characteristics of SPRINT eligible sample based on NHANES data.  
 995 Eligibility requirements include age ≥ 50, SBP ≥ 130, eGFR > 20, ACR < 600 mg/g and no  
 996 history of stroke or diabetes.

Characteristic	Proportion (%)
% Prior CVD	15.6
% CKD	16.3
% Stage 3b CKD	3.6
% Stage 3a + ACR > 10 mg/g	6.6
% Stage 3a + ACR ≤ 10 mg/g	6.1
% Senior (age ≥ 75)	34.6
% Female	49.8
% Black	8.1
% Hispanic	7.4
% SBP 130-139 on no BP lowering medications	15.2
% with FRS < 15% per 10 yrs	4.5

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998

### 3.2 Recruitment: Informed Consent, Screening, Baseline

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#### Recruitment

1001

The SPRINT recruitment goals are described above. Specific community resources will be used to target women and minority/under-served populations to ensure adequate representation of these groups in SPRINT. Recruitment strategies that have worked well in other trials related to hypertension and CKD will be used. Centralized training for CCN and Clinical Site staffs regarding recruitment issues will be provided before recruitment begins.

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The goal of participant recruitment is to create a trial population that will ensure adequate event rates for statistical power while maximizing participant safety and generalizability to the population for which the intervention is intended. A multifaceted approach to screening and enrollment is essential to achieve the recruitment goal. For this multicenter trial, recruitment strategies targeting both existing populations within the clinical practice of the research sites as well as individuals from outside these practice settings will be used to identify potentially eligible participants.

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The Recruitment, Retention and Adherence Subcommittee will play a significant role in monitoring the progress of study-wide recruitment and provide a forum for advising the CCNs and clinical sites on problem identification, goal setting, strategy deployment and evaluation in their efforts to achieve site and study-wide recruitment goals. This may include guidance for enhancing the recruitment of ethnic groups, women and the elderly. The Subcommittee will also contribute to the development of the recruitment tools including culture-, gender- and age-specific materials to promote enrollment among these important subgroups.

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1025 **3.2.1 Regulatory and Ethical Considerations, including the Informed Consent**  
1026 **Process**

1027 The study will be conducted in accordance with Good Clinical Practice (GCP), all  
1028 applicable subject privacy requirements, and the guiding principles of Helsinki, including  
1029 but not limited to:

- 1030
- 1031 1. Local Institute Review Board (IRB)/Central IRB review and approval of  
1032 study protocol and any subsequent amendments.
  - 1033 2. Subject informed consent for main trial, SPRINT MIND, genetic testing,  
1034 and post trial contact, and any ancillary studies. The study consent will  
1035 contain the six essential elements from GCP guidelines that include:
    - 1036 • Research statement, reasonably foreseeable risks or discomforts,  
1037 reasonably expected benefits to subjects or others, appropriate  
1038 alternatives, extent of confidentiality, compensation or treatment  
1039 for injury.
    - 1040 • Additional elements where appropriate such as unforeseeable  
1041 risks to subjects, embryos, or fetuses, investigator-initiated  
1042 termination of participation, additional costs, significant new  
1043 findings, authorization for release of protected health Information  
1044 for research purposes.
  - 1045 3. Investigator reporting requirements.

1046  
1047 Written informed consent and Health Insurance Portability and Accountability Act  
1048 (HIPAA) authorization must be obtained from each person prior to enrollment into  
1049 SPRINT. In collaboration with the CCNs, the SPRINT Coordinating Center will provide  
1050 full details and template documents for the above procedures in the Manual of  
1051 Procedures and provide training to the investigators and clinical staff on regulatory and  
1052 ethical considerations. All study personnel will be responsible for completing and  
1053 remaining current with all applicable human subjects' protection, good clinical practice  
1054 and data security and privacy training requirements

1055  
1056 **3.2.2 Existing Populations in the Clinical Site Practices**

1057 Methods for identifying potentially eligible participants within the clinical practice of the  
1058 research settings may include: a targeted review of medical records or databases for  
1059 those meeting the trial's inclusion criteria, referrals from providers/employees within the  
1060 practice and/or from practice participants themselves. Additional approaches may also  
1061 include written materials such as direct mailing and/or advertisement on such items as  
1062 appointment reminders.

1063  
1064 **3.3. Screening Visits/ Baseline Visits**

1065  
1066 **Screening Activity Considerations**

1067 Each SPRINT clinical center should consult their local IRB regarding approval  
1068 requirements to access internal medical record searches for potential SPRINT patients.  
1069 Depending upon the institution, prior approvals for data transfer agreements may be  
1070 needed to obtain de-identified patient information. Pursuant to such agreements  
1071 investigators may be required to sign a privacy agreement to protect the patient's  
1072 protected health information (PHI) as well as comply with other policies and procedures  
1073 as defined by the institution's designated privacy, security and compliance services.

1074

1075 SPRINT clinical centers will work with the respective CCNs to complete Health  
1076 Insurance Portability and Accountability Act (HIPAA) Privacy rule documents,  
1077 preparatory to research waivers and training prior to patient medical record searches.  
1078 Once local regulatory requirements have been approved, investigator plans to identify  
1079 potential study patients may be implemented. Large scale data base searches, stratified  
1080 by key specified inclusion criteria may also yield a global assessment of the potentially  
1081 eligible study population. Other study parameters (e.g. age, race, gender CKD status,  
1082 etc.) can be added to further specify the eligible population.

1083  
1084 Prior to conducting prescreening and screening activities, it may also be necessary to  
1085 request additional approvals beyond the IRB (e.g. physician approval or consultation for  
1086 a screening referral to the SPRINT clinic). Participant informed consent must also be  
1087 obtained prior to performing any procedures related to the trial.

### 1088 1089 **Screening Visits/Baseline Visit**

1090 The following are key elements of the screening and baseline visits and are outlined in  
1091 the study assessments and procedures below:

1092

#### 1093 **Screening Visit(s)**

- 1094 1. Verify participant's interest in study.
- 1095 2. Obtain in person study consent and HIPAA authorization for main trial, and if  
1096 applicable, SPRINT MIND, genetic testing and any ancillary studies
- 1097 3. Continue collection of screening information, including such items as contact  
1098 information, additional eligibility information including BP measurement, concomitant  
1099 medications, and medical history.

1100

#### 1101 **Baseline visit (Randomization Visit)**

- 1102 1. Confirmation that all inclusion/exclusion criteria satisfied
- 1103 2. Verification of participant consent and HIPAA authorization.
- 1104 3. Verification of participant contact information
- 1105 4. Obtain a Release of Information, as permitted by local policy, to collect event and  
1106 serious adverse event (SAE) documentation
- 1107 5. Completion of the study randomization procedure and baseline data collection,  
1108 including obtaining BP, ECG, and blood and urine samples for analysis and storage at  
1109 the central lab

1110

1111 Data obtained from the screening, and randomization visits must be supported in the  
1112 patient's source documentation. Visit data will be entered into the SPRINT database  
1113 within a specified time frame determined by the SPRINT Coordinating Center.

1114

## 1115 Chapter 4 – Intervention

1116

1117 *In Protocol Version 5.0, the below intervention is included for informational*  
1118 *purposes only. The blood pressure intervention, which randomized participants*  
1119 *to a blood pressure treatment goal of <120 mm Hg or <140 mm Hg, has been*  
1120 *discontinued as a result of the Data and Safety Monitoring Board (DSMB)*  
1121 *recommendation to unmask trial investigators and notify participants of the lower*  
1122 *rate of cardiovascular outcomes and total mortality in the intensive arm.*

1123

1124 *Participants' blood pressure management is being transitioned from SPRINT to*  
1125 *the participants' health care providers. Participants are instructed to continue*  
1126 *taking their antihypertensive medications and to contact their primary health care*  
1127 *provider. Participants' health care providers should resume responsibility for*  
1128 *managing their patients' antihypertensive medication and setting their blood*  
1129 *pressure goals.*

1130

1131 *Participants will continue on their current SPRINT medications until they see their*  
1132 *personal physician or health care provider, or unless a change is required for*  
1133 *safety purposes. Once a participant's provider has again assumed care of the*  
1134 *participant, the study staff will no longer manage the participant's blood pressure,*  
1135 *but we will ask participants to come to their regularly scheduled visits until*  
1136 *closeout visits begin. However, for participant convenience during the transition*  
1137 *and closeout periods, the trial will provide participants with trial medication,*  
1138 *including a 3-month supply at the closeout visit. If the health care provider makes*  
1139 *changes to the participant's blood pressure medications, the study will provide*  
1140 *these medications if they are part of the SPRINT formulary.*

1141

### 1142 **Blood Pressure Goals**

1143

1144 Participants eligible for the trial will be randomized to one of two goals: SBP <120 mm  
1145 Hg for the more intensive goal (Intensive Group) and SBP <140 mm Hg for the less  
1146 intensive goal (Standard Group). Figures 4.1 and 4.2 describe the treatment algorithms  
1147 for the two treatment groups. Although there are no diastolic blood pressure (DBP)  
1148 inclusion criteria, participants in both groups with DBP ≥90 mm Hg will be treated to a  
1149 DBP goal of <90 mm Hg if needed after meeting the SBP goal, because of the many  
1150 trials documenting the CVD benefits in treating to a DBP goal <90 mm Hg.

1151

### 1152 **Antihypertensive Classes (Agents)**

1153

1154 Use of once-daily preparations of antihypertensive agents will be encouraged unless  
1155 alternative dosing frequency (e.g., BID) is indicated/necessary. One or more medications  
1156 from the following classes of agents will be provided by the study and intended for use in  
1157 managing participants in both randomization groups to achieve study goals:

1158

- 1159 • Angiotension converting enzyme (ACE)-inhibitors
- 1160 • Angiotension receptor blockers (ARBs)
- 1161 • Direct vasodilators
- 1162 • Thiazide-type diuretics
- 1163 • Loop diuretics
- 1164 • Potassium-sparing diuretics

- 1165 • Beta-blockers
- 1166 • Sustained-release calcium channel blockers (CCBs)
- 1167 • Alpha1-receptor blockers
- 1168 • Sympatholytics

1169  
1170 Combination products will be available, depending on cost, utility, or donations from  
1171 pharmaceutical companies

### 1172 1173 **Selection of Antihypertensive Medications**

1174  
1175 The SPRINT trial is testing a treatment strategy question regarding different SBP goals  
1176 and not testing specific medications. The SPRINT BP treatment protocol is flexible in  
1177 terms of the choice and doses of antihypertensive medications, but there should be  
1178 preferences among the drug classes, based on CVD outcome trials results and current  
1179 guidelines. NHLBI is updating various guidelines. The update of hypertension  
1180 recommendations, JNC-8, should be available early in the recruitment phase of SPRINT.  
1181 These updates, along with any new scientific developments, will be considered during  
1182 and following SPRINT protocol development and throughout the trial.

1183  
1184 The investigator may select among the available SPRINT antihypertensive medications  
1185 for initiation of therapy. Other drugs not supplied by the trial may also be used as the  
1186 investigator determines appropriate. However, all antihypertensive regimens should  
1187 include one or more drug classes with strong CVD outcome data from large randomized  
1188 controlled hypertension trials, i.e., a thiazide-type diuretic, calcium channel blocker, ACE  
1189 inhibitor or ARB. Current evidence, the most recent JNC guidelines and over 40 years  
1190 of clinical trial experience in hypertension support the inclusion of a thiazide-type diuretic  
1191 as one of the agents for patients without compelling reasons for another medication, or  
1192 contraindication or intolerance to a thiazide-type diuretic. (ALLHAT, 2002;Beckett and  
1193 others, 2008;Chobanian and others, 2003;Psaty and others, 1997;SHEP, 1991) Other  
1194 classes associated with substantial reductions in CVD outcomes in hypertension trials,  
1195 e.g. ACE inhibitors, ARBs, and calcium channel blockers, combine effectively with  
1196 thiazides for lowering BP (Julius and others, 2004). ACE inhibitors and ARBs also  
1197 combine well with CCBs; if three drugs are needed, a thiazide-type diuretic, a RAS  
1198 blocker (ACE inhibitor or ARB, but usually not both), and CCB make a very effective and  
1199 usually well-tolerated regimen (Calhoun and others, 2009). The preference for the order  
1200 in which these agents are selected is left to the investigator as long as the SBP goals  
1201 are achieved. A loop diuretic may be needed in addition to or in place of a thiazide-type  
1202 diuretic for participants with advanced CKD.

1203  
1204 Beta-adrenergic blockers, which were recommended in JNC-7 among the 4 preferred  
1205 classes after diuretics, are now considered to be less effective in preventing CVD events  
1206 as primary treatment of hypertension compared with thiazide-type diuretics, CCBs, and  
1207 RAS blockers (Lindholm, Carlberg, and Samuelsson, 2005) However, there are patients  
1208 for whom beta-blockers should be part of the initial therapy, namely those with coronary  
1209 artery disease, including chronic stable angina or previous MI (Rosendorff and others,  
1210 2007).

1211  
1212 Finally, although renoprotective benefits have been demonstrated in CKD patients with  
1213 proteinuria, ACE inhibitors (and likely other RAS blockers) are less effective than other  
1214 classes in lowering BP and in preventing CVD events in African American and elderly

1215 hypertensive patients unless combined with a diuretic or CCB (Julius and others,  
1216 2004;Mancia and others, 2007;National Collaborating Centre for Chronic Conditions,  
1217 2006;Wright and others, 2005;Wright and others, 2008).

1218  
1219 Since more than three drugs will be necessary in many participants to reach the  
1220 intensive SBP goal, other classes will also be available in SPRINT. These include the  
1221 potassium-sparing diuretics, spironolactone and/or amiloride, which are very effective as  
1222 add-on agents for BP-lowering in “resistant hypertension” (Calhoun and others, 2008).  
1223 However, they should be used with careful monitoring in participants with CKD or any  
1224 tendency to hyperkalemia. Alpha-blockers have been used effectively as add-on  
1225 therapy in the AASK, ACCORD and Anglo-Scandinavian Cardiac Outcomes (ASCOT)  
1226 trials. However, alpha-blockers should be used only in combination with one or more  
1227 other agents proven to reduce CVD events in hypertensive patients (ALLHAT, 2003).  
1228 Sympatholytics, direct vasodilators, and/or loop diuretics may also be added for BP  
1229 control in combination with agents proven to reduce CVD events.

1230  
1231 Among thiazide-type diuretics, the most consistent and robust CVD outcome data have  
1232 been seen with chlorthalidone (ALLHAT, 2002;SHEP, 1991). Chlorthalidone 12.5-25  
1233 mg/d has been shown to be more effective in lowering BP over 24 hours than  
1234 hydrochlorothiazide 25-50 mg/d (Ernst and others, 2006). Among CCBs, amlodipine has  
1235 been used in far more hypertension CVD outcome trials than any other agent and has  
1236 more robust CVD outcome data. Amlodipine should be considered first when a CCB is  
1237 to be used. In the presence of significant proteinuria, amlodipine should probably be  
1238 used in conjunction with a RAS blocker. If a non-dihydropyridine CCB (e.g., diltiazem) is  
1239 to be used, it should not be combined with a beta-blocker.

1240  
1241 The ACCORD experience (The ACCORD Study Group, 2010) has shown that a  
1242 treatment strategy that includes a variety of classes, can produce a 14 mm Hg delta in  
1243 SBP between the two randomized groups. The average number of antihypertensive  
1244 drugs used to produce this difference was 3.4 and 2.1 in the Intensive and Standard  
1245 Groups, respectively. It is anticipated that the study participants in the CKD subgroup of  
1246 SPRINT will require a greater number of antihypertensive drugs to reach the lower BP  
1247 goal (Cushman and others, 2008)

#### 1248 1249 **Visit Frequency**

1250  
1251 For both randomized groups, routine visit frequency will be monthly for the first three  
1252 months after randomization, then every three months for the duration of the trial.  
1253 “Monthly visits will continue in the Intensive Group until SBP <120 mm Hg (or no more  
1254 titration planned) and in the Standard group whenever SBP  $\geq$  160 mm Hg.” Additional  
1255 visits will be scheduled as needed for management of adverse effects or for monitoring  
1256 significant medication changes or other clinical issues.

#### 1257 1258 **Intensive BP Goal Group (Figure 4.1)**

1259  
1260 The SBP goal for the Intensive Group, <120 mm Hg, should be achievable in the  
1261 majority of participants within 8-12 months of follow-up based on the ACCORD  
1262 experience (The ACCORD Study Group, 2010). For most participants in the Intensive  
1263 Group, a two- or three-drug regimen of a diuretic and either an ACE inhibitor or ARB  
1264 and/or a CCB should be initiated at randomization. If a diuretic is contraindicated or not  
1265 tolerated, an ACE inhibitor or ARB plus a CCB should be initiated. A beta-blocker

1266 should be included in the initial regimen, usually in combination with a diuretic, if there is  
1267 a compelling indication for a beta-blocker. Drug doses should be increased and/or  
1268 additional antihypertensive medications should be added at each visit in the Intensive  
1269 Group, usually at monthly intervals, until the participant's goal of <120 mm Hg has been  
1270 reached or the investigator decides no further antihypertensive medications may be  
1271 added.

1272  
1273 SPRINT provides a unique opportunity to determine both the efficacy and safety of  
1274 intensive BP control in elderly populations. However, based on limited data, there is a  
1275 concern that this population may be less tolerant of aggressive BP lowering. Therefore,  
1276 in participants  $\geq 75$  years of age randomized to the intensive BP goal who are on 0-1  
1277 antihypertensive medications and have baseline SBP <140 mm Hg, antihypertensive  
1278 therapy may be initiated with a single agent at the discretion of the investigator with a  
1279 return visit scheduled in one month. If the participant is asymptomatic at the first post-  
1280 randomization visit and SBP  $\geq 130$  mm Hg, a second agent will be added and titration  
1281 continued as indicated in above.

### 1282 1283 **Milepost Visits**

1284  
1285 “Clinical inertia” in hypertension management, where clinicians fail to intensify therapy  
1286 despite patients not being at goal BP, has been observed in both clinical practice  
1287 (Berlowitz and others, 1998) and clinical trial settings (Cushman and others, 2002). For  
1288 this reason, “Milepost Visits” were used in the intensive BP group in the ACCORD trial to  
1289 assist in reaching goal SBP (Cushman and others, 2007). For SPRINT participants in  
1290 the Intensive Group, Milepost Visits will be every 6 months throughout follow-up,  
1291 beginning at the 6-month visit. If the SBP is not <120 mm Hg at a Milepost Visit, then an  
1292 antihypertensive drug from a class different from what is being taken should be added,  
1293 unless there are compelling reasons to wait. A “Milepost Exemption Form” will be  
1294 completed whenever a new drug is not added at a Milepost Visit in which the  
1295 participant's BP is not <120 mm Hg to document the reason for not adding a drug and to  
1296 outline a plan for making progress toward goal in that participant. Milepost Visit  
1297 procedures do not apply to the Standard Group. Once the Intensive Group participant  
1298 has been prescribed 5 drugs at maximally tolerated doses, if the BP remains above goal  
1299 at subsequent Milepost Visits, it will be permitted to substitute a different class into the  
1300 regimen instead of adding another drug or increasing the dose of a drug. However,  
1301 additional (more than 5) drugs may be needed to achieve goal SBP in some participants.  
1302 Medication adherence will be assessed routinely in SPRINT and should be evaluated  
1303 especially carefully for participants not at goal on 4 or more medications. Strategies to  
1304 enhance adherence are described in brief in Chapter 5 and in detail in the Manual of  
1305 Procedures and Adherence Binder.

### 1306 1307 **Standard BP Goal Group (Figure 4.2)**

1308  
1309 The SBP goal for the Standard Group, <140 mm Hg, should be achievable in the  
1310 majority of participants within 3-6 months, based on the ACCORD experience (The  
1311 ACCORD Study Group, 2010). The standard BP protocol is designed to achieve a SBP  
1312 of 135-139 mm Hg in as many participants as possible. Participants in this group may or  
1313 may not be on treatment with one or more antihypertensive medications. If  
1314 antihypertensive medication(s) is indicated per protocol, consideration should be given  
1315 to including a thiazide-type diuretic as initial therapy or as part of the regimen, unless  
1316 there is a compelling indication for another drug class or intolerance to a thiazide.

1317 At the randomization visit, Standard Group participants on previous antihypertensive  
1318 drug therapy should be converted to SPRINT medications or no medications, depending  
1319 on what the investigator believes is most likely to achieve a SBP level between 135-139  
1320 mm Hg. Because we expect a decrease in average SBP within the Standard Group  
1321 following randomization due to improved adherence, lifestyle counseling, and intra-  
1322 individual variation, sometimes described as “regression to the mean”, treatment should  
1323 not be intensified at the randomization visit for Standard Group participants unless SBP  
1324  $\geq 160$  mm Hg or there is a compelling reason to add medication, e.g., management of  
1325 fluid balance in participants with CKD. Following the randomization visit, medication  
1326 dose titration or addition of another drug is indicated if SBP is  $\geq 160$  mm Hg at a single  
1327 visit or is  $\geq 140$  mm Hg at two successive visits.

1328  
1329 Because it is not known if lowering SBP to the more intensive SPRINT goal of  $< 120$  mm  
1330 Hg, compared with the standard goal of  $< 140$  mm Hg, is beneficial, neutral, or harmful in  
1331 patients such as those entered into the SPRINT trial, careful step-down (a reduction of  
1332 the dose or number of antihypertensive drugs) is allowed for participants in the Standard  
1333 Group. Down-titration was not permitted in the HOT Trial if DBP was well below the goal  
1334 for a participant (Hansson and others, 1998) – this likely contributed to the small  
1335 differences in achieved BP between the three randomized groups and limited the study's  
1336 ability to detect differences in outcomes. Therefore, down-titration was included in the  
1337 ACCORD and AASK standard BP protocols and was successful in generating the  
1338 planned differences in BP between treatment arms. Down titration should be carried out  
1339 if the SBP is  $< 130$  mm Hg at a single visit or  $< 135$  mm Hg at two consecutive visits  
1340 (Figure 4.2).

1341

#### 1342 **Diastolic Blood Pressure Treatment**

1343

1344 Once the SBP goal has been achieved in any participant, the antihypertensive regimen  
1345 should be intensified if DBP remains  $\geq 100$  mm Hg at a single visit or  $\geq 90$  mm Hg at two  
1346 successive visits to achieve DBP  $< 90$  mm Hg. The visit intervals and decisions for  
1347 titration (other than the BP levels) will be similar to those used for the SBP goal. Since  
1348 beta-blockers reduce DBP more than SBP relative to other antihypertensive  
1349 medications, a beta-blocker could be considered for such participants (Cushman and  
1350 others, 2001).

1351

#### 1352 **Use of Home BP Devices**

1353

1354 Home BP devices will not be provided to all participants by the trial. Since virtually all  
1355 BP outcome trials have used office BP determinations and home readings are subject to  
1356 more bias and error, in SPRINT titration of medications to goal should be based on office  
1357 readings rather than home BP determinations.

1358

#### 1359 **Assessment of Orthostatic Hypotension (OH), Measurement of Standing Blood 1360 Pressure**

1361

1362 Standing BP will be measured at screening, baseline, 1 month, 6 months, 12 months,  
1363 and annually thereafter, and the close-out visit, using the same BP device that is used to  
1364 measure seated BP. After seated determinations, participants will be asked to stand.  
1365 Beginning when their feet touch the floor, BP will be taken one minute later in the same  
1366 arm used for the seated measurements, using the BP device. Participants will be asked  
1367 after the standing determination if they had any symptoms of orthostatic hypotension

1368 during the standing BP measurement. The Coordinating Center will calculate BP  
1369 change using the standing measurements minus the mean of the seated measurements.  
1370

1371 Participants with standing SBP <110 mm Hg will not be eligible for randomization (may  
1372 be rescreened if corrected). However, the detection of asymptomatic orthostatic  
1373 hypotension, i.e., orthostatic hypotension unaccompanied by orthostatic symptoms of  
1374 dizziness, presyncope or syncope, will not influence the antihypertensive drug treatment  
1375 algorithm. Symptomatic orthostatic hypotension will be managed as described in  
1376 "Management of Symptomatic Orthostatic Hypotension" (see Manual of Procedures).  
1377

#### 1378 **4.1 Lifestyle Recommendations and Background Therapy** 1379

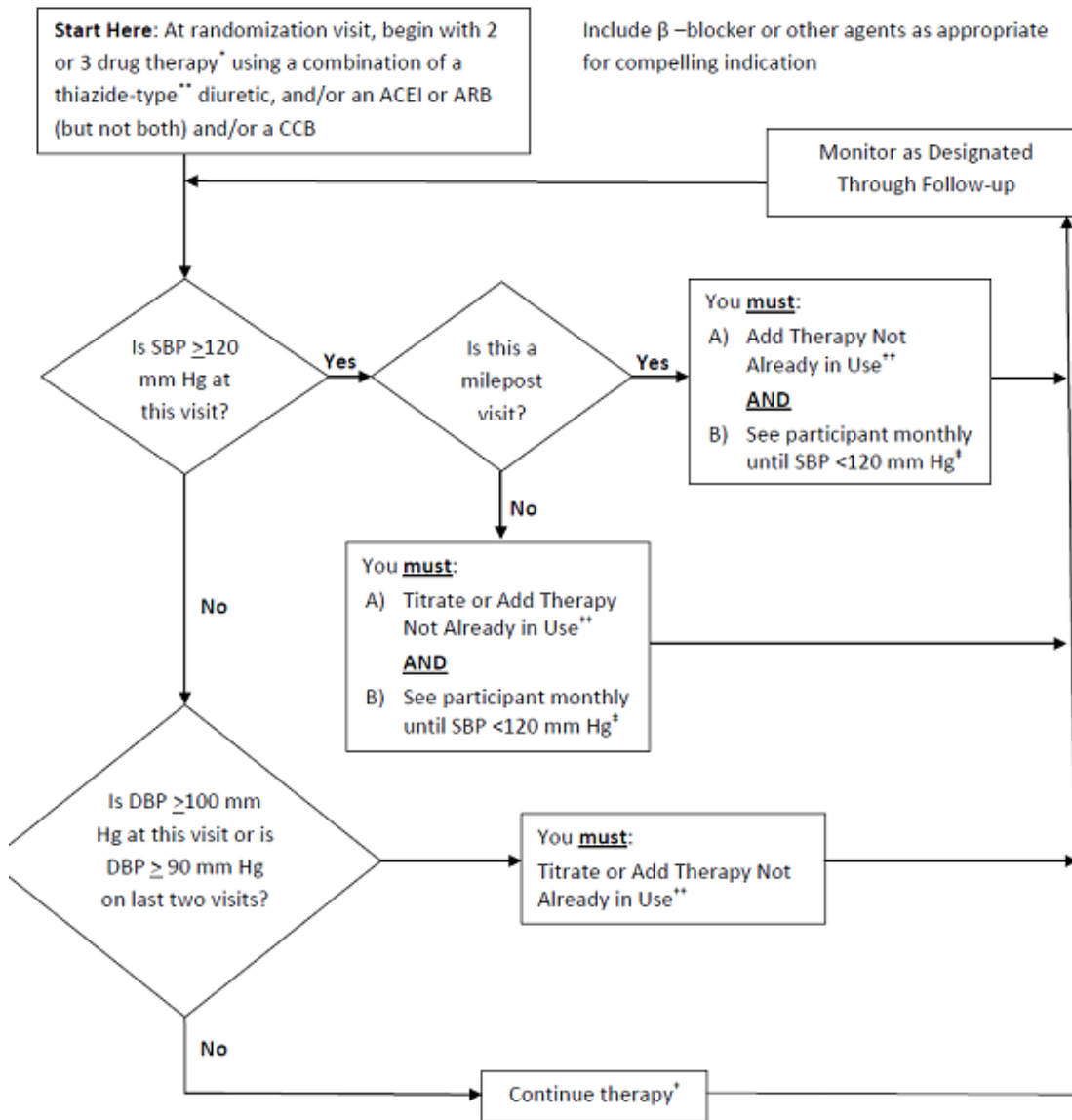
1380 The purpose of including lifestyle recommendations and background therapy in SPRINT  
1381 is twofold. First, it fosters high quality general medical care in all SPRINT participants in  
1382 accordance with current practice guidelines. Second, it is intended that background  
1383 therapies will be utilized equally across both study arms in order to minimize the  
1384 differences in the effects of non-study strategies on the SBP or CV outcomes between  
1385 arms. The background therapy recommendations will be provided to the participants  
1386 and their physicians. Background therapy is considered part of usual recommended  
1387 care for patients at risk of CVD and, as such, is not covered by research study costs.  
1388 The delivery of these background therapies will be left up to the participants' own  
1389 clinicians.  
1390

1391 The Lifestyle and Background Therapy Working Group will coordinate the provision of  
1392 the most current and relevant participant educational materials to be made available for  
1393 study-wide use. These will include the topics of medical nutrition therapy, weight  
1394 management, physical activity, smoking cessation, and anti-thrombotic therapy, and will  
1395 complement educational materials related to the BP interventions that are part of the  
1396 trial. Unlike most educational materials for BP, the SPRINT materials will not include  
1397 specific goals for BP as these will depend on the participants' randomized treatment  
1398 assignment. Specific recommendations will include: a) weight loss in those who are  
1399 overweight or obese; b) adoption of a diet rich in fruits, vegetables and low-fat dairy  
1400 products (the DASH diet) with appropriate modifications for participants with CKD; c)  
1401 reduction in sodium intake to recommended levels; d) reduction of alcohol consumption  
1402 to recommended levels; and e) participation in regular aerobic exercise. SPRINT  
1403 participants will be encouraged to stop smoking (if a current smoker) and to follow  
1404 current guidelines for testing for and treatment of dyslipidemia and the use of  
1405 antithrombotic therapy.  
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Figure 4.1 Treatment Algorithm for Intensive Group (Goal SBP < 120 mm Hg)



\* May begin with a single agent for participants 75 years old or older with SBP < 140 on 0-1 meds at study entry. A second medication should be added at the 1 Month visit if participant is asymptomatic and SBP ≥ 130.

\*\* May use loop diuretic for participants with advanced CKD

† Unless side effects warrant change in therapy

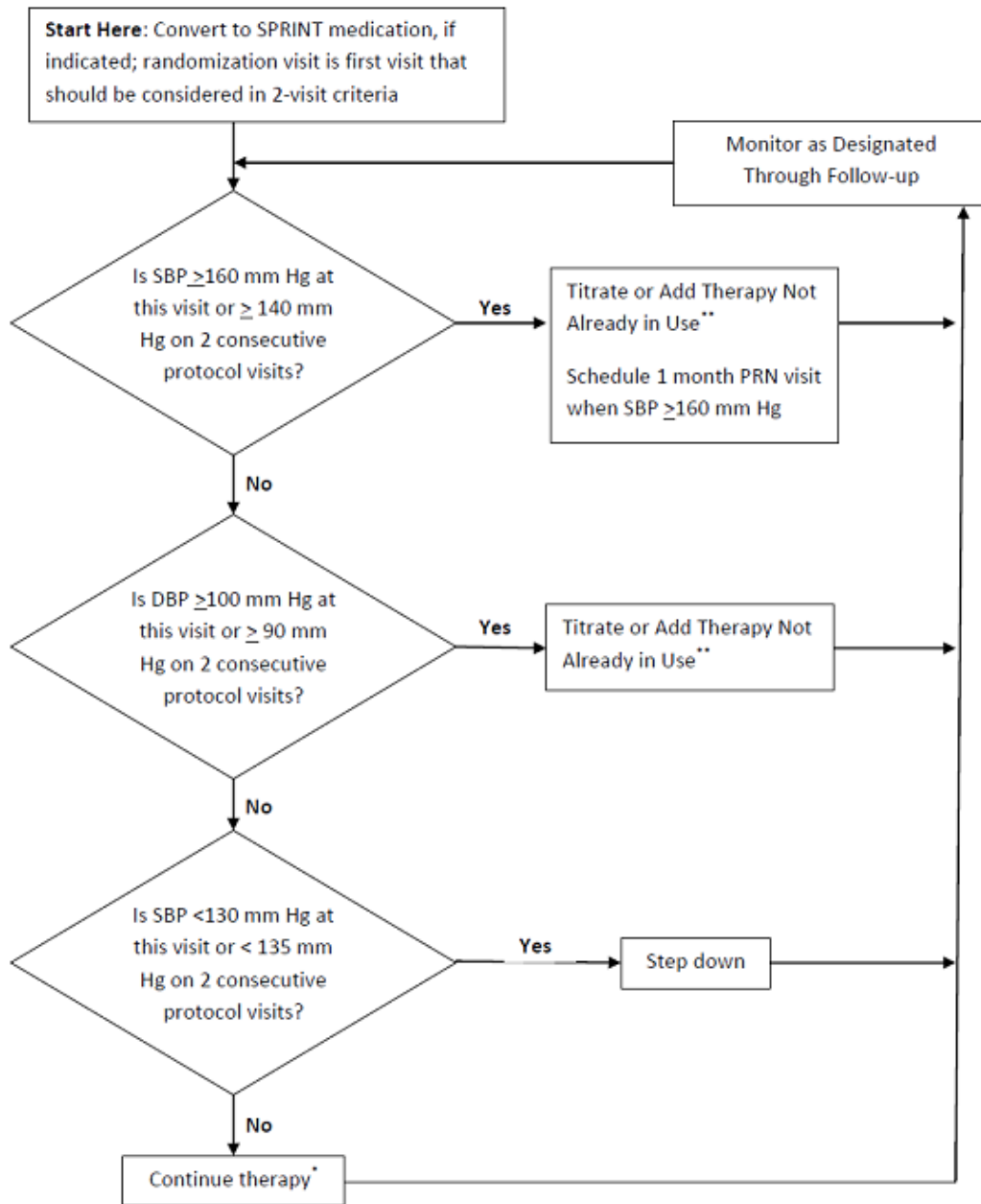
\*\* Consider consulting with the Clinical Center Network before adding a fifth anti-hypertensive medication

† Or until clinical decision made that therapy should not be increased further

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Figure 4.2 Treatment Algorithm for Standard Group (Goal SBP < 140 mm Hg)



Include  $\beta$ -blocker or other agents as appropriate for compelling indications

\* Unless side effects warrant change in therapy

\*\* Consider consulting with the Clinical Center Network before adding a fifth anti-hypertensive medication

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## **Chapter 5 – Measurements and Follow-up**

### **5.1.1 Schedule of Follow-Up Visits**

Post-randomization follow-up visit schedules for data collection do not differ by treatment group assignment. However, the visit schedule for treatment, that is achieving the BP goals, may differ by group while blood pressure goals are being met because of PRN visits not shown on Table 5.1. Additional information on treatment schedules is contained in Chapter 4 describing the SPRINT BP intervention. For data collection in both randomized groups, all participants will have post-randomization visits at Months 1, 2, 3, 6, and every 3 months thereafter. For the purpose of event ascertainment, all participants in both treatment groups will be queried regarding the occurrence of a possible event on the same schedule, specifically every 3 months.

### **5.1.2 Procedures by Visit**

Scheduled examination components are shown by visit in Table 5.1. Assessments performed at the various visits include blood and urine collection, physical measures, and questionnaires. Assessments will be performed on the same schedule for both randomization groups. Baseline characteristics to define the patient population include sociodemographics, anthropometrics, BP, pulse, current and past medical history, concomitant medications, laboratory, dementia screening, cognitive function (subset), MRI (subset) and quality of life measurements. A physical examination is included for safety but is not standardized, and left to the discretion of the investigator.

## **5.2. Blood and urine collection and laboratory assays**

Specific laboratory assessments (e.g. serum creatinine, fasting serum glucose, etc) are important for determining eligibility status. During follow-up, laboratory results will be used to monitor and adjust therapy in efforts to maintain blood pressure goals, assess safety (e.g. serum potassium concentrations), and to assess for study-related outcomes (e.g. deterioration of estimated glomerular filtration rate or increased protein excretion).

Serum, plasma, and urine samples will be stored for future measurements of other less traditional CV risk factors. White blood cells will be collected at baseline for DNA extraction for future genetic studies. It may prove possible to identify subgroups, defined by specific genes or genetic markers, which respond differentially to the various blood pressure treatment strategies.

## **5.3. Physical Examination Measures**

### **5.3.1 Seated Blood Pressure and Pulse**

Seated blood pressure and pulse are measured at each clinic visit after a rest period using an automated device or manual devices if necessary. The preferred method is the automated device as it offers reduced potential for observer biases and decreased demand on staff in terms of training and effort in data collection.

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**Table 5.1. Measures and Frequency**

	Screening /RZ	1 mo	2 mo	3 mo	6 mo	9 mo	1 yr	Q 3 mo	Q 6 mo	2 yr	3 yr	4 yr	Close Out A*	Close Out B**
<b>Blood collection</b>														
Chemistry profile		X		X	X				X		X		X	
Fasting Chemistry profile	X						X			X		X		X
Fasting glucose	X									X		X		X
Fasting lipid profile	X						X			X		X		X
Fasting serum and plasma storage	X						X			X		X		X
Genomic material	X													
Complete Blood Count (CBC)***													X	X
<b>Urine collection</b>														
Albumin, creatinine	X				X		X			X	X	X	X	X
Fasting urine storage	X						X			X		X		X
<b>Physical measures</b>														
Seated blood pressure, pulse, & medication adjustment	X	X	X	X	X	X	X	X		X	X	X	X	X
Standing blood pressure	X	X			X		X			X	X	X	X	X
Weight	X						X			X	X	X	X	X
Height	X													
ECG	X									X		X		X
Physical examination	X						X			X	X	X	As required locally	As required locally
4 meter walk (≥ 75 ONLY)	X						X			X	X	X	X	X
<b>Questionnaires</b>														
Medical history	X													
Sociodemographics	X													
Alcohol use	X													
Smoking	X						X			X	X	X	X	X
Concomitant medications	X						X			X	X	X	X	X
Adherence & Adverse Events		X	X	X	X	X	X	X		X	X	X	X	X
Outcomes Ascertainment				X	X	X	X	X		X	X	X	X	X
<b>Health related quality of life</b>														
EQ-5D	X						X			X	X	X	X	X
Veterans Rand 12	X						X			X	X	X	X	X
PHQ-9 Depression	X						X			X	X	X	X	X
Patient satisfaction/Morisky	X						X					X		X
<b>Health related quality of life (subsets)</b>														
Falls Efficacy (FESI-I)	X				X		X			X	X	X		X
Sexual Function (FSFI/IEFF)	X				X		X			X	X	X		X

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1472  
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MIND Questionnaires/Tests	Screening or RZ	2 yr	4 yr	Close Out A*	Close Out B**
<b>Dementia Screening</b>					
MoCA	X	X	X		X
Digits Symbol Coding Test	X	X	X		X
Logical Memory Test Story A	X	X	X		X
<b>Cognitive Battery (subset)</b>					
Hopkins Verbal Learning Test	X	X	X		X
Trail Making Tests A and B	X	X	X		X
Digit Span	X	X	X		X
Boston Naming Test	X	X	X		X
Modified Rey-Osterrieth Figure	X	X	X		X
Verbal Fluency Animals	X	X	X		X

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**\*Close-out Visit A – Participants who have completed year 4 visit by the date of the site approval of this protocol amendment**

**\*\*Close-out Visit B – Participants who have NOT completed year 4 visit by the date of site approval of this protocol amendment**

**\*\*\*Complete Blood Count (CBC) will only be performed on participants included in the MRI study**

### 5.3.2 Standing (Orthostatic) Blood Pressure

Standing BP will be measured at screening, baseline, 1 month, 6 months, 12 months, and annually thereafter, and the close-out visit, using the same BP device that is used to measure seated BP. After seated determinations, participants will be asked to stand. Beginning when their feet touch the floor, BP will be taken one minute later in the same arm used for the seated measurements, using the BP device. Participants will be asked after the standing determination if they had any symptoms of orthostatic hypotension during the standing BP measurement. The Coordinating Center will calculate BP change using the standing measurements minus the mean of the seated measurements.

### 5.3.3 Anthropometric Measurements (Weight and Height)

Body fat is a significant predictor for subclinical and clinically manifested cardiovascular disease. In addition, exercise and dietary modification with the goal of reducing total body fat may facilitate blood pressure control. Anthropometric measures gathered for SPRINT include height and weight for the calculation of body mass index.

1502 **5.3.4 Electrocardiography**

1503

1504 A 12-lead ECG is obtained at baseline and at the 2 and 4 year follow-up visits and close-  
1505 out visit, if the participant has not yet reached the 4 year follow-up visit, to ascertain the  
1506 occurrence of silent (unrecognized) MI, primarily, as well as atrial fibrillation and left  
1507 ventricular hypertrophy. The baseline ECG is used to identify previous (including silent)  
1508 MIs, and to identify evidence of left ventricular hypertrophy.

1509

1510 **5.3.5 Physical Examination**

1511

1512 The physical examination includes components of a systems-based examination  
1513 deemed necessary for safety by the SPRINT site investigator. Elements of the  
1514 examination to be completed may vary depending upon the health status and any  
1515 symptoms reported by the participant, the time and type of visit (initial, interval, annual,  
1516 close-out). The physical examination will not be standardized or data entered, but will be  
1517 available in the source documents for each participant.

1518

1519 **5.3.6 Four meter walk**

1520

1521 Participants who are 75 years old or older at baseline will be asked to complete a timed  
1522 4 meter walk to assess physical function. This will be done at baseline, annually, and at  
1523 the close-out visit.

1524

1525 **5.4. Questionnaires**

1526

1527 **5.4.1 Medical History**

1528

1529 A detailed history of cardiovascular disease is collected at screening. The presence of  
1530 CVD and CKD prior to entry into the study serves as an eligibility and stratification factor.  
1531 Data regarding the duration of chronic kidney disease and the presence of complications  
1532 are important for descriptive purposes, subgroup analyses, and prognostic analyses.

1533

1534 **5.4.2 Sociodemographics**

1535

1536 Information is collected during screening/baseline regarding age, race and ethnicity,  
1537 gender, level of education, marital status, persons living with participants and United  
1538 States (zip) postal code. These data will be used to identify eligible participants and to  
1539 characterize the final study population.

1540

1541 **5.4.3 Smoking/alcohol use**

1542

1543 Consumption of alcohol and tobacco have important implications on cardiovascular risk,  
1544 and adherence to medication regimens. Participants will be assessed at baseline for  
1545 lifetime tobacco exposure, alcohol intake and binge drinking. At annual assessments  
1546 and at the close-out visit, current smoking will be assessed.

1547

1548 **5.4.4 Concomitant Medications**

1549

1550 Information regarding the participants' concomitant non-study medication therapy is  
1551 collected and documented at baseline and then reviewed and revised at annual follow-  
1552 up visits as well as at the close-out visit. Appropriate sources for obtaining this

1553 information include participant report, current pharmacy action profiles, and verification  
1554 of medications documented in the medical record. Although data are collected on all  
1555 current therapies, emphasis is placed on concurrent antihypertensive, cardiovascular,  
1556 chronic kidney disease and dementia medications as well as background risk reduction  
1557 therapy such as aspirin and lipid-lowering drugs.  
1558

#### 1559 **5.4.5 Monitoring Adherence**

1560  
1561 Adherence to antihypertensive medications will be assessed as follows:  
1562

1563 First, an adherence scale will be administered to all participants at the baseline, 12 month and  
1564 48 month visits, and the close-out visit if the participant has not reached their 48M visit at the  
1565 time of close-out, in order to identify low adherence.  
1566

1567 Secondly, at every medication management visit, participants will be administered a single  
1568 item to screen for low adherence. If the participant's response to this item indicates a possible  
1569 problem with adherence, or if the participant is not at the appropriate blood pressure target,  
1570 study personnel will address the specific issues and barriers for each study participant that  
1571 may be preventing optimal adherence. In such instances, administration of the Adherence  
1572 Scale (to identify reasons for nonadherence) is recommended, as is use of the materials and  
1573 procedures described in the adherence binder. Details regarding the adherence monitoring  
1574 procedure, scoring algorithm for the Adherence Scale and the procedures to follow when low  
1575 adherence is identified are provided in the MOP.  
1576

#### 1577 **5.4.6 Adverse events**

1578  
1579 Adverse event ascertainment and reporting is described in chapter 8.  
1580

#### 1581 **5.4.7 Study-related outcomes**

1582  
1583 Both randomized groups will be assessed for study related outcomes in the same way  
1584 and on the same schedule. After randomization, participants will be assessed every 3  
1585 months for cardiovascular and renal outcomes. Medical records will be collected for  
1586 adjudication of study outcomes as described in Chapter 9. Clinical center staff will use  
1587 available resources and contact information to assess vital status annually on  
1588 participants not attending study visits.  
1589

#### 1590 **5.4.8 Health-Related Quality of Life**

1591  
1592 All participants will be assessed for the effect of interventions on health-related quality of  
1593 life (see Chapter 7). HRQL data will be collected at Baseline, 12 months and annually  
1594 thereafter, as well as at the close-out visit. Depression using the PHQ-9 scale will be  
1595 assessed at baseline and annually thereafter, and at the close-out visit. A modified  
1596 TSQM General Satisfaction subscale will be administered at baseline and at 1 and 4  
1597 years. A subset of participants will undergo additional data collection related to fall self-  
1598 efficacy and sexual functioning at baseline, 6 months and annually thereafter. This same  
1599 subset will receive the fall self-efficacy at the close-out visit, if the participant has not yet  
1600 reached the 4 year follow-up visit.  
1601  
1602  
1603

1604 **5.4.9 MIND Battery: Dementia Screening**

1605

1606 All participants will undergo a dementia screening at baseline, 24M, and 48M or close-  
1607 out visit (only if the participant has not completed the 48M MIND tests). The tests will  
1608 include the Montreal Cognitive Assessment (MoCA), Digit Symbol Coding test, and  
1609 Logical Memory test. A subset of 2800 participants will undergo an additional  
1610 comprehensive battery of neurocognitive tests conducted at baseline, Month 24, and  
1611 Month 48 or close-out visit (only if the participant has not completed the 48M MIND  
1612 tests). In addition, participants who trip the dementia screening battery also will receive  
1613 this comprehensive battery of neurocognitive tests. In addition to the neurocognitive  
1614 tests, a subsample of 640 MIND participants will have a Baseline and Month 48 MRI  
1615 examination.

1616

1617 **5.4.10 Consent for Future Contact**

1618

1619 At the close-out visit, participants will be asked to sign an addendum to the informed  
1620 consent for future contact.

1621

1622 **5.5. Medications and Adherence**

1623

1624 **Adherence**

1625

1626 As part of a central pretrial training session, all investigators and clinical coordinators will  
1627 receive instruction on adherence issues. Additionally, study staff will periodically have  
1628 refresher and retraining instruction in the overall adherence program throughout the trial.  
1629 Also critical to maintaining good adherence is the routine discussion of participants who  
1630 show problems with adherence and brain-storming about problem-solving strategies  
1631 during clinic team meetings and Study Coordinator meetings and conference calls. Of  
1632 particular importance is the involvement of all members of the clinic team, including clinic  
1633 leadership, in adherence-related monitoring and problem-solving.

1634

1635 **Drug Dispensing, Ordering, Storage, and Disposal**

1636 Drug Dispensing

1637

1638 The complexity created by the large number of medications and multiple treatment  
1639 strategies employed by SPRINT requires substantial attention to the process of  
1640 medication dispensing. All study medications dispensed to the participants will be  
1641 labeled and identified with the study name, participant's name, medication name,  
1642 strength and quantity, directions for use, and authorized prescriber's name. An  
1643 emergency study-related phone number for study drug information will also appear on  
1644 the label. All participants are to be verbally counseled on medication administration.  
1645 Written instructions will also be provided.

1646

1647 Participants receive medication supplies at regularly scheduled visits in sufficient  
1648 quantity to last until the next scheduled visit. Medication dispensing may occur in the  
1649 intervening periods between visits in case of emergency, loss, or schedule changes. A  
1650 tracking mechanism is maintained for all dispensing actions. It is recommended that  
1651 authorized dispensing personnel be limited in number to assure proper adherence with  
1652 established accountability and dispensing procedures.

1653



1654 Drug Supply Ordering

1655 Each Clinical Site, upon completion of procedures for study initiation, will receive a  
1656 standard initial shipment (determined by the Coordinating Center and prepared by the  
1657 Drug Distribution Center (DDC)) of study drug supplies for the trial. It is expected that  
1658 this initial shipment will suffice for a specified number of visits for a given number of  
1659 randomized participants. Subsequent ordering of inventory will be managed by the site,  
1660 primarily through the web-based inventory system. Sites are responsible for  
1661 appropriately managing their inventory and are able to customize their medication  
1662 quantities to suit the prescribing practices of their site.

1663  
1664 The DDC in consultation with each Clinical Site sets inventory levels for each item.  
1665 When an item reaches the reorder point, additional stock is automatically shipped from  
1666 the DDC.

1667  
1668 Drug Receipt and Storage

1669 Drug shipments are sent to the Clinical Site in care of a designated staff member. The  
1670 shipment is inspected for damage and its contents reconciled with the accompanying  
1671 SPRINT Shipping Notice. The inventory is logged using the established tracking  
1672 mechanism. Packing slips are filed in a secure location. Any damage or discrepancies in  
1673 the shipment are to be reported promptly to the DDC for corrective action. Each Clinical  
1674 Site is responsible for storing the study drug supplies in a locked, secure area with  
1675 limited access. Manufacturer recommendations and local policies for drug storage are  
1676 followed.

1677  
1678 Drug Disposal

1679  
1680 Clinical Sites are authorized to destroy SPRINT stock locally, complying with any local  
1681 policies and procedures. Destruction will be documented via the web-based inventory  
1682 system. All study drugs are labeled with an expiration date. Prior to expiration, the DDC  
1683 will automatically ship replacement stock based on the current electronic inventory  
1684 profile. Once replacement stock is received the clinical site will destroy expired stock and  
1685 document destruction as described above.

1686

## 1687 **Chapter 6 – SPRINT MIND**

1688

### 1689 **6.1 SPRINT-MIND Overview**

1690

1691 SPRINT-MIND is an integral part of the overall SPRINT study and all SPRINT  
1692 participants will participate in one or more components of SPRINT-MIND. There are  
1693 three objectives of SPRINT-MIND. The primary objective is to determine whether a  
1694 strategy of intensive blood pressure lowering to target systolic blood pressure (SBP)  
1695 <120 mm Hg versus a standard treatment target of <140 mm Hg will produce a greater  
1696 reduction in the incidence of all-cause dementia. The second objective is to determine  
1697 whether global cognitive function measured in key specific domains of cognition will  
1698 decline less in persons randomized to a SBP goal of <120 mm Hg versus a standard  
1699 treatment goal of <140 mm Hg in a representative sub-sample of approximately 2800  
1700 SPRINT participants. The third objective is to assess whether MRI-derived changes in  
1701 brain structure differ by treatment assignment in a subset (approximately 640) of the  
1702 2800 participants.

1703

### 1704 **6.2 Study Hypotheses and Aims**

1705

#### 1706 **6.2.1 All-cause Dementia**

1707

1708 Primary hypothesis: Over an average of 60 months, the incidence of all-cause dementia  
1709 will be lower in SPRINT participants assigned to the intensive SBP treatment arm  
1710 compared to their counterparts assigned to the standard SBP treatment arm. This  
1711 hypothesis will be tested in all SPRINT participants.

1712

#### 1713 **6.2.2 Cognitive Decline**

1714

1715 Secondary hypothesis: Over an average of 48 months, the rate of global decline in  
1716 cognition measured across key domains of cognition will be lower in the intensive SBP  
1717 treatment arm compared to the standard SBP treatment arm. This hypothesis will be  
1718 tested in a representative subset of approximately 2800 participants enrolled in SPRINT.

1719

#### 1720 **6.2.3 MRI Brain Changes**

1721

1722 The Primary brain MRI hypothesis is that over an average of 48 months, the volume  
1723 small vessel ischemic disease (SVID) will be lower in SPRINT participants assigned to  
1724 the intensive SBP treatment arm compared to their counterparts assigned to the  
1725 standard SBP treatment arm. An additional hypothesis is that total brain volume will also  
1726 be greater (thus less atrophy) in the intensively treated group. The MRI sub-study will be  
1727 conducted in approximately 640 participants chosen from the 2800 subset of participants  
1728 selected in 6.2.2.

1729

### 1730 **6.3 Study Design**

1731

#### 1732 **6.3.1 Study Population**

1733

1734 We will ascertain incident all-cause dementia in all participants enrolled in SPRINT. In  
1735 addition, approximately 2800 participants will be selected to receive additional cognitive  
1736 assessments at baseline, 24 months, and 48 months (or the close-out visit if the 48

1737 month tests have not been administered) in order to examine changes in global and  
1738 domain-specific cognition. Participants participating in the MRI substudy will, at baseline,  
1739 generally be required to reside within 1.5 hours travel distance to a designated study  
1740 MRI Scanner. The components of the two cognitive batteries selected to assess  
1741 dementia incidence and decline in cognition are listed in Table 5.1 of Chapter 5.  
1742

## 1743 **6.4 Procedures for Identifying Incident All-Cause Dementia in SPRINT (see Figure** 1744 **6.1).**

### 1745 **6.4.1 Overview**

1746 A 3-step process will be used to ascertain incident cases of all-cause dementia. First, to  
1747 identify possible cases of dementia a brief Cognition Screening Battery will be  
1748 administered to all participants. Participants who score below the pre-designated  
1749 screening cut-point for possible cognitive impairment during follow-up will be  
1750 administered a more comprehensive and detailed neurocognitive test battery (the  
1751 Extended Cognitive Assessment Battery) plus the Functional Assessment Questionnaire  
1752 (FAQ) which assesses impairments in daily living skills as a result of cognitive  
1753 impairments. Last, all the above available tests and questionnaire data will be submitted  
1754 to a centralized, web-based system for adjudication by a panel of dementia experts who  
1755 will assign final study classifications of probable dementia (PD), mild cognitive  
1756 impairment (MCI) or no impairment (NI).  
1757  
1758

### 1759 **6.4.2 Cognition Screening Battery**

1760 A brief screening battery consisting of 3 well-validated neurocognitive tests will be  
1761 administered to all participants at study randomization and repeated at years 2, 4 (or  
1762 close-out if the Year 4 testing has not occurred. This battery requires 15 minutes or less  
1763 to administer.  
1764  
1765

1766 Tests included in the SPRINT-MIND Cognition Screening Battery were selected because  
1767 they are sensitive to detecting dementia, easy to administer and brief. They are:  
1768

- 1769 1. The Montreal Cognitive Assessment (MoCA) The MoCA (Nasreddine et al.,  
1770 2005) is part of the NIH Toolbox and is a reliable and valid brief screening  
1771 instrument for characterizing global cognitive functioning. It has been used  
1772 previously to screen for dementia and MCI with sensitivity of >85%. The MoCA  
1773 has several sub-scales that can be used to characterize more specific cognitive  
1774 functions.  
1775
- 1776 2. Digit Symbol Coding test (DSC) The DSC ((Wechsler, 1996b; Wechsler D., 1981)  
1777 is a sub-test of the Wechsler Adult Intelligence Scale-IV. It measures  
1778 psychomotor speed and working memory. The DSC and its predecessor the  
1779 Digit Symbol Substitution test have been extensively used and normed.  
1780
- 1781 3. Logical Memory test (LM): The LM test is a sub-test of the Wechsler Memory  
1782 Scale-IV(Wechsler, 1996a; Wechsler, 1996a). It measures episodic verbal  
1783 memory and has extensive normative data. Episodic verbal memory is an  
1784 especially sensitive predictor of early Alzheimer's dementia and amnesic MCI.  
1785  
1786

1787 The sensitivity and specificity of the Cognition Screening Battery to detect  
1788 participants with poorer cognitive function will be evaluated on an ongoing basis during  
1789 the trial by using available baseline cognition data from SPRINT. We estimate 20-25% of  
1790 participants will trip the battery and receive a brief assessment of the impact  
1791 of their cognitive function on daily life (the 10 item FAQ). At the years 2 and 4 (or close-  
1792 out visit if the Year 4 tests have not been administered, participants who trip the  
1793 screening battery will also be administered the SPRINT Extended Cognitive Assessment  
1794 Battery and the FAQ for adjudication of incident dementia. In order to achieve the 20-  
1795 25% target, various cut-points for the Cognition Screening Battery will be compared and  
1796 adjustments will be made to maximize study efficiency and economy during the trial.

#### 1797 **6.4.3 SPRINT Extended Cognitive Assessment Battery**

1798 The Extended Cognitive Assessment Battery will provide a more comprehensive and  
1799 detailed assessment of specific major cognitive functions (memory, language,  
1800 visuospatial skills, executive function) that are necessary for classification of dementia  
1801 and for detecting domain-specific changes. During follow-up years 2 and 4 (or the close-  
1802 out visit if the Year 4 tests have not been administered), participants scoring in the  
1803 impaired range on the Cognition Screening Battery will be administered the Extended  
1804 Cognitive Assessment Battery at their next scheduled visit (typically a blood pressure  
1805 assessment and medication distribution visit). This entire battery requires less than 40  
1806 minutes including scoring and data entry and less than 30 minutes in persons without  
1807 significant memory impairment.

1808  
1809 The neurocognitive tests comprising the Extended Cognitive Assessment Battery are:

- 1810
- 1811 1) The Hopkins Verbal Learning Test (HVLT) (Brandt and Benedict, 2001): A  
1812 measure of episodic verbal learning and memory, this test is a 12-item list  
1813 learning and memory task with immediate recall, delayed recall and recognition  
1814 components.  
1815
  - 1816 2) The Trail Making Test: Parts A and B (Reitan R.M., 1958): The Trail Making Test  
1817 (TMT) is a two-part test measuring speed of processing and executive function.  
1818 The times to complete Part A and Part B are the primary measures of interest.  
1819
  - 1820 3) Digit Span test (Wechsler D., 1981): The Digit Span test (DST), a subtest of the  
1821 Wechsler Adult Intelligence Scale-IV, requires the participant to recite gradually  
1822 increasing series of digits forward and backward. The DST measures  
1823 concentration and working memory.  
1824
  - 1825 4) The Boston Naming Test (Kaplan E et al., 1983) The Boston Naming Test (BNT)  
1826 is used to assess language function. The participant is asked to name familiar  
1827 objects from simple drawings. The number of correctly identified objects is the  
1828 variable of interest. We will use a validated short form that includes 15 items.  
1829
  - 1830 5) The Modified Rey-Osterrieth Complex Figure (mRey-O). (Saxon, 2003) The  
1831 mRey-O measures of visuospatial and visuomotor function and non-verbal  
1832 memory by having participants copy and reproduce from memory a multi-  
1833 component figure. For ease of use and scoring reliability, the mRey-O figure will  
1834 be faxed to the CC and scored centrally.  
1835

1836 6) Category Fluency-Animals. The animal fluency task requires the participant to  
1837 spontaneously name as many animals as possible in 60 seconds. It provides an  
1838 assessment of semantic fluency.  
1839

#### 1840 **6.4.4 Additional measures**

1841  
1842 **Functional Assessment Questionnaire (FAQ).** Since impairment of daily functioning is  
1843 required for a classification of dementia, we also will administer, either locally (by  
1844 certified SPRINT clinic staff) or centrally (by certified SPRINT staff from the coordinating  
1845 center), the FAQ, a 10-item, validated questionnaire assessing functional status (Pfeffer  
1846 and others, 1982), to a person previously designated by the participant who is familiar  
1847 with his/her current abilities. Administration of the FAQ will be limited to participants in  
1848 the 2800 and those participants whose Cognition Screening Battery indicates possible  
1849 impairment. Items assess functions like managing money and remembering names of  
1850 familiar persons.  
1851

#### 1852 **6.4.5 Alternative cognitive assessment.**

1853  
1854 If participants cannot come to the clinic for their follow-up exams or if they reside in  
1855 nursing homes, study personnel will complete either a home or nursing home visit.  
1856 Technicians conducting the home visit must be MIND certified. The Screening Battery  
1857 and the Extended Battery can be administered during home visits.  
1858

1859 Telephone assessment of general cognitive function is now standard practice in many  
1860 large trials assessing for dementia outcomes. For SPRINT participants unable to receive  
1861 a face-to-face cognitive assessment by certified SPRINT staff at their local clinic, a  
1862 telephone assessment of cognition status to assess for incident dementia will be  
1863 performed centrally by SPRINT certified staff. The components of the **phone interview**  
1864 are:  
1865

1866 **Modified Telephone Interview for Cognitive Status (TICS-M)**, a validated  
1867 instrument requiring <10 minutes (Welsh, 1993)

1868 **Category Fluency-Animals**

1869 **Oral Trail Making Test** (Ricker et al., 1996)

1870 **FAQ** to a contact  
1871

1872 For participants unable to be interviewed in-person or by phone, a previously identified  
1873 contact will be administered:  
1874

1875 **The Dementia Questionnaire (DQ).** The DQ (Ellis , 1998;Kawaset al, 1994) is a  
1876 semi-structured interview designed for a knowledgeable proxy to provide  
1877 information regarding the participant's cognitive and behavioral functioning and  
1878 other health information needed to make a diagnosis of dementia and MCI and to  
1879 identify causes of cognitive impairment. Again, it will only be administered in the  
1880 absence of an in-person or phone assessment and may be performed either by  
1881 local or central staff who are SPRINT certified. The DQ will also be obtained on all  
1882 participants who died more than 1 year after their last MIND testing.  
1883

### 1884 **6.5 Adjudication of Dementia, MCI or No Impairment**

1885  
1886 A primary goal of SPRINT MIND will be to determine the incidence of all-cause dementia  
1887 in SPRINT and its relation to the treatment assignment. Final classification (Dementia,

1888 MCI or No Impairment) will be made by a panel of experts consisting of neurologists,  
1889 geriatricians, psychiatrists and neuropsychologists with recognized expertise in dementia  
1890 blinded to study assignment and blood pressure data. Data used in the adjudication will  
1891 include all available cognitive test data (SPRINT Cognition Screening Battery, SPRINT  
1892 Extended Cognitive Battery), functional status assessments (FAQ or DQ) and additional  
1893 data including demographic information and medical history. Each suspected case  
1894 identified by our scoring criteria (see 6.4) will be randomly assigned to two members of  
1895 the Adjudication Committee for review. Adjudicators will independently review all the  
1896 available data via a web-based system before recording their classification-Dementia,  
1897 MCI or No Impairment. Each adjudicator will be masked to the other's classification and  
1898 to the participant's treatment assignment. If the two adjudicators' classifications agree,  
1899 then the classification will become final. Disagreements will be resolved at periodic face-  
1900 to-face meetings or by phone conferences between adjudicators and additional  
1901 members of the Adjudication Committee until consensus is achieved. These procedures  
1902 have been successfully used by our team in other large clinical trials including the  
1903 Gingko Evaluation of Memory Study (GEMS) (DeKosky et al, 2008) and the Women's  
1904 Health Initiative Memory Study (WHIMS) (Shumaker et al, 2004).

1905  
1906 Participants classified as having dementia will no longer be assessed for cognitive  
1907 function. Those not classified as having dementia will continue to receive regularly  
1908 scheduled cognitive assessments with the screening and extended cognitive batteries  
1909 when indicated.

#### 1910 1911 **6.5.1 Diagnostic Criteria for Dementia**

1912  
1913 Criteria used for identifying dementia will be those described in the Diagnostic and  
1914 Statistical Manual of the American Psychiatric Association-Fourth Edition (DSM-IV).  
1915 These are:

- 1916 • Significant decline in memory and at least one additional cognitive domain; and
- 1917 • Significant functional impairment due to cognitive problems; and
- 1918 • Cognitive deficits are not due to obvious reversible causes such as acute  
1919 illness, metabolic disturbances, infections, mood disorders or substance-  
1920 induced conditions; and cognitive deficits do not occur exclusively during the  
1921 course of delirium.

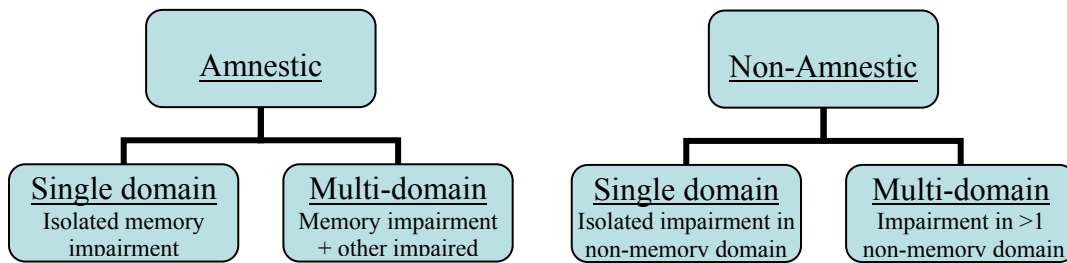
1922 No attempt to classify dementia subtype will be made.

#### 1923 1924 **6.5.2 Diagnostic Criteria for MCI**

1925  
1926 While not a primary or secondary outcome, MCI syndrome is important because of its  
1927 relevance to dementia. MCI represents a transitional state between no cognitive  
1928 impairment and dementia and specific subtypes of MCI are highly predictive of  
1929 subsequent dementia. Thus, identifying MCI will provide valuable information about pre-  
1930 dementia cognitive impairment related to the SPRINT intervention. Criteria to be used  
1931 for identifying mild cognitive impairment syndrome are those described by Winblad et al.,  
1932 which are:

- 1933 • Observation by participant or proxy of cognitive decline; and
  - 1934 • Deficit in performance in one or more cognitive domains; and
  - 1935 • Absence of significant functional impairment attributable to cognition; and
  - 1936 • No diagnosed dementia
- 1937

1938 MCI will be further sub-classified into 4 categories using criteria adapted from Winblad,  
1939 et Al. (Winblad et al, 2004) as follows:



1942  
1943  
1944  
1945  
1946  
1947  
1948  
1949  
1950  
1951 Specific cognitive tests in the Cognition Screening Battery and the Extensive Cognitive  
1952 Assessment Battery will be used to subtype adjudicated cases of MCI.

### 1953 1954 **6.6 Baseline classification of cognitive status:**

1955  
1956 Rare cases of dementia, where the participant or their personal physician are unaware  
1957 of the diagnosis, may be identified during baseline cognitive testing. In participants  
1958 scoring below the cut-point on the Screening Battery, we will administer the FAQ to a  
1959 contact in order to determine the presence of impaired daily function related to  
1960 cognition (see 6.4.2).

### 1961 1962 **6.7 Definition of Cognitive Change Over Time Outcome (Extended Cognitive 1963 Assessment Battery Sub Sample).**

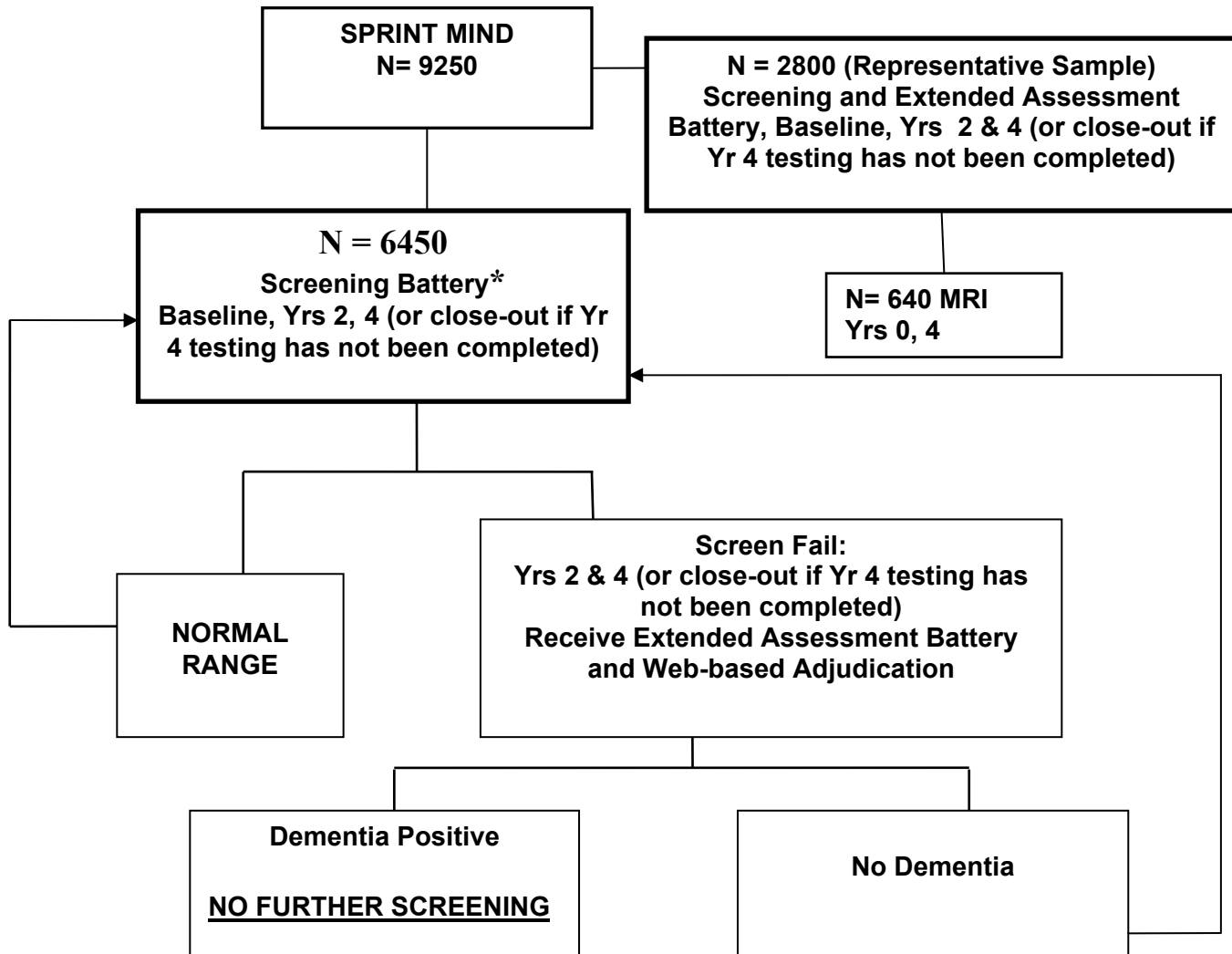
1964  
1965 Each test score from the Cognition Screening Battery and the Extended Cognitive  
1966 Assessment Battery will be used to measure decline in cognitive function. The primary  
1967 outcomes will be composite scores for two domains: 1) Memory, consisting of the  
1968 Hopkins Verbal Learning Test, Logical Memory and the Modified Rey Osterrieth Figure,  
1969 and 2) Processing Speed, consisting of Trails Making Tests and Digit Symbol Coding  
1970 Test. Prior to analysis of this outcome, we will review the science related to summary  
1971 scores for cognitive function and may make modifications which will be specified prior to  
1972 initiation of the analysis.

### 1973 1974 **6.8 Quality Control and Training**

1975  
1976 At each clinical site, at least one person will be identified to serve as the trained and  
1977 certified cognitive technician. Technicians will be trained during a central, intensive  
1978 training session held in conjunction with the overall SPRINT training. Training will  
1979 include review of the MIND protocol and procedures for administration of the test  
1980 batteries, demonstrations of each component of the SPRINT MIND test batteries, and  
1981 opportunities to practice with feedback from trainers. When a level of competence is  
1982 attained, technicians will receive certification and approval to administer the test  
1983 batteries to SPRINT participants. During the course of the study as additional staff are  
1984 needed, certified technicians will train new technicians and submit materials to the MIND  
1985 Coordinating Center for review. Technicians will be recertified throughout the course of  
1986 the trial by review of audio taped administrations. Technicians will be encouraged to  
1987 communicate questions or problems to the SPRINT MIND Coordinating Center.

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Figure 6.1.



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\*At baseline, participants scoring below cutoffs specified during trial will also receive the FAQ.



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## **Chapter 7 – Health-Related Quality of Life and Economic Analyses**

### **7.1. Introduction**

In addition to the cardiovascular, renal and cognitive outcomes, SPRINT is well poised to examine differences in health-related quality of life (HRQL) as a result of its blood pressure interventions. Differences in HRQL may affect adherence, and thus the effectiveness of the two interventions. It is also reasonable to anticipate that in some cases, the intensive arm may result in diminished HRQL relative to the standard arm due to a number of factors:

- side effects of specific medications or increased numbers and/or doses of medications required to achieve the <120 mm Hg goal,
- increased occurrence of hypotensive symptoms, which may not only result in higher rates of falls and fractures, but also an increased fear of falling which may limit the participant’s perceived ability to engage in activities of daily living, and/or
- reduced perfusion pressures and medication side effects which may contribute to erectile dysfunction in men, and possible sexual dysfunctions in women.

On the other hand, the intensive arm may result in improved general HRQL versus the standard arm due to reduced number of medical events and more favorable physical and cognitive function. The effects of the two interventions upon HRQL are further nuanced by the possibility that some participants in either treatment arm may adjust to decrements in health status by changing their internal perception of favorable HRQL, known as “response shift”.

There may also be potential health cost tradeoffs of the intensive versus standard treatment. While the intensive arm is anticipated to result in higher short-term costs due to more frequent office visits and greater medication use, this arm may also result in lower long-term costs from event-related hospitalizations and other medical costs if the treatment approach is efficacious in reducing these medical events. Assuming the primary outcomes are as hypothesized, examining the HRQL and cost-effectiveness of the intensive and standard treatment arms will be important determinants of the potential adoption of the intensive BP control in clinical practice, and will be informative in identifying subgroups of patients for whom intensive or standard BP control is most appropriate.

### **7.2. Hypotheses**

#### **7.2.1 HRQL Hypotheses**

The hypotheses generated for the HRQL measures are:

- Overall HRQL (Entire sample, Veterans RAND-12) Intensive control of blood pressure compared to standard control will result in worse HRQL at the 1-year assessment, but better HRQL at the 5-year assessment. The effect will be greater in those with lower baseline HRQL and greater number of comorbid conditions at baseline.

- 2049 • Falls Self-efficacy (Subsample, Falls Self Efficacy Scale) Intensive control of  
2050 blood pressure compared to standard control will result in less favorable fall-  
2051 related self-efficacy at the 1-year assessment. The effect will be the greater in  
2052 older participants, those with lower baseline HRQL, and those with a greater  
2053 number of baseline comorbid conditions. By Year 5, intensive control of blood  
2054 pressure will result in more favorable fall-related self-efficacy compared to  
2055 standard control.
- 2056 • Sexual function (Subsample, Modified Female Sexual Function Assessment  
2057 /International Index of Erectile Function) Intensive control of blood pressure  
2058 compared to standard control will decrease sexual function among men and  
2059 women participants at one year. By year 5, the intensive treatment participants  
2060 will report more favorable sexual function compared to participants in the  
2061 standard treatment.

## 2064 7.2.2 Cost-Effectiveness Hypotheses

2066 The primary hypotheses generated for the economic and cost-effectiveness analyses  
2067 are:

- 2069 • Intensive control of blood pressure compared to standard control will result in  
2070 higher healthcare costs and utilization in the first year due to the greater  
2071 number of office visits, medications, and lab tests likely required to achieve  
2072 the intensive control targets.
- 2073 • Intensive control of blood pressure compared to standard control will result in  
2074 lower healthcare costs and utilization over the study period due to decreased  
2075 events and related health costs among intensive control participants.
- 2076 • The incremental cost-effectiveness ratio will be  $\leq$ \$100,000/Quality Adjusted  
2077 Life Years (QALY) gained when compared to the standard intervention.

## 2081 7.3. Health-Related Quality of Life Measures

### 2083 7.3.1 Rationale for Selection

2085 The SPRINT HRQL instruments were selected based upon the following criteria:  
2086 (1) inclusion of the major dimensions shown in the literature to be affected by  
2087 hypertension and its treatment; (2) brevity; (3) responsiveness to treatment-related  
2088 changes, and (4) appropriateness for the age range, racial/ethnic diversity, and  
2089 anticipated medical conditions of the participants in SPRINT.

2091 To reduce participant burden, some HRQL instruments will be administered to the entire  
2092 SPRINT sample, while others will be administered only in a subsample of participants.  
2093 All HRQL instruments will be self-administered unless participants require assistance  
2094 due to sensory, motor, or cognitive deficits in which case the instruments will be  
2095 administered by clinic staff or family/friends accompanying the participant to the clinic  
2096 visit. For Spanish-speaking participants, Spanish versions of all HRQL instruments will  
2097 be administered to participants at all assessment points who indicate at baseline that

2098 they do not have sufficient written English fluency to complete the instruments in  
2099 English.

2100

### 2101 **7.3.2 Health-Related Quality of Life (HRQL) Measures**

2102

2103 **Veterans RAND 12-item (VR-12) questionnaire.** The VR-12 is a shorter version of the  
2104 VR-36 (which is derived from the SF-36). Changes of the VR-12 relative to the SF-12  
2105 have lowered the floor and ceiling, improved the distributional properties, increased  
2106 reliability, and improved discriminant validity of the physical and mental health summary  
2107 scores. Validated conversion formulas allow for direct comparisons to prior studies  
2108 using the SF-36 or SF-12. The VR-12 will be administered to all SPRINT participants at  
2109 baseline and at annual visits thereafter, as well as at the close-out visit.

2110

2111 **Fall Self-Efficacy Scale International (FES-I)** The FES-I, shortened version, consists  
2112 of seven items which the respondent answers on a 1-4 scale, indicating level of concern  
2113 for falling. The activities are getting dressed or undressed, taking a bath or shower,  
2114 getting in or out of a chair, going up or down stairs, reaching for something above your  
2115 head or on the ground, walking up or down a slope, and getting out to a social event. An  
2116 evaluation of the Short FES-I found good internal and 4-week test-retest reliability. The  
2117 correlation between the Short FES-I and the FES-I was 0.97. The Short FES-I will be  
2118 administered among a subsample of SPRINT participants.

2119

2120 **International Index of Erectile Function (IIEF)** The IIEF-5 is the 5-item short form of  
2121 the original 15-item IIEF, and was developed specifically for use in clinical settings to  
2122 supplement physical examination and patient history. IIEF-5 scores can be classified into  
2123 the following categories; severe erectile dysfunction (ED), moderate ED, mild to  
2124 moderate ED, mild or no ED. Scores less than 21 have 98% sensitivity and 88%  
2125 specificity for the presence of ED. The IIEF-5 will be administered in a male subsample  
2126 of SPRINT participants.

2127

2128 **Female Sexual Function Assessment (FSFI)** The FSFI is a 19-item survey that  
2129 assesses female sexual function over the past four weeks in 6 domains (desire, arousal,  
2130 lubrication, orgasm, satisfaction, and pain). Utilizing recently proposed modifications to  
2131 the FSFI, participants not sexually active over the past four weeks would complete only  
2132 4 items, substantially reducing respondent burden. The FSFI has high internal  
2133 consistency (Cronbach alpha > 0.8). This assessment will be administered in a female  
2134 subsample of SPRINT participants.

2135

2136 **Patient Satisfaction (Bharmal and others, 2009)** A modified Treatment Satisfaction  
2137 Questionnaire for Medication (TSQM) General Satisfaction subscale will be administered  
2138 at baseline (based on current blood pressure medications being taken, if any) and at 1  
2139 and 4 years (or close-out for those participants who have not reached the 48M visit at  
2140 the time of close-out). This corresponds with the administration of the Morisky  
2141 Adherence scale, which will allow for analyses of the relationship between satisfaction  
2142 and adherence at these time points.

2143

2144 **Patient Health Questionnaire-9 (PHQ-9)** The PHQ-9 is a self-report measure of  
2145 depression that has been recommended by the AHA Advisory Panel on Depression and  
2146 Coronary Heart Disease, has a low response burden (9 items; 2-3 minutes to complete),  
2147 excellent reliability, and good sensitivity and specificity with depression diagnoses. This

2148 assessment will be done at baseline, annually, and at the close-out visit on all  
2149 participants.

2150

### 2151 **7.3.3 Health State Utility Measures**

2152

2153 **EQ-5D** is a self-administered 5-item instrument including mobility, self-care, usual  
2154 activities, pain/discomfort and depression. There are three responses to each question  
2155 (no, moderate, or severe limitations). This commonly used measure of health utilities  
2156 will be used to convert quality of life and health status into quality adjusted life-years  
2157 (QALYs) for cost-effectiveness analysis. The EQ-5D will be administered to all  
2158 participants at baseline, annually and at the close-out visit.

2159

## 2160 **7.4. Cost-Effectiveness Assessment**

2161

### 2162 **7.4.1 Rationale**

2163

2164 It is expected that the intensive therapy for hypertension will not only reduce  
2165 cardiovascular events but will be more cost-effective over the long-term. The two primary  
2166 measures of cost-effectiveness are the incremental cost per QALY and life-year gained.  
2167 The primary cost-effectiveness hypothesis is that the intensive blood pressure treatment  
2168 will be cost-effective as compared to the standard treatment. This question will be  
2169 addressed by conducting incremental cost-effective analyses in which the net costs and  
2170 net effectiveness of intensive therapy defined by the main trial to standard therapy will  
2171 be calculated and expressed as a series of ratios.

2172

2173 For QALYs, the cost-effectiveness hypothesis is that the ratio of costs per QALY (as  
2174 measured by the EQ-5D) will be significantly less (i.e., more favorable cost-  
2175 effectiveness) for the intensive intervention than for the standard intervention. Costs will  
2176 be discounted to weigh future costs less heavily than present ones.

2177

### 2178 **7.4.2 Effectiveness**

2179

2180 The primary endpoints defined by the main trial are considered as primary outcome  
2181 measures for this economic evaluation. The primary effectiveness measures will be life-  
2182 years gained and QALY gained. The measure of life-year gained is determined by the  
2183 difference in number of life-years between intensive therapy and standard therapy.  
2184 QALYs adjust life-years gained by the quality of the participant's overall HRQL during  
2185 these life-years gained.

2186

### 2187 **7.4.3 Costs**

2188

2189 All direct medical costs associated with treatment of hypertension and its complications  
2190 and costs for treating adverse effects of the therapy will be considered. These costs will  
2191 include costs of inpatient care, outpatient care, medications, medical equipment,  
2192 supplies, laboratory tests, and professional services. The participant's costs such as  
2193 waiting time, transportation, lodging, and informal care arising from the disease will not  
2194 be included. Likewise, opportunity costs of premature death, productivity loss, and long-  
2195 term disability will not be considered in this study.

2196

2197

2198

2199 **7.4.3.1 Cost Data Collection**

2200

2201 Hospitalizations are the primary cost drivers in most cost-effectiveness analyses, and  
2202 SPRINT has proposed obtaining hospitalization events via multiple sources. Patient  
2203 report of hospitalizations, along with emergency department (ED) visits, stays in  
2204 rehabilitation facilities, and day-surgery admissions, are obtained every 3 months during  
2205 scheduled SPRINT study visits. Discharge summaries and other pertinent records  
2206 (including reason for hospitalization and length of stay) will be obtained from  
2207 hospitalizations, Emergency Department visits, rehabilitation stays, and day-surgery  
2208 admissions related to outcome events and potential adverse events (including  
2209 cardiovascular, renal, and cerebrovascular disorders; dementia; falls) which will  
2210 constitute many of the admissions that might be expected to differ by arm. Because of  
2211 the large proportion of VA and Medicare patients in SPRINT, we also will be able to  
2212 determine hospitalizations, dates of admission, length of stay, and reason for admission  
2213 via Medicare and VA databases for those hospitalizations for which we do not have  
2214 discharge summaries. For the limited number of remaining patient reports for which we  
2215 have neither discharge summaries nor database information, we will perform regression  
2216 analyses of reported vs. actual length of stay and costs for all those with such data to  
2217 estimate the costs of the undocumented hospitalizations. Cost estimates for  
2218 hospitalizations will be based on DRG-specific Medicare cost weights. For professional  
2219 costs associated with hospitalizations we plan to obtain these costs from Medicare and  
2220 VA databases as available in a subsample and use these data to estimate professional  
2221 costs for the entire sample based on these subsample analyses. We will also explore  
2222 whether these databases allow us to obtain costs associated with ED visits, stays in  
2223 rehabilitation facilities, and day surgery admissions.

2224

2225 **7.4.3.2 Intensive and Standard Therapy Non-Research Costs**

2226

2227 For medications, we plan to use study medication logs to obtain the medications  
2228 prescribed by the study. This log also includes blood pressure lowering medications  
2229 prescribed by other healthcare providers. Medication costs will be estimated using  
2230 median wholesale price. We will obtain information on non-study prescribed  
2231 medications (concomitant medications) from participants annually and will estimate costs  
2232 for these medications based on the most commonly used doses in clinical practice. We  
2233 will not obtain cost data on non-study related labs, as this source of utilization is not  
2234 expected to differ by group. To estimate non-research related costs for the SPRINT  
2235 office visits, we plan to obtain estimated CPT codes (minus research-specific activities)  
2236 from clinic staff for a random subset of these visits to estimate costs via Medicare  
2237 payment rates. Non-study outpatient visits will not be obtained but will be estimated with  
2238 non-study medication costs by age using national health care expenditure data.

2239

2240 **7.4.3.3 Data Analysis for Cost-Effectiveness**

2241

2242 Two methods of cost-effectiveness analysis (CEA) and cost-utility analysis (CUA) will be  
2243 used in the economic evaluation. The ratios of cost to outcome derived from CEA/CUA  
2244 are used to compare cost-effectiveness among treatment strategies. An incremental  
2245 cost-effectiveness ratio (ICER) will be calculated, which provides a summary of the cost-  
2246 effectiveness of one intervention relative to the other.

2247

2248 The basic formula to calculate incremental CEA ratio and CUA ratio of a specific  
2249 treatment A relative to the reference treatment B is presented as following:

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$$ICER_{CEA} = \frac{(\text{Mean Cost}_{\text{treatment A}} - \text{Mean Cost}_{\text{treatment B}})}{(\text{Mean Effect}_{\text{treatment A}} - \text{Mean Effect}_{\text{treatment B}})}$$

$$ICER_{CUA} = \frac{(\text{Mean Cost}_{\text{treatment A}} - \text{Mean Cost}_{\text{treatment B}})}{(\text{Mean QALY}_{\text{treatment A}} - \text{Mean QALY}_{\text{treatment B}})}$$

The ratio of incremental cost to incremental effectiveness represents cost-effectiveness of the intensive BP treatment. Bootstrap methods will be used to calculate confidence intervals for cost-effectiveness ratios. All costs will be adjusted to the baseline year using the medical component of the Consumer Price Index. Future costs and outcomes will be discounted by 3%. Estimates of utilization over time will be adjusted for the presence of censored data with variable follow-up. Sensitivity analysis will explore the effect of correlations between costs and outcomes, which will also be empirically examined in the cost and outcome data.

QALYs will be calculated by summing the area under each individual's QALY curve (constructed by plotting the EQ-5D scores for each interview during follow-up). The estimates of mean differences in costs and outcomes – which will be used to create net health benefits and the cost per QALY ratios -- will be derived from multivariable regression analyses. For the evaluation of the difference in costs, the dependent variable in the regression will either be costs or the natural log of costs (determination of the form of the dependent variable will be based on statistical tests of its distribution). If the dependent variable used in the analysis is the log of costs, a smearing retransformation will be used to estimate the absolute difference in costs between the treatment groups.

## 2278 **Chapter 8 – Safety Monitoring and Reporting**

2279

### 2280 **8.1 Introduction**

2281

2282 The SPRINT trial is testing whether lowering SBP to a goal of <120 mm Hg results in  
2283 better outcomes than a goal of <140 mm Hg in patients at risk for CVD events. SPRINT  
2284 is not a study of specific anti-hypertensive agents. All antihypertensive agents provided  
2285 by the trial or recommended by SPRINT have been approved by the Food and Drug  
2286 Administration (FDA) and are routinely prescribed for lowering blood pressure.

2287

2288 Patient safety will be carefully monitored in SPRINT. Each participating investigator has  
2289 primary responsibility for the safety of the individual participants under his/her care. In  
2290 addition, an independent Data and Safety Monitoring Board (DSMB) will have primary  
2291 responsibility for monitoring the accumulating study data for signs of adverse trends in  
2292 morbidity/mortality and treatment-related serious adverse events.

2293

### 2294 **8.2 Participant population**

2295

2296 Participants enrolled in SPRINT have elevated risk for CVD outcomes. Inclusion and  
2297 exclusion criteria for SPRINT were set in order to maximize safety while facilitating  
2298 inclusion of a trial population at risk for the major trial outcomes. Exclusions are outlined  
2299 in Section 3.1.

2300

2301 Potentially Vulnerable populations: The SPRINT population includes a significant  
2302 proportion of older adults (>75 years), some of whom may become cognitively impaired  
2303 during the course of the trial. Thus, participants are asked to identify a contact person at  
2304 the time of enrollment that can provide information about the participant as it relates to  
2305 the study. In addition, participants with CKD may need care coordination or referral to a  
2306 nephrologist during the study. Various management issues in patients with eGFR  
2307 values lower than 30 ml/min/1.73m<sup>2</sup> may arise including dietary issues and the effects of  
2308 CKD on pharmacokinetics, pharmacodynamics and side-effects of various drugs. All  
2309 participants, including those with CKD, will be managed according to current national  
2310 guidelines. If patients with this level of renal impairment are not already followed by a  
2311 nephrologist and the investigator feels it is needed, he/she will coordinate with the  
2312 participant's primary care physician regarding the recommendation for renal follow-up.

2313

### 2314 **8.3 Safety Monitoring**

2315

2316 Several types of safety issues and serious adverse events may occur in SPRINT and  
2317 participants will be monitored for these regularly throughout the study.

2318

#### 2319 **8.3.1 Expected Events:**

2320

2321 The potential adverse effects of the blood pressure drugs used in SPRINT have been  
2322 well documented. For example, electrolyte abnormalities (hyponatremia or hypokalemia  
2323 are known to be associated with diuretics; hyperkalemia and short-term decline in GFR  
2324 with RAAS blockers, hyperkalemia with potassium-sparing drugs; as well as bradycardia  
2325 with beta blockers and calcium channel blockers). Participants will be monitored  
2326 routinely with interviews, vital signs, targeted physical examination and laboratory tests  
2327 to ensure safety (Chapter 5, Table 5.1). In addition, site clinicians may also obtain local

2328 labs and ECG's if safety is a concern at non-scheduled intervals. Clinical alerts are  
 2329 generated when safety parameters are exceeded. (Table 8.1). Expected events are not  
 2330 considered serious adverse events (SAEs) unless they meet criteria for an SAE (see  
 2331 8.3.2).  
 2332

2333 Table 8.1 Clinical Safety Alerts  
 2334

Measure	Alert Value
Serum sodium	< =132 or >150 mEq/L
Serum potassium	<3.0 or >5.5 mEq/L
Serum creatinine	Increase by at least 50% to a value $\geq$ 1.5 mg/dL since the last study lab (usually 6 months apart).
Heart rate	<40
ECG	acute MI, complete heart block, or bradycardia <40 bmp
PHQ-9 (depression screen)	Positive response to question on suicidal ideation
Dementia Assessment	Adjudicated dementia

2335

2336

### 2337 8.3.2 Adverse Events and Serious Adverse Events

2338

2339 An adverse event (AE) is defined as any untoward or unfavorable medical occurrence in  
 2340 a human subject, including any clinically significant abnormal sign (for example,  
 2341 abnormal physical exam or laboratory finding), symptom, or disease, temporally  
 2342 associated with the subject's participation in the research, whether or not considered  
 2343 related to the subject's participation in the research. The burden of collecting and  
 2344 reporting data on every possible AE in SPRINT is excessive and side effects from the  
 2345 drugs to be used in SPRINT have been well defined in previous studies. Therefore, in  
 2346 SPRINT, sites will report all serious adverse events and selected AEs to the  
 2347 Coordinating Center.  
 2348

2349

2349 Consistent with NHLBI guidelines and OHRP policy, SAEs are adverse events that meet  
 2350 any of the following criteria:

2351

- fatal or life-threatening,
- result in significant or persistent disability,
- require or prolong hospitalization,
- result in a congenital anomaly/birth defect, or
- are important medical events that investigators judge to represent significant hazards or harm to research participants and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (e.g. hospitalization, death, persistent disability).

2352

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2359



2360 Any adverse event that meets any of these criteria will be documented and reported as a  
2361 serious adverse event. In addition, a select list of other important events (see manual of  
2362 procedures for details and definitions), regardless of whether they resulted in  
2363 hospitalization, will also be considered SAEs in SPRINT, including:

- 2364 • Injurious falls
- 2365 • Syncope
- 2366 • Unexpected events for which the investigator believes that the SPRINT  
2367 intervention caused the event or contributed to the immediate cause of the  
2368 event

2369  
2370 Participants will be queried for SAEs and selected AEs at quarterly clinic visits.  
2371

### 2372 **8.3.3 Modification of treatment in response to safety concerns**

2373  
2374 SPRINT is testing two different SBP treatment goals. The study physician may add,  
2375 increase or reduce the dose, stop, or change antihypertensive drugs in the interest of  
2376 participant safety. Depending on the situation, the change may be temporary or  
2377 permanent. Situations that may require temporary reduction or elimination of a study  
2378 medication include: side effects, worsening congestive heart failure, acute kidney injury,  
2379 symptomatic hypotensive episodes, and other illnesses. Orthostatic hypotension is  
2380 usually related to specific drug classes and not BP level per se and thus should NOT  
2381 usually alter target blood pressure goals. The MOP contains a section on management  
2382 of symptomatic orthostatic hypotension.

## 2383 2384 **8.4 Safety Reporting**

### 2385 2386 **8.4.1 Clinical Safety Alerts**

2387  
2388 Clinical Safety Alerts (section 8.3.1. and Table 8.1) are provided to the site clinician for  
2389 his/her action. When any laboratory measurement attains a defined alert level, the  
2390 Central Laboratory will immediately notify the clinical site and the CCN. Site clinicians  
2391 may also obtain local labs if safety is a concern at non-scheduled intervals. Site  
2392 clinicians are responsible for timely review of all labs drawn locally and when central lab  
2393 results become available. ECGs will be done at specified visits and read by the ECG  
2394 reading center. However, if a participant has one of a short list of abnormalities (reported  
2395 on the ECG by the machine), such as acute MI, complete heart block, or bradycardia  
2396 <40 beats/minute, the ECG will be reviewed by the site clinician immediately (see ECG  
2397 section of the SPRINT MOP).

### 2398 2399 **8.4.2 Serious Adverse Events**

2400  
2401 At each quarterly visit, SPRINT staff will specifically query participants for serious  
2402 adverse events. In addition, information on serious adverse events may also be reported  
2403 to study staff spontaneously by participants through telephone calls or emails between  
2404 study visits. In addition to local reporting requirements, all serious adverse events will  
2405 be recorded by clinic staff and forwarded to the CC Medical Safety Officer **within 72**  
2406 **hours** of knowledge of the event. SAEs will be collected and reported from screening to  
2407 the end of the study follow-up period for an individual participant. SAEs will be followed  
2408 until resolution, stabilization, or until it is determined that study participation is not the  
2409 cause.  
2410

2411 The Coordinating Center will be responsible for timely reporting to the NIH and the  
2412 DSMB. The Coordinating Center will provide reports of serious adverse events for  
2413 review by the DSMB at their meetings.  
2414

## 2415 **8.5 Data Safety Monitoring Board**

2416  
2417 A **Data Safety Monitoring Board (DSMB)** is established, with responsibility to monitor  
2418 all aspects of the study. The **Medical Safety Officer** reports to the DSMB for issues  
2419 related to participants' safety. This independent Data and Safety Monitoring Board will  
2420 be established to monitor data and oversee participant safety. Members will be  
2421 appointed by the NHLBI to provide oversight of the trial and its ancillary studies. The  
2422 SPRINT DSMB may include experts in cardiovascular medicine (particularly  
2423 hypertension), kidney disease, clinical trials, geriatrics, biostatistics, quality of life, cost  
2424 effectiveness, cognitive function and other areas as needed. DSMB participants include  
2425 the Steering Committee Chair and Vice-Chair, CC PI and senior staff, and  
2426 representatives from the NHLBI and other NIH sponsors. The DSMB normally meets  
2427 twice a year to monitor safety, to advise the NHLBI about study progress and  
2428 performance, and to make recommendations to the NHLBI regarding study continuation  
2429 and protocol changes. In addition, the CC may provide data to the DSMB Chair to  
2430 ensure early identification of any major adverse outcomes of therapy. The DSMB has  
2431 the responsibility to recommend to the NHLBI whether the trial should continue, whether  
2432 the protocol should be modified, or whether there should be early termination. The  
2433 DSMB will provide reports to the NHLBI through the Executive Secretary, who will be  
2434 appointed by the NHLBI. Recommendations by the DSMB must be approved by the  
2435 NHLBI prior to implementation.  
2436  
2437  
2438

## 2439 **Chapter 9 – Clinical Outcome Measures**

2440

### 2441 **9.0 Outcomes**

2442

2443 This chapter describes the SPRINT primary and secondary clinical outcomes. Clinical  
2444 events occurring during follow-up will be ascertained primarily through surveillance of  
2445 self-reported events, laboratory, and ECG data collected by the study and classified by  
2446 members of the Morbidity and Mortality subcommittee masked to treatment assignment.  
2447 Additional sources, including searches of the National Death Index (NDI), will also be  
2448 used to augment follow-up data.

2449

### 2450 **9.1 Primary Outcome**

2451

2452 The primary outcome measure for SPRINT will be major CVD events, defined as the  
2453 composite endpoint comprised of the first occurrence of a

2454

- fatal or non-fatal myocardial infarction (MI),
- non-MI acute coronary syndrome (non-MI ACS),
- fatal or non-fatal stroke,
- fatal or non-fatal heart failure (HF), or
- death attributable to cardiovascular disease (CVD).

2455

2456

2457

2458

2459 MI and non-MI ACS are defined in Section 9.1.1; stroke is defined in Section 9.1.2; HF is  
2460 defined in Section 9.1.3, and CVD death is defined in Section 9.1.4. The SPRINT  
2461 Manual of Procedures contains the full details of these definitions.

2462

#### 2463 **9.1.1 MI and Non MI ACS**

2464

2465 **9.1.1.1 MI:** Defined as the death of part of the myocardium due to an occlusion of a  
2466 coronary artery from any cause, including spasm, embolus, thrombus or rupture of a  
2467 plaque. SPRINT will use standard case definitions for both fatal and nonfatal MI based  
2468 on the combination of symptoms, elevation in biomarkers, and/or ECG findings. The  
2469 algorithm for classifying MI includes elements of the clinical presentation (signs and  
2470 symptoms), results of cardiac biomarker determinations, and ECG readings, and is  
2471 based on a 2003 Scientific Statement (Luepker and others, 2003). The definition  
2472 includes MI that occurred during surgery/procedure and MI aborted by thrombolytic  
2473 therapy or procedure. SPRINT adjudicators will be guided by specific, pre-specified  
2474 definitions and operational rules. Adjudicators will use their clinical interpretation of the  
2475 ECGs and other available evidence for the event to classify MI cases as definite,  
2476 probable, or possible, with all included in the primary outcome (Luepker and others,  
2477 2003). MI will be ascertained both from adjudication of hospital records for clinical  
2478 events and also from the finding of new significant Q waves from the standardized  
2479 interpretation of the study visit-obtained ECG (silent or unrecognized MI). MIs that  
2480 present clinically will include Q wave, ST elevation and non-ST elevation infarctions  
2481 (segment elevation myocardial infarction (STEMI) and Non-ST Segment elevation  
2482 myocardial infarction (NSTEMI), as well as aborted MI and post-intervention MI.

2483

2484 **9.1.1.2 Non-MI ACS:** Defined as hospitalization for evaluation and treatment of an  
2485 accelerating or new symptom pattern consistent with coronary artery insufficiency  
2486 without meeting the definition of MI, but requiring evaluation to rule-out MI on clinical  
2487 presentation. Non-MI ACS in SPRINT will also require objective findings of coronary  
2488 ischemia, including any of the following: history of previous catheterization with

2489 significant obstruction or previous revascularization; significant obstructive lesion(s) on  
2490 coronary catheterization during index hospitalization and/or intervention for  
2491 revascularization; ischemic ECG changes or imaging findings on exercise or  
2492 pharmacologic stress testing associated with the index hospitalization; or resting ECG  
2493 findings consistent with ischemia occurring with symptoms during the index  
2494 hospitalization.

2495

### 2496 **9.1.2 Stroke**

2497

2498 **9.1.2.1 Stroke:** SPRINT will use standard case definitions for both fatal and nonfatal  
2499 stroke. Stroke will be defined based on all available data, including symptoms and  
2500 signs, imaging of the brain and large vessels, and cardiac testing, e.g.,  
2501 echocardiography. Adjudicators will use their clinical judgment based on the available  
2502 evidence to classify each case, and will be guided by pre-specified definitions and  
2503 operational rules. Stroke is generally defined as neurological deficit of cerebrovascular  
2504 cause that persists beyond 24 hours or is interrupted by death within 24 hours (World  
2505 Health Organization, 1978 Cerebrovascular Disorders (Offset Publications). Geneva:  
2506 World Health Organization. ISBN 9241700432. Exclusionary conditions for stroke  
2507 include major brain trauma, intracranial neoplasm, coma due to metabolic disorders or  
2508 disorders of fluid or electrolyte balance, peripheral neuropathy, or central nervous  
2509 system infections. Stroke will be classified as brain infarction, subarachnoid  
2510 hemorrhage, intraparenchymal hemorrhage, other hemorrhage, other type, or unknown  
2511 type. In SPRINT, brain infarction (ischemic stroke) is defined as a new lesion detected  
2512 by computed tomography or magnetic resonance imaging or, in the absence of a new  
2513 lesion on available imaging, clinical findings consistent with the occurrence of stroke that  
2514 lasted for more than 24 hours (N Engl J Med 2001;345:1444-51). Brain infarctions will  
2515 be further sub-typed using the Causative Classification of Stroke system as evident,  
2516 probable, or possible cases of large artery atherosclerosis, cardio-aortic embolism, small  
2517 artery occlusion, other causes, and undetermined causes (Ay and others,  
2518 2007). Strokes following invasive cardiovascular interventions will also be classified as  
2519 such.

2520

### 2521 **9.1.3 HF**

2522

2523 **9.1.3.1 HF:** Defined as hospitalization, or emergency department visit requiring treatment  
2524 with infusion therapy, for a clinical syndrome that presents with multiple signs and  
2525 symptoms consistent with cardiac decompensation/inadequate cardiac pump function.  
2526 Adjudication will use the ARIC study adjudication system (Rosamond and others, 2009).  
2527 The SPRINT HF outcome will include definite or possible acute decompensation,  
2528 including HF with preserved left ventricular ejection fraction as well as HF with reduced  
2529 ejection fraction. HF cases may also be adjudicated as chronic stable HF but this is not  
2530 considered a SPRINT outcome. In SPRINT, HF will include a variety of clinical  
2531 presentations, including acute or subacute HF as the primary reason for hospital  
2532 admission or for emergency department visit where HF was diagnosed and intravenous  
2533 treatment was given. The identification and classification of HF cases will rely on  
2534 multiple pieces of key clinical data as well as adjudicators' clinical judgment, guided by  
2535 specific, pre-specified definitions and operational rules. No identification of HF should  
2536 rely on a single piece of data such as the presence of dyspnea or of edema, a low  
2537 ejection fraction, or an increased brain natriuretic peptide (BNP) value. Adjudicators will  
2538 use both the data available and clinical judgment to distinguish between "definite" and  
2539 "possible" decompensated HF. "Definite" decompensated HF will be assigned when

2540 decompensation is clearly present based on available data (satisfies criteria for  
2541 decompensation). “Possible” decompensation will be assigned when decompensation is  
2542 possibly but not definitively present, typically where the presence of co-morbidity could  
2543 account for the acute symptoms (chronic obstructive pulmonary disease (COPD)  
2544 exacerbation, for example).  
2545

2546 For participants with advanced CKD with or without chronic dialysis, the ascertainment  
2547 of HF can be particularly difficult, since the fluid overload can be purely the consequence  
2548 of fluid retention by the kidney or absence of kidneys. Under these circumstances, the  
2549 adjudicators will again use their best judgment, utilizing all available information.  
2550

#### 2551 **9.1.4 CVD Death**

2552  
2553 **9.1.4.1 CVD Death:** SPRINT will use standard case definitions for classification of CVD  
2554 death. Definite CVD events will be defined based on temporal relationship to a  
2555 documented event (e.g., hospitalization for MI or for stroke), or postmortem findings of  
2556 an acute CVD event. Probable coronary heart disease (CHD) death (Luepker, 2003) will  
2557 be defined based on autopsy findings consistent with chronic CHD, prior history of CHD  
2558 or documented symptoms consistent with CHD prior to death, and the absence of  
2559 another likely cause of death. Possible fatal CHD will be adjudicated based on death  
2560 certificate information consistent with an underlying CHD cause and no evidence of a  
2561 non-coronary cause. Stroke deaths will be categorized based on the temporal  
2562 relationship between the stroke event and death, in cases where the underlying cause of  
2563 death is attributed to stroke. Proximal stroke death is a death attributed to stroke and  
2564 occurring within 30 days of stroke; remote stroke death is underlying cause attributed to  
2565 stroke and more than 30 days from stroke to death. Other forms of CVD death will also  
2566 be adjudicated and include ruptured abdominal aortic aneurysm, and documented  
2567 arrhythmia.  
2568

#### 2569 **9.2 Secondary Outcomes**

2570  
2571 In addition to the primary outcome, SPRINT will assess additional clinical outcomes in  
2572 order to more fully evaluate the relative effects of treating to a SBP goal lower than the  
2573 currently recommended goal. In order to do so, data will be collected on secondary and  
2574 other trial outcomes. Main secondary outcomes are included in the analysis plan in  
2575 Chapter 10.  
2576

2577 **9.2.1 Main secondary cardiovascular composite outcome:** The main secondary  
2578 composite outcome of SPRINT is comprised of the first occurrence of any of the  
2579 components of the primary outcome and all cause mortality. A major and analogous  
2580 secondary outcome of CVD-free survival, defined as survival without any of the primary  
2581 or secondary CVD outcomes, will also be examined because of the significant proportion  
2582 of elderly in the trial and the public health importance of the issue of CVD in that age  
2583 group. All cause mortality and components of the primary outcome will also be  
2584 examined.  
2585

2586 **9.2.2 Main secondary renal outcome:** The main secondary renal outcome of SPRINT  
2587 will be the composite of a 50% decrease in eGFR or development of ESRD requiring  
2588 chronic dialysis or kidney transplantation. This outcome applies to the CKD subgroup  
2589 only.  
2590

2591 **9.2.3 Main secondary cognitive outcomes:** SPRINT MIND will evaluate the incidence  
2592 of all-cause dementia as adjudicated by an expert panel as the most important outcome  
2593 for the MIND study. The second most important outcome is cognitive impairment among  
2594 the Extensive Cognitive Assessment Battery participants will be tested with the full  
2595 assessment battery (6.4.1.3 and 6.6.2). Each test score from the full assessment  
2596 battery will be classified as indicating “impairment (1)” or “no impairment (0)” based on  
2597 norms. A sum of impairment scores will be calculated indicating the total number of  
2598 impairments. Detailed definitions of these outcomes are contained in chapter 6.  
2599

2600 **9.2.4 Additional secondary outcomes:** In addition to the secondary outcomes  
2601 specified in Chapter 10, other outcomes will also be examined separately and combined  
2602 with other outcomes in composites (e.g., CVD-free survival defined above):

- 2603 • Peripheral arterial disease, including carotid and peripheral revascularization,  
2604 abdominal aortic aneurysm repair, and other objectively defined PAD events
- 2605 • Coronary revascularization
- 2606 • Transient Ischemic Attack (TIA): TIA in SPRINT will be defined as one or more  
2607 transient episodes of the sudden onset of a focal neurological deficit, no lesion on  
2608 brain imaging consistent with the deficit, and no signs or symptoms consistent with  
2609 seizures, migraine, or other non-vascular causes.
- 2610 • ECG diagnosed Left Ventricular Hypertrophy (LVH): ECG-diagnosed LVH will be  
2611 defined primarily using the sex-specific Cornell voltage criteria. Other ECG-LVH  
2612 criteria mentioned in the American Heart Association (AHA)/American College of  
2613 Cardiology (ACC) statement on ECG changes associated with cardiac chamber  
2614 hypertrophy (Hancock and others, 2009) will be also considered.
- 2615 • Atrial fibrillation or flutter: In SPRINT, atrial fibrillation/flutter will be primarily detected  
2616 from the scheduled study ECGs using Minnesota ECG classification (Minnesota  
2617 code 8.3). Other sources of detection include hospital discharge ICD code (ICD-10  
2618 code 148 or ICD-9 code 427.3) and self-report.
- 2619 • Other renal outcomes
  - 2620 ○ Incident CKD, defined as a >30% decrease in eGFR and an end value of <60  
2621 ml/min/1.73M<sup>2</sup>. This outcome applies only to the non-CKD subgroup. This  
2622 decrease in eGFR requires a confirmatory value in the next available official  
2623 SPRINT lab check.
  - 2624 ○ Incident albuminuria, defined as a doubling of urinary albumin-to-creatinine  
2625 (ACR) ratio from a value <10 mg/g to a value of >10 mg/g. This outcome  
2626 applies to CKD and non-CKD subjects. This increase in ACR requires a  
2627 confirmatory value in the next available official SPRINT lab check.

2628  
2629  
2630  
2631  
2632

## 2633 **Chapter 10 – Statistical Considerations**

2634  
2635 The SPRINT Trial has a single primary objective and several key secondary objectives,  
2636 some of which will be addressed within a number of subgroups whose target size has  
2637 been guided by power computations. The primary objective is to determine whether the  
2638 intensive BP treatment strategy will, when compared to a standard BP treatment  
2639 strategy, reduce the incidence of serious cardiovascular events, defined as MI, stroke,  
2640 heart failure, non-MI acute coronary syndrome or other cardiovascular death. This will  
2641 be tested in all SPRINT participants.

2642  
2643 The key secondary objectives are to determine whether the intensive BP strategy  
2644 reduces the incidence of:

- 2645 1) total mortality,
- 2646 2) progression of CKD,
- 2647 3) probable dementia,
- 2648 4) cognitive impairment, and
- 2649 5) white matter lesions detected by MRI.

2650  
2651 The primary analysis of each of these objectives will be in different groups of  
2652 participants. The analysis plan to address the primary and each secondary objective is  
2653 described below, followed by estimates of the required sample size for each.

### 2654 2655 **10.1 Analysis Plan**

2656  
2657 This section describes some of the key pre-specified analyses directed at the study's  
2658 primary and key secondary objectives. Many other outcomes and measurements, such  
2659 as blood pressure, adverse event experiences, health related quality of life, cost, and  
2660 results of assays performed on blood and urine specimens will also be analyzed.

#### 2661 2662 **10.1.1 Analysis of the Primary Outcome in all Randomized Participants**

2663  
2664 The primary analysis will apply Cox proportional hazards regression (Cox, 1972) to all  
2665 randomized participants to compare the time from randomization to the first occurrence  
2666 of the primary CVD composite endpoint between the randomized BP groups. The model  
2667 will include an indicator for intervention arm as its sole predictor variable. Clinical site at  
2668 randomization will be a stratifying factor. Follow-up time will be censored at the last date  
2669 of event ascertainment. The p-value from the primary analysis will be based on the chi-  
2670 square statistic from a likelihood ratio test obtained from proportional hazards models  
2671 with and without the term for intervention arm. This likelihood ratio test will constitute the  
2672 primary test of statistical significance for the primary analysis.

2673  
2674 Primary comparisons of intervention groups will be performed according to the intention-  
2675 to-treat principle. All randomized participants in these analyses will be grouped  
2676 according to their intervention assignment at randomization, regardless of adherence.

#### 2677 2678 **10.1.2 Secondary analyses supporting the primary analysis**

2679  
2680 **10.1.2.1 Secondary outcomes.** A number of secondary outcomes will be analyzed to  
2681 clarify the interpretation of the results of the primary analysis. These will include:

- 2682 a) all myocardial infarction,

- 2683 b) all stroke,
- 2684 c) non-MI acute coronary syndrome,
- 2685 d) all heart failure,
- 2686 e) CVD mortality,
- 2687 f) total mortality, and
- 2688 g) a composite of total mortality and the primary composite outcome (i.e. major
- 2689 CVD event- free survival).
- 2690

2691 Each of these will be analyzed using a proportional hazards model as described for the  
2692 primary analysis. These will be reported with 95% confidence intervals and nominal p-  
2693 values without an adjustment for multiple comparisons, since the intent is to articulate a  
2694 pattern of effects closely related to the primary outcome, rather than to provide additional  
2695 tests of efficacy.

2696  
2697 **10.1.2.2 Subgroup analyses.** In addition to the analysis of the secondary outcomes  
2698 described above, a set of analyses will be reported to explore whether intervention  
2699 effects on the primary and confirmatory secondary outcomes are consistent across  
2700 subgroups of interest. These subgroups are:

- 2701 a) CKD (defined as eGFR < 60 at randomization) vs. non-CKD,
- 2702 b) senior vs. non-senior (aged  $\geq 75$  at randomization vs. aged <75),
- 2703 c) male vs. female,
- 2704 d) black vs. non-black,
- 2705 e) with and without a history of CVD at randomization (as defined in Chapter 3), and
- 2706 f) tertiles of systolic blood pressure at baseline.
- 2707

2708 The subgroups defined by CKD, age and race are motivated by biologically plausible  
2709 hypotheses. For each subgroup analysis, a proportional hazards model will be used that  
2710 is similar to the one described for the primary analysis above, but with additional terms  
2711 identifying subgroup membership and the intervention by subgroup interaction. The  
2712 nominal p-value for the interaction term using a likelihood ratio test will be reported along  
2713 with within subgroup estimates of the intervention effect and associated nominal 95%  
2714 confidence intervals. We will report the Hommel adjusted p-values for the interaction  
2715 effects.

### 2716 **10.1.3 Non-cardiovascular clinical outcomes**

#### 2717 2718 **10.1.3.1. Acute vs. chronic effects of intervention**

2719  
2720 It is possible that the intervention will have some acute adverse effects due to under-  
2721 perfusion of various organs, notably the kidney and the brain, which are major targets of  
2722 SPRINT. In the long term, however, lower SBP may protect these organs from  
2723 hypertension-related damage. We will examine the possibility of acute effects as part of  
2724 the data monitoring plan, particularly if differential adverse effects are observed early in  
2725 the trial; we also will examine the possibility of acute effects as part of the data analysis  
2726 at the end of the trial.

#### 2727 2728 **10.1.3.2 Renal outcomes**

2729  
2730 Renal outcomes are of particular importance in SPRINT, both to assess the incidence of  
2731 new kidney disease among participants free of CKD at baseline and to assess the  
2732 progression of kidney disease among those with CKD at baseline. Because some  
2733



2734 outcomes are more interpretable in either people with CKD or without CKD at baseline,  
2735 some analyses will be restricted to these subgroups.

2736  
2737 The primary hypothesis for the renal outcomes is whether, in the subgroup with CKD at  
2738 baseline, the rate of a composite of a 50% decrease in eGFR or ESRD undergoing  
2739 chronic dialysis or kidney transplantation is lower in the intensive intervention arm. The  
2740 decline in eGFR must be seen on two visits at least three months apart. This will be  
2741 analyzed using a proportional hazards model as described for the primary CV analysis.

2742  
2743 A number of additional analyses related to this hypothesis will also be performed. These  
2744 will include:

- 2745 a) incident CKD in the non-CKD subgroup, defined as a 30% decline from baseline  
2746 eGFR to a value of  $<60 \text{ mL/min/1.73m}^2$  (observed on two visits at least 3 months  
2747 apart. There must be a decrease of at least 30% AND the end value of this  
2748 decrease must be  $<60 \text{ mL/min/1.73m}^2$  in order to satisfy this endpoint criterion) or  
2749 ESRD  
2750 b) incident albuminuria, defined as a doubling of urinary albumin-to-creatinine  
2751 (ACR) ratio from a value  $<10 \text{ mg/g}$  to a value of  $>10 \text{ mg/g}$ . This outcome applies  
2752 to CKD and non-CKD subjects. This increase in ACR must be observed at two  
2753 visits at least 3 months apart.

2754  
2755 *Subgroup analyses.* Analyses of the renal outcomes will be by CKD and non-CKD  
2756 strata. Within each strata, assessments of the renal composite endpoint will be by  
2757 subgroups. The analytical approach will be the same as for the primary CV analysis as  
2758 described in 10.1.2.2. The renal subgroups are:

- 2759 a) urinary albumin/creatinine ratio ( $>300 \text{ mg/g}$  and  $\leq 300 \text{ mg/g}$ ),  
2760 b) black vs. non-black,  
2761 c) senior vs. non-senior (aged 75+ at randomization vs. aged  $<75$ ),  
2762 d) male vs female,  
2763 e) eGFR (median split)

2764 The subgroups defined by albumin/creatinine ratio, age and race are motivated by  
2765 biologically plausible hypotheses. The main renal outcome composite is defined  
2766 differently for the CKD and non-CKD strata, so that these will be separate analyses.

### 2767 2768 **10.1.3.3 Dementia and cognitive outcomes.**

2769  
2770 The primary outcome for SPRINT MIND will be the first identification of adjudicated  
2771 dementia. Cox proportional hazards models (as described above for the SPRINT  
2772 primary outcome) will be used to compare the time from randomization to the first  
2773 identification of dementia between the two treatment arms. All participants will be  
2774 screened for dementia at baseline.

2775  
2776 *Secondary analyses.* Secondary analyses in the areas of cognitive function, small  
2777 vessel ischemic disease (SVID) lesion load, and mild cognitive impairment will also be  
2778 performed to support the primary analysis.

2779  
2780 *Cognitive Function.* A cognitive assessment battery will be administered at baseline and  
2781 2 and 4 years post-randomization and at the close-out visit (if the year 4 testing has not  
2782 been completed) in a subsample of 2800. The primary outcomes will be composite  
2783 scores for two domains: 1) Memory, consisting of the Hopkins Verbal Learning Test,  
2784 Logical Memory and the Modified Rey Osterrieth Figure, and 2) Processing Speed,

2785 consisting of Trails Making Tests and Digit Symbol Coding Test. Changes in impairment  
2786 over time will be compared between the two treatment arms.

2787  
2788 Supporting analyses will also be conducted on the effect of the interventions on  
2789 individual domains of memory over 48 months. Follow-up test scores will be compared  
2790 using mixed-effects analysis of covariance models (Laird, 1982). Mixed-effects models  
2791 allow for departure from linearity in the relationship between the outcome and time.  
2792 Estimates of the difference in mean levels of the outcome between control and  
2793 intervention groups will be obtained using maximum likelihood techniques. Sensitivity of  
2794 results to missing data will be investigated through the use of multiple imputation  
2795 techniques (Rubin, 1987).

2796  
2797 *Magnetic Resonance Imaging (MRI)*. Other than age, hypertension is the strongest  
2798 correlate of SVID. Total SVID lesion load including abnormal white matter, abnormal  
2799 gray matter and abnormal basal ganglia will be the SPRINT measure of total SVID lesion  
2800 load. Differences in total SVID lesion between treatment groups at 48 months will be the  
2801 main outcomes of the MRI component. Furthermore, differences in total brain volume  
2802 will also be compared after 48 months. These measures are continuous and will be  
2803 analyzed using mixed effects analysis of covariance models as described above.

2804  
2805 *Mild Cognitive Impairment (MCI)*. This outcome is defined as the time to the first of two  
2806 consecutive occurrences of MCI. Analytical methods used for dementia will be applied  
2807 to the analyses of MCI, in those free of MCI at baseline. Furthermore, these same  
2808 methods will be applied to the analyses of the first cognitive impairment defined as the  
2809 first event classified either as MCI or dementia in those free of MCI at baseline.

2810  
2811 *Subgroups*. Analyses of the cognitive outcomes will also explore the intervention effects  
2812 within subgroups. The analytic approach will be the same as for the primary CV analysis  
2813 as described in 10.1.2.2. The subgroups are:

- 2814 a) CKD (defined as eGFR < 60 at randomization) vs. non-CKD,
- 2815 b) senior vs. non-senior (aged 75+ at randomization vs. aged <75),
- 2816 c) male vs. female,
- 2817 d) black vs. non-black,
- 2818 e) with and without a history of CVD at randomization (as defined in Chapter 3),
- 2819 f) tertiles of systolic blood pressure at baseline,
- 2820 g) MCI at baseline (yes vs. no),
- 2821 h) orthostatic hypotension (yes vs. no).

2822  
2823 The subgroups of CKD, age, and MCI are motivated by biologically plausible  
2824 hypotheses.

#### 2825 2826 **10.1.4 Other analyses**

2827  
2828 We expect to explore fully the rich set of data that SPRINT will obtain. Exploratory  
2829 analyses of biologically plausible subgroups are of particular interest. Some of these will  
2830 be further articulation of supporting subgroup analyses described above, such as  
2831 analysis of continuous baseline factors as continuous variables rather as pre-specified  
2832 categorical variables. Other analyses will involve baseline variables that are not listed  
2833 in the pre-specified subgroup but which may modify treatment effect, such as diastolic  
2834 blood pressure or presence of the metabolic syndrome.

2835

2836 **10.1.5 Missing data**

2837

2838 Consistent with an intention-to-treat analysis, we will categorize all participants by their  
2839 randomization group, regardless of compliance, in our primary analyses. For those  
2840 participants lost to follow-up, we plan to use all available information until the time of  
2841 death or loss to follow-up.

2842

2843 Our approach to handling missing outcomes in clinical trials is consistent with the  
2844 opinion of Molenberghs and Kenward (2007, p9), who state that while ignorable,  
2845 missing-at-random (MAR) analyses are reasonable for the primary analysis, exploration  
2846 of the sensitivity of conclusion to the MAR assumption may include models which allow  
2847 for missingness that is not random. If loss to follow-up is related to the level of the  
2848 outcome being analyzed (e.g. as often occurs when analyzing health related outcomes),  
2849 then results obtained under the assumption of independent loss to follow-up may be  
2850 biased. The magnitude of this problem will be investigated by using measurements  
2851 taken at previous visits to predict loss to follow-up. Variables determined to predict loss  
2852 to follow-up will be included in our predictive models in order to satisfy the conditions  
2853 described by Little and Rubin (1987) for the data to be considered MAR. Maximum  
2854 likelihood techniques will be used to estimate parameters. If necessary, other  
2855 approaches may be examined in consideration of how robust the results will be and  
2856 whether they provide appropriately conservative estimates for the trial.

2857

2858 In order to explore the possibility of a relationship between ESRD and CV outcomes, we  
2859 will conduct sensitivity analyses which treat ESRD as a censoring point for the primary  
2860 outcome. This exploration may include an auxiliary composite outcome combining the  
2861 events in the primary outcome and ESRD.

2862

2863 Robustness of inferences to missing outcome data will be further explored in sensitivity  
2864 analyses. These analyses will include examination of several “worst-case” scenarios,  
2865 including opposite and pooled imputation approaches (Wittes, Lakatos & Probstfield  
2866 1989; Proschan et al., 2001). These types of scenarios are members of a broad class  
2867 that can be parameterized as pattern mixture models (Little 1993) and allow for  
2868 examination of sensitivity of conclusions to missing-not-at-random (MNAR) mechanisms  
2869 (Mohlenberg and Kenward, 2007).

2870

2871 The MRI substudy involves two assessments—one at baseline and one at 48 months—  
2872 in 640 participants, thus limiting the range of analytic strategies. We recommend using  
2873 maximum likelihood based general linear models for analyzing outcomes. Intracranial  
2874 volume will be included as a covariate. The validity of the MAR assumption can be  
2875 improved by including baseline covariates that predict missingness. If loss to follow-up  
2876 is related to the unobserved cognitive outcome then our results may be biased. Again,  
2877 some modeling and sensitivity analysis options may be considered if necessary.

2878

2879 **10.2 Sample Size Estimation and Power Calculations**

2880

2881 **10.2.1 Primary Outcome**

2882

2883 We have assumed a 2.2 %/yr event rate of the primary outcome in the standard group, a  
2884 20% effect size for the intervention (hazard ratio of 0.8), a two-year uniform recruitment  
2885 period, a total study length of 5 years and 10 months, a 2 %/yr rate of loss to follow-up,  
2886 and a two-sided test at the 5% level. With these assumptions, power for a variety of

2887 sample sizes is presented in Table 1. Power is also presented for hazard ratios of 0.78  
 2888 and 0.82 and for event rates of 2.0 and 2.4 %/yr. A sample size of 9250 provides high  
 2889 power for a hazard ratio of 0.8 (representing a 20% effect) and a 2.2 %/yr event rate.  
 2890 This sample size would also provide over 80% power for an effect of 18% (hazard ratio  
 2891 of 0.82) with an event rate of 2.2 %/yr and would have reasonable power of 77.3% even  
 2892 with a smaller than assumed event rate of 2.0 %/yr and an 18% effect. Depending on  
 2893 the observed event rate and treatment effect, the table below shows that sample sizes of  
 2894 8500 to 10000 would be consistent with study goals.  
 2895

Table 1: Power for the SPRINT primary outcome.									
	Event Rate								
	2.0 %/yr			2.2 %/yr			2.4 %/yr		
N\Hazard Ratio	0.78	0.8	0.82	0.78	0.8	0.82	0.78	0.8	0.82
8500	89.4	82.7	73.7	91.9	85.9	77.6	93.9	88.6	80.9
8750	90.3	83.7	75.0	92.6	86.9	78.7	94.5	89.5	82.0
9000	91.0	84.7	76.1	93.3	87.8	79.8	95.0	90.3	83.0
<b>9250</b>	<b>91.7</b>	<b>85.7</b>	<b>77.3</b>	<b>93.9</b>	<b>88.7</b>	<b>80.9</b>	<b>95.5</b>	<b>91.0</b>	<b>84.0</b>
9500	92.4	86.6	78.3	94.4	89.4	81.9	95.9	91.7	85.0
9750	93.0	87.4	79.4	94.9	90.2	82.9	96.4	92.4	85.9
10000	93.6	88.2	80.4	95.4	90.9	83.8	96.7	93.0	86.7

2896  
 2897 If the event rate in the standard therapy arm is substantially less than 2.2%, we may ask  
 2898 that the DSMB consider recommending a two year extension of the trial.  
 2899

### 2900 10.2.2 Summary

2901  
 2902 For the primary outcome under the assumptions detailed below, with 9250 participants,  
 2903 the SPRINT study is designed to have

- 2904 • 88.7% power to detect a treatment effect of 20% of intensive blood pressure control compared with standard blood pressure control,
- 2905
- 2906 • 81.9% power to detect a treatment effect of 20% of intensive blood pressure control compared with standard blood pressure control among participants with estimated glomerular filtration rates of <60 ml/min/1.73m<sup>2</sup> at baseline,
- 2907
- 2908 • 84.5% power to detect a treatment effect of 25% of intensive blood pressure control compared with standard blood pressure control among participants at least 75 years old at baseline,
- 2909
- 2910 • 96% power to detect a 20% effect and 80% power to detect a 15% effect for incident dementia, the primary outcome for SPRINT MIND.
- 2911
- 2912
- 2913
- 2914

2915 These estimates of power are valid under the following assumptions:

- 2916 • The primary outcome for SPRINT is a composite of fatal CVD, MI, stroke, heart failure, and non-MI acute coronary syndrome.
- 2917
- 2918 • The event rate for this composite outcome is
  - 2919 ○ 2.2 %/yr in the standard BP arm,
  - 2920 ○ 4 %/yr among participants with eGFR <60 ml/min/1.73m<sup>2</sup>, and
  - 2921 ○ 3.5 %/yr among participants ≥75 years old.
- 2922 • The event rate for the SPRINT MIND primary outcome of incident dementia is 3.1%/yr.
- 2923
- 2924 • There are
  - 2925 ○ 9250 participants in SPRINT,

- 2926 ○ 4300 participants with eGFR < 60 ml/min/1.73m<sup>2</sup>, and
- 2927 ○ 3250 participants ≥75 years old.
- 2928 • Participants are recruited uniformly over 2 years.
- 2929 • Minimum follow-up is 3 years, 10 months which assumes that closeout visits
- 2930 occur uniformly over a 4 month period.
- 2931 • Two-sided tests at the 0.05 level are used.
- 2932 • Annual loss to follow-up is 2 %/yr (3 %/yr for incident dementia).

2933  
2934 Additional computational details and a justification for the assumed event rates are  
2935 included in the appendix.

2936  
2937 **10.2.3 Power for the MIND primary outcome**

2938  
2939 Power for the MIND primary outcome is presented in Table 10.2 for a range of event  
2940 rates with 9250 participants, 5 years and 10 months of follow-up, 2 years of recruitment,  
2941 and 3 %/yr loss to follow-up. Details of the event rate estimation are given in Appendix  
2942 3.

2943

Table 10.2. Power for the SPRINT MIND primary outcomes.					
	Event Rate (%/yr)				
Hazard Ratio	3.1	3.2	3.3	3.4	3.5
0.80	96.3	96.7	97.1	97.4	97.7
0.85	79.0	80.2	81.3	82.4	83.4

2944  
2945

2946 **10.3 Statistical Reports**

2947 **10.3.1 Steering Committee Reports**

2948  
2949 Periodic reports will be generated for the Steering Committee, CCNs and Clinical Sites.  
2950 These reports will include information on recruitment, loss to follow-up, adherence,  
2951 baseline covariate information on the comparability of treatment groups, and adverse  
2952 events. Information will be stratified by CCNs and Clinical Sites. Other reports will  
2953 include information on quality control for central facilities and data entry.

2954

2955 **10.3.2 Data and Safety Monitoring Board Reports**

2956  
2957 The role and composition of the Data and Safety Monitoring Board are described  
2958 elsewhere (Chapter 13.6). Meetings of the DSMB will be held at least annually. Material  
2959 for these meetings will be distributed two weeks in advance of the meetings. Up-to-date  
2960 statistical analyses will be provided to the DSMB in preparation for their meetings. The  
2961 analyses will include data on recruitment, outcome measures, any side-effects or safety  
2962 concerns, adherence, and quality control, and will be designed in cooperation with the  
2963 DSMB. Interim analyses of the intervention effectiveness will be performed at times  
2964 coinciding with the meetings of the DSMB, and will be controlled to protect the overall  
2965 Type I error of the trial. These results will be for the use of the DSMB and will not be  
2966 revealed to the investigators. The purpose of these analyses will be for the DSMB to  
2967 assess the trial progress with respect to intervention efficacy and safety, for possible  
2968 recommendations regarding early termination of the trial.

2969

2970 We will work with the DSMB to finalize the monitoring plan. We include here a potential  
2971 starting point for those discussions.

2972 Interim analyses will be performed periodically for the DSMB. Monitored parameters will  
2973 include the following:  
2974 1. SBP separation between groups  
2975 2. SBP distribution within groups  
2976 3. Primary outcome results  
2977 4. Adverse events  
2978 5. Laboratory alerts  
2979 6. Recruitment progress  
2980 7. Other event rates, and event rates by subgroups  
2981 8. Enrollment overall and by subgroups such as level of eGFR and CKD category  
2982

2983 Sequential monitoring and early stopping. Incidence rates of outcomes will be monitored  
2984 throughout the trial and used for interim analyses of efficacy and futility. Group  
2985 sequential methods for event rates will be used to control the Type I error to be 0.05  
2986 across these repeated analyses. Critical values for interim testing will be defined based  
2987 on an O'Brien-Fleming type bound and will use a spending function to allow flexibility in  
2988 the number and timing of interim analyses. Information time will be defined based on the  
2989 expected number of events under the null hypothesis. With this approach, interim tests  
2990 early in the trial are conservative and the reduction in the overall power of the trial  
2991 caused by interim testing is small. If needed, conditional power calculations will be used  
2992 to assess the futility of continuation in the presence of a negative treatment effect.  
2993

2994 The monitoring plan will include consideration of the hypothesis that early adverse  
2995 effects may occur and then be followed by long-term beneficial effects. Because kidney  
2996 function will be measured at baseline, 1, 3, and 6 months, we will be able to analyze the  
2997 acute impact of our intervention on kidney function. Because of the study design,  
2998 episodes of acute kidney injury (AKI) that are of more than a transient nature will be  
2999 identified as changes in chronic kidney function, consistent with contemporary  
3000 paradigms acknowledging the interrelationships between AKI and CKD. Episodes of AKI  
3001 will be specifically sought in review of medical records in appropriate patients as adverse  
3002 events. Regarding the possibility of acute cognitive decline, spontaneously reported  
3003 SAEs would be the source of such information.  
3004

3005 At each meeting, the DSMB will review data on adverse events and other safety issues  
3006 to make an overall recommendation to the NIH concerning the safety of continuing  
3007 SPRINT. Consistent with NIH policy, each SPRINT CCN Principal Investigator will  
3008 receive a report summarizing the DSMB review of the adverse event data. Principal  
3009 Investigators are responsible for providing this report to their sites and institutional IRB.  
3010

### 3011 **10.3.3 Website Reports**

3012

3013 The Coordinating Center will prepare many reports and place them on the SPRINT  
3014 website. These reports enable a user to click on a static link which starts a real-time  
3015 report processed by SAS and returned as output in the user's web browser. These  
3016 reports access live data and run within seconds. Examples of real-time reports on  
3017 randomization and screening activities include: number of clinics actively recruiting,  
3018 percent at target (overall, to date, and by demographic subgroups such as women and  
3019 race/ethnic group). Clinical Sites will have access to live data showing exactly where  
3020 their clinic stands in relation to their recruitment goals and those of the other Clinical  
3021 Sites, as well as projections of activity needed to meet their goals. Committee members

3022 will have expanded access to information across all Clinical Sites for the purpose of  
3023 monitoring recruitment performance for the trial as a whole.  
3024

3025 **Chapter 11 – Data Management**

3026

3027 **11.1 Overview: Use of the World Wide Web**

3028

3029 All Clinical Center Networks and Clinical Sites will use the World Wide Web (WWW) to  
3030 enter SPRINT data collected on forms from participants seen within the Clinical Sites.

3031 Each Clinical Site will have a password protected area on the SPRINT home page  
3032 through which data will be entered. Documentation of the data entry system will be  
3033 maintained at the CC. In addition, training materials for measurement and data entry  
3034 personnel will be available in downloadable format on the SPRINT web site. Site-  
3035 specific reports relating to participant demographics, recruitment goals, etc., among  
3036 other reports, will be available on the web site.

3037

3038 Data security in the web-based data system uses 128-bit encryption and Secure Socket  
3039 Layer (SSL). Once data has been received at the CC, recovery from disasters such as  
3040 natural phenomenon (water, fire, or electrical) is possible through the ability to  
3041 reconstruct both the database management system and the data up to the last back-up  
3042 through the use of nightly backups. This will ensure optimal recovery of data systems in  
3043 the event of a disaster. Back-up tapes are kept in a locked, fire and waterproof storage  
3044 cabinet away from the computer room. Additional back-up tapes will be stored at another  
3045 location on the Wake Forest University Health Sciences campus. CCNs and clinical  
3046 sites have local procedures for back-up and recovery of data following a disaster. As a  
3047 supplement to those plans, the SPRINT CC will have all participant contact information  
3048 to minimize the chance for disruption of communication with participants regarding study  
3049 medications and test results.

3050

3051 **11.2 Flow of Data from Trial Units to Databases**

3052

3053 **11.2.1 Data from Clinical Sites and Clinical Center Networks**

3054

3055 Participant Randomization: SPRINT will use an internet-based, web browser  
3056 randomization procedure. Clinical Sites access the randomization application through  
3057 the study web site. Access to this application is password protected and its  
3058 communications are encrypted. Once security requirements are satisfied, a series of  
3059 questions identify and verify the eligibility of the participant prior to allowing  
3060 randomization of the participant.

3061

3062 Participant Tracking: The Participant Tracking System (PTS) is a fully integrated tracking  
3063 and notification system that advises clinic staff about participant follow-up windows, and  
3064 projects clinic and laboratory workload for a week at a time (longer if necessary).

3065 Tracking a participant begins at screening and continues automatically throughout the  
3066 project by integrating participant follow-up data with predetermined follow-up "windows".  
3067 When a participant is enrolled into the study, a schedule of target dates for each of the  
3068 visits is automatically generated. The report details the recommended "windows" that  
3069 each visit should fall into and a case file is created for the participant.

3070

3071 Data Entry: The images on the data entry screens mirror the data collection forms for  
3072 ease and accuracy of entry. Typically, as participant visits are completed, and hard copy  
3073 forms are filled out, the clinic coordinator reviews each form for accuracy and  
3074 completeness, including laboratory reports and any supporting documentation (hospital



3075 records, etc.). Once any data problems have been resolved, data are entered by clinic  
3076 staff into the computer via the web-based browser application. During data entry, a  
3077 variety of programmed edit checks are performed for key variables. When the edit  
3078 checks fail, data may be flagged for further review or prevented from becoming part of  
3079 the study database. Also, a sample of key forms may be double-keyed for additional  
3080 quality control.

3081

### 3082 **11.2.2 Data from Central Laboratory and ECG Reading Center**

3083

3084 Laboratory specimens and electrocardiographic data are sent to the Central Laboratory  
3085 and ECG Reading Center from the Clinical Sites on a fixed schedule. The Central  
3086 Laboratory and ECG Reading Center provide results to the CC on live internet feed.  
3087 Depending on clinic needs, reports will be sent to assist in the clinical functions (e.g.,  
3088 providing timely feedback to the clinic on any measurement that exceeds a predefined  
3089 alert level).

3090

### 3091 **11.2.3 Central Database Edits**

3092

3093 At regular intervals, data queries will be carried out on the computerized databases at  
3094 the CC to perform consistency checks on key variables and forms. Although much of  
3095 this will have been done at the data entry level in the clinic, this additional pass through  
3096 the data serves as a quality control check.

3097

### 3098 **11.3 Feedback to Clinical Sites and Clinical Center Networks**

3099

3100 Data edit reports will be generated to help ensure that data are entered in timely and  
3101 complete manner. These reports will include both the assessment for each Clinical Site  
3102 of the time between data collection and entry, and the generation of reports by the CC of  
3103 missing items. These reports will be provided to the Clinical Center Networks, Clinical  
3104 Sites, and study committees on a regular basis so that data collection items that are  
3105 troublesome can be identified and Clinical Sites not meeting study standards can be  
3106 notified. CCN Coordinators will have access to all data reports for Clinical Sites within  
3107 their network via the study website and will be asked to follow-up on any action that  
3108 needs to be taken.

3109

### 3110 **11.4 Confidentiality**

3111

3112 The confidentiality of all participant information (including but not limited to any genetic  
3113 analysis) must be protected at the Clinical Sites, the CCNs, and the CC. Paper records  
3114 and computer files must be appropriately safeguarded from unauthorized access.

3115

3116 Paper and/or electronic records for study participants will be stored at the Clinical Sites.  
3117 Copies of records identified by participant identification number pertaining to SAEs and  
3118 study-defined clinical events, including necessary medical records, will be stored at the  
3119 CC. These records will receive the same care as would ordinary medical records. They  
3120 will be stored in locked filing cabinets and/or filing rooms within secure office space or, if  
3121 uploaded through the study website, they are stored in a non-url accessible area that  
3122 can be accessed only through the SPRINT website. Only study personnel who have  
3123 completed SPRINT training in data handling will have access to study forms.

3124

3125 Similar care will be used in the handling of the computer records of study data stored at  
3126 each Clinical Site. Access to the data in any local SPRINT database will be controlled  
3127 by a system of user identification names and passwords. Each Clinical Site staff  
3128 member must complete the SPRINT data handling training program before being given  
3129 an ID and password to use the data system. The privileges allowed to each ID can be  
3130 individually specified by the local CCN Coordinator. All passwords stored within the  
3131 system will be encrypted using SSL encryption.

3132  
3133 Confidentiality of information within the CC will be protected through a variety of  
3134 procedures and facilities:

- 3135
- 3136 1. The confidential nature of the data collected, processed, and stored at the CC is  
3137 explained to all new personnel.
  - 3138
  - 3139 2. All access to CC office space containing data is controlled through a single door,  
3140 which is locked with a keypunch lock. This door remains locked at all times.
  - 3141
  - 3142 3. All participant data sent to the CC is encrypted as described above.
  - 3143
  - 3144 4. All participant data stored on the Wake Forest University's servers are likewise  
3145 encrypted. In addition, all such databases are protected by passwords that must  
3146 be supplied before the data can be accessed.
  - 3147
  - 3148 5. All study documents containing individually identifiable data are produced on  
3149 printers within the CC's secure office space.
  - 3150
  - 3151 6. The CC will obtain a Certificate of Confidentiality for SPRINT, which prevents  
3152 researchers from being forced to disclose identifying information by certain legal  
3153 proceedings.

3154  
3155  
3156  
3157  
3158

## 3159 **Chapter 12 – Quality Control**

3160

### 3161 **12.1 Introduction**

3162

3163 Data integrity and quality are among the highest priorities in SPRINT. This feature is  
3164 reflected in the details provided in the protocol regarding initial screening and  
3165 recruitment of participants, data acquisition at baseline and follow-up visits, outcome  
3166 definition and assessments, reading and/or interpretation of the results, and their  
3167 analysis and publication. There are two primary purposes for quality control: to  
3168 document the level of quality and to provide feedback to the clinical, reading and  
3169 laboratory centers in order to maintain and improve the quality of the study data over the  
3170 course of the trial. The Measurement Procedures and Quality Control Committee will  
3171 establish guidelines for quality assurance and quality control, detailed in the Manual of  
3172 Procedures.

3173

3174 Quality control monitoring in SPRINT will involve the CC, the CCN hubs, and various  
3175 SPRINT committees and other groups, although the Measurement Procedures and  
3176 Quality Control Subcommittee will monitor quality control and quality assurance activities  
3177 for the study overall, integrating input from these other groups. For example, the  
3178 Recruitment, Retention and Adherence Subcommittee will monitor progress toward  
3179 achieving recruitment goals, and the SPRINT MIND subcommittee will monitor the  
3180 quality of assessment with the cognitive battery. The CC will generate reports and  
3181 supply them to the CCN hubs for their sites, to the Measurement Procedures and Quality  
3182 Control Subcommittee for all sites and entities, and to other involved groups for the  
3183 activities in their purview. The CCN hubs will be responsible for tracking the  
3184 performance of sites within their Networks, and for following up with their sites on areas  
3185 of concern. The Measurement Procedures and Quality Control Subcommittee will  
3186 conduct monitoring for the trial overall, will raise issues on specific sites and  
3187 communicate them to the CCN hub for follow-up, will monitor the central facilities (ECG  
3188 reading center and central lab), and will report any areas of concern to the Steering  
3189 Committee for consideration, as needed.

3190

3191 This chapter outlines the type of quality assurance activities that will be conducted in the  
3192 SPRINT Trial. Two phrases are used. The first, quality assurance, is the collection of  
3193 manuals and procedures that will be in place to assure the integrity of the data. A  
3194 subset of these procedures is referred to as quality control, which describes the  
3195 monitoring and analytic activities that assess performance during data collection and its  
3196 processing.

3197

### 3198 **12.2 Manual of Procedures**

3199

3200 As with any multicenter study, standardization of study procedures is very important in  
3201 the SPRINT Trial. The MOP includes the detailed descriptions of all trial procedures.  
3202 This MOP is used for training purposes and as a reference for all study investigators and  
3203 staff. The MOP is an important aspect of efforts to standardize study procedures across  
3204 clinical sites in the SPRINT Trial.

3205

3206 Key study procedures will be standardized; these include the use of a central lab and  
3207 ECG reading center, and standard forms, equipment, and procedures in the clinics for

3208 BP measurement and other data collection procedures. Furthermore, standard event  
3209 definitions and event validation procedures will be used.

3210

### 3211 **12.3 Study Forms and Data Entry Procedures**

3212

3213 Quality assurance concepts were employed during the development of forms. Forms  
3214 can be printed with accompanying question-by-question instructions for easy reference.  
3215 Web-based data entry screens will be developed from the forms, and enable the  
3216 incorporation of range and logical checks at the time of data entry. These features will  
3217 contribute to quality assurance.

3218

### 3219 **12.4 Training**

3220

3221 Training of staff and pilot testing of procedures will be crucial to standardize procedures  
3222 and assure data quality. SPRINT uses two different training models: central training for  
3223 study staff and the train-the-trainer approach. In the central training aspects of the  
3224 SPRINT training effort, all relevant staff members from all clinical sites will be convened  
3225 in a single, centrally administered face-to-face training session. This approach is cost-  
3226 efficient and contributes to uniformity of the training experience and thereby to uniformity  
3227 of data quality across sites. In the train-the-trainer aspect of the SPRINT training effort,  
3228 CCN hub staff will provide training sessions to persons who were unable to attend the  
3229 central training session and to newly hired staff as turnover occurs. In addition, the CCN  
3230 hubs will organize training and refresher training sessions, as needed, including CCN  
3231 remedial training in specific areas targeted by quality control monitoring for a specific  
3232 site.

3233

### 3234 **12.5 Data Queries**

3235

3236 The Coordinating Center will be responsible for data editing, which will include checks  
3237 for missing data, unrealistic values, and crosschecks for inconsistencies. Data will be  
3238 checked on form submission and any data queries presented to the data entry staff for  
3239 immediate resolution, if possible. The CC will also produce data query reports on the  
3240 website that summarize the number and types of queries by clinic and network. Clinical  
3241 center staff will be responsible for reviewing and resolving the data queries in a timely  
3242 manner. Reports, including reports on timeliness of data entry and query resolution, will  
3243 be shared with the Measurement Procedures and Quality Control Subcommittee and the  
3244 corresponding CCN hub investigators and staff for quality control purposes.

3245

### 3246 **12.6 Quality Control Reports**

3247

3248 The Measurement Procedures and Quality Control Subcommittee will develop quality  
3249 indicators, both to document data quality and to provide feedback to individual clinical  
3250 sites, which will be tracked in routine quality control reports in the SPRINT Trial. All  
3251 reports will be generated by the CC and distributed to the Subcommittee, to the  
3252 corresponding CCN hub, and/or to other relevant groups (e.g., the SPRINT MIND  
3253 subcommittee for those measures). Investigators and staff at the CCN hubs will be  
3254 responsible for disseminating reports and feedback to the appropriate investigators and  
3255 staff at the clinics in their networks. These reports will be used to inform discussions  
3256 that will take place during regularly scheduled telephone contacts and site visits.  
3257 Additional information about these processes is contained in the MOP.

3258 Quality Control reports will focus on measures of process, impact, and outcomes.  
3259 Examples of process measures that will be tracked for quality control purposes include:  
3260 1. Days between data collection and data entry  
3261 2. Percent of forms with late data entry  
3262 3. Number of participants with missed or late visits by contact, number of missed  
3263 or late visits clinic-wide, and number of participants missing two or more  
3264 consecutive visits  
3265 4. Number, name and dose of prescribed antihypertensive medications for  
3266 individual participants

3267  
3268 Examples of impact measures that will be tracked for quality control purposes include:  
3269 1. Number (and percent) of participants at goal according to the BP target  
3270 assignment as assessed by in-clinic BP measurements.

3271  
3272 Examples of outcome measures that will be tracked for quality control purposes include:  
3273 1. Submission of medical record documentation for reported study events by the  
3274 clinical site (e.g., timeliness, completeness)  
3275 2. Proportion of participants with ECG submitted to central ECG Reading Center  
3276 overall and by quality grade  
3277 3. Proportion of participants with urine samples submitted for albuminuria  
3278 assessment  
3279 4. Proportion of participants with blood samples submitted to central lab  
3280 5. Percent agreement of individual study adjudicators with the final outcome  
3281 assignments for cases adjudicated

3282  
3283 Details of the various quality control procedures are contained in the Manual of  
3284 Procedures. In general, the CC will generate reports and analyses on progress at the  
3285 clinical sites on an agreed upon schedule appropriate to the study phase. Reports will  
3286 most often be developed at the level of the clinical site but may also include patient-level  
3287 reports by site, technician-level reports by site, and summary reports study-wide and  
3288 within and across CCNs. The CC will supply these reports to the Measurement  
3289 Procedures and Quality Control Subcommittee, to other relevant Subcommittees, and to  
3290 the corresponding CCN hub investigators and staff.

### 3291 3292 **12.6.1 Deviations from protocol**

3293  
3294 Adherence to the study protocol is crucial to collection of high quality data and to the  
3295 internal validity of the trial. Thus, the Intervention Subcommittee will define important  
3296 deviations from the intervention protocol for tracking purposes. A clinic-site-specific  
3297 report describing important protocol deviations will be disseminated by the CC to the  
3298 respective CCNs for quality control purposes. Copies of these reports and a summary  
3299 report describing important protocol deviations and plan for corrective actions on a  
3300 study-wide basis will be shared with the Measurement Procedures and Quality Control  
3301 Subcommittee and the Steering Committee.

### 3302 3303 **12.6.2 Monitoring the Clinical Centers in the Networks**

3304  
3305 Primary responsibility for clinical site monitoring in SPRINT will be assigned to the  
3306 corresponding CCN hub. CCN hub investigators and staff will be responsible for

3307 monitoring performance at each of their clinical sites. The CCN hub monitoring team will  
3308 coordinate research activities of the study within their network and maintain effective  
3309 communications with clinical sites, other clinical center networks, the coordinating  
3310 center, project office and study central units (Central Lab, ECG Reading center, MRI  
3311 Reading Center and Drug Distribution Center). One of the primary roles of CCN hubs is  
3312 to monitor clinical sites in all aspects of trial operations and performance and to assist in  
3313 problem solving related to all aspects of the main study and ancillary studies. Site  
3314 monitoring can and will be performed using regular communications including email,  
3315 conference calls, site visits and other means.

3316

## 3317 **12.7 Site Initiation**

3318

3319 Clinical site initiation to enroll and randomize participants is dependent upon completion  
3320 of a series of preliminary tasks. These include completion of appropriate regulatory  
3321 approvals (IRBs), and letters of agreement. Site staff training, certification, and receipt  
3322 of all study supplies including medications will need to be completed as well as the  
3323 development of a recruitment plan. CCNs will provide the appropriate assistance to their  
3324 clinical sites toward these ends, which may include site visits to ensure that the study  
3325 enrollment and randomization process follows proper study procedures.

3326

## 3327 **12.8 Site Visits**

3328

### 3329 **12.8.1 CCNs to clinical sites**

3330

3331 During the course of the trial, clinical center network personnel will site visit clinical sites  
3332 in their network at specified intervals, and as needed. The scope of these visits is broad  
3333 and can include but is not limited to regulatory requirements, study communications, site  
3334 initiation, site staffing, and general site performance. A minimum standard for all site  
3335 visits content and frequency is detailed in the MOP; however, areas of emphasis and/or  
3336 additional monitoring may vary according to the circumstances of a specific site and site  
3337 visit. Site visits may be conducted to evaluate performance deficits in one or more  
3338 critical areas, such as consistent departures from the protocol or MOP. Site visits are  
3339 also an opportunity for refresher training and/or training of new staff, as needed. Site  
3340 visit frequency and visit procedures can be found in more detail within the appropriate  
3341 section of the MOP.

3342

3343 Site visitors will include CCN hub and site staff and investigators as deemed appropriate.  
3344 As needed, representatives from the coordinating center, project office, other CCNs, and  
3345 study committees may attend these visits.

3346

3347 A summary of the site visit will be presented to the clinical site investigator and staff at  
3348 the conclusion of the site visit. The CCN staff will prepare a written site visit report within  
3349 a reasonable time-frame post visit. Copies of the site visit report will be sent to the  
3350 clinical site investigator, the coordinating center, the project office, and the CCN.  
3351 Additional copies of the site visit report may be requested by other SPRINT Study  
3352 entities.

3353

3354 A sample of site visit reports may be reviewed by the Measurement Procedures and  
3355 Quality Control Committee or other study committees with recommendations for follow-  
3356 up actions and/or reporting changes as needed.

3357

3358 **12.8.2 Coordinating Center to CCN hubs**

3359

3360 The SPRINT Coordinating Center will periodically site visit each CCN hub in order to  
3361 monitor and ensure high performance throughout the trial. Representatives from the  
3362 NIH SPRINT project office (including NHLBI, NIA, NIDDK, and NINDS) and study  
3363 leadership may also attend.

3364

3365 **12.8.3 Project Office to Coordinating Center**

3366

3367 Representatives from the NIH SPRINT project office and study leadership will visit the  
3368 coordinating center in order to monitor and ensure high performance throughout the trial.

3369

3370 **12.9 Laboratory and ECG Center Quality Control**

3371

3372 The SPRINT Measurement Procedures and Quality Control Subcommittee will work with  
3373 the Coordinating Center, the Central Laboratory and the ECG Reading Center to  
3374 develop quality control procedures to ensure high quality data, including monitoring  
3375 clinical site performance as well as performance of the Central Laboratory and ECG  
3376 Reading Center. The results of quality control procedures performed at the Central  
3377 Laboratory and the ECG Reading Center will be reported on a regular basis to the  
3378 Measurement Procedures and Quality Control Subcommittee and by them to the  
3379 Steering Committee.

3380

3381 Core Laboratory for Blood and Urine Assays

3382

3383 Clinical site performance in acquisition, handling, storage and shipping of specimens will  
3384 be tracked by the Central Laboratory and the Measurement Procedures and Quality  
3385 Control Subcommittee. The first step in quality assurance at the site level consists of the  
3386 training and certification process for staff within the clinical sites. Other steps include  
3387 maintaining logs of equipment checks at each clinical site according to the Manual of  
3388 Operations; observation of technicians performing all steps of sample collection and  
3389 processing during site visits; reviewing study forms; reviewing and tracking the condition of  
3390 samples received at the Central Laboratory for problems in shipment; and periodic analysis  
3391 of the study data for participant compliance with fasting, where required, and for signs of  
3392 problems in drawing or processing, such as hemolysis. Reports on clinical center  
3393 performance will be submitted regularly by the Central Laboratory to the CCN hubs and  
3394 the SPRINT Measurement Procedures and Quality Control Subcommittee.

3394

3395 Performance of the Central Laboratory will be monitored regularly by the SPRINT  
3396 Measurement Procedures and Quality Control Subcommittee. Quality Control  
3397 procedures in the laboratory for assays include the use of the internal Laboratory  
3398 Manual, training and certification of Laboratory staff, Laboratory participation in external  
3399 standardization and certification quality control programs, and implementation of the  
3400 SPRINT internal quality control program. Process measures, such as turn-around time  
3401 for the Laboratory reporting back relevant analyte results to the clinical sites, will also be  
3402 monitored. Particular attention will be paid to the feed-back of pre-specified laboratory  
3403 alerts to the Clinical Sites by the Central Laboratories.

3404

3405 As part of the internal quality control program specified in the manual of operations, the  
3406 Central Laboratory will regularly provide summaries of the internal quality control results to  
3407 the Coordinating Center, including the following information for each assay: (1) monthly  
3408 summary statistics (n, mean, and standard deviation) on all quality control pools, including

3409 new pools being overlapped to replace established QC pools; (2) summaries of any  
3410 unusual problems or conditions noted. The SPRINT Measurement Procedures and  
3411 Quality Control Subcommittee will review these reports for evidence of trends with time  
3412 in results on these pools.

3413

3414 ECG

3415 Clinical site performance in acquisition and submission of ECG tracings will be tracked by  
3416 the Reading Center and by the Measurement Procedures and Quality Control  
3417 Subcommittee. The first step in quality assurance at the site level consists of the training  
3418 and certification process. All SPRINT staff acquiring ECGs must be certified, consisting  
3419 of the successful recording and transmission to EPICARE of three successive, adequate  
3420 quality ECGs. The ECG Reading Center will continuously monitor ECG quality and will  
3421 identify errors in acquisition. Each tracing submitted will be graded for quality and used  
3422 to compile continuous quality trend analysis data for each clinical site. Quality control  
3423 grade reports will be regularly submitted to the CCN hubs and to the SPRINT  
3424 Measurement Procedures and Quality Control Subcommittee.

3425

3426 The ECG Reading Center has an internal quality control protocol that monitors  
3427 performance of ECG coding and measurement. This includes regular monitoring of the  
3428 repeatability and accuracy of editing ECG waveforms of the digital (electronic) ECGs,  
3429 and procedures to safeguard against change in trends due to change in ECG reading  
3430 software. The SPRINT Measurement Procedures and Quality Control Subcommittee will  
3431 monitor performance of ECG coding and measurement within the ECG Reading Center  
3432 by regularly reviewing the results of the center's quality control reports.

3433

3434

3435

3436



## 3437 **Chapter 13 – Study Organization**

3438

### 3439 **13.1 Overview**

3440

3441 The SPRINT organizational structures and responsibilities are similar to those of other  
3442 large multicenter clinical trials sponsored by government or industry. The National  
3443 Heart, Lung, and Blood Institute (NHLBI) initiated this study, and the National Institute of  
3444 Diabetes and Digestive and Kidney Diseases (NIDDK) is a co-sponsor of the main  
3445 SPRINT trial. The National Institute of Neurological Disorders and Stroke (NINDS) and  
3446 the National Institute on Aging (NIA) are jointly sponsoring the SPRINT MIND study.  
3447 Five Clinical Center Networks and a Coordinating Center work together through the  
3448 Steering Committee to successfully design and conduct the trial (see Figure 13.1). In  
3449 addition, there is a Central Laboratory, an ECG Reading Center, an MRI Reading Center  
3450 and a Drug Distribution Center. Scientific leadership is provided by the Steering  
3451 Committee. External oversight is provided by Institutional Review Boards and a Data  
3452 and Safety Monitoring Board.

3453

### 3454 **13.2 Clinical Center Networks and Clinical Sites**

3455

3456 SPRINT participants will be recruited, randomized, treated, and followed through a  
3457 system of five CCNs. Each CCN consists of collaborating clinical sites, which are  
3458 medical facilities and/or individual practices involved in the initial evaluation, enrollment,  
3459 treatment and follow-up of participants in the trial. Each CCN and clinical site will be  
3460 responsible for timely recruitment and protocol adherence in accordance with the  
3461 SPRINT protocol and MOP. In addition, the CCNs will contribute to the study's scientific  
3462 leadership and operational management, and each CCN Principal Investigator (PI) will  
3463 participate in Steering Committee and other investigator meetings. The clinical sites will  
3464 collect data at the local level in accordance with the study protocol and the manual of  
3465 operations, and will manage each participant's hypertension treatment. For all  
3466 participants recruited, the CCNs and clinical sites will be responsible for achieving the  
3467 goals specified in the protocol for adherence to study treatment and retention of study  
3468 participants. The CCN will have the primary responsibility for overseeing their clinical  
3469 sites and timely evaluation and correction of recruitment, adherence, and retention  
3470 problems, including development and implementation of alternative strategies to achieve  
3471 the stipulated goals, and funding the related activities. It is anticipated that each CCN  
3472 will conduct periodic site visits within its network of clinical sites to supervise recruitment,  
3473 adherence, and retention activities and to ensure high quality performance. The CCN  
3474 activities will be coordinated with the CC, and may include site visits conducted by the  
3475 CC, along with other organizational components of the study. The CCNs will collaborate  
3476 closely with and assist the CC in implementation and standardization of the protocol  
3477 within its network.

3478

### 3479 **13.3 The Coordinating Center**

3480

3481 The CC, with input from the SPRINT Steering Committee, will be responsible for  
3482 coordinating protocol writing activities, including protocol drafting and finalization;  
3483 developing and distributing forms and the MOP; training trial personnel in standardized  
3484 protocol implementation and data collection; generating and distributing numerous  
3485 reports (including specific recruitment goals and projections); providing rapid feedback to  
3486 the CCN and Central Units on the quality of data submitted and proposed corrections;

3487 developing and maintaining trial databases and related internal and public websites;  
3488 collecting, managing, and analyzing all trial data; developing and overseeing the web-  
3489 based adjudication of clinical events and endpoints; preparing reports for the DSMB;  
3490 ensuring that the provisions of the manual of operations are carried out by all  
3491 investigating groups; and providing timely and high quality statistical analysis expertise  
3492 as required to prepare presentations and manuscripts. The CC will conduct periodic  
3493 visits to each CCN in order to monitor and ensure high performance throughout the trial.  
3494

3495 The CC will oversee 4 Central Units: the Drug Distribution Center, the Central  
3496 Laboratory, the ECG Reading Center, and the MRI Reading Center.  
3497

3498 The Central Laboratory will serve as a repository for immediate and future analyses of  
3499 urine and blood specimens. The Central Laboratory will be responsible for the  
3500 development and distribution of specific measurement procedures, and laboratory  
3501 analyses, and for participating in quality assurance activities related to laboratory  
3502 measures. Periodic reports will be generated to address sample acquisition quality for  
3503 each clinical site and assay performance, and these will be provided to the CCNs and  
3504 the Measurements, Procedures and Quality Control (MPQC) Subcommittee for review.  
3505

3506 The ECG Reading Center will provide central interpretation of ECGs. The ECG Reading  
3507 Center will develop procedures for obtaining and transmitting ECG data from the clinical  
3508 sites to ensure the highest quality data collection. Periodic reports will be generated to  
3509 address ECG quality for each clinical site, and these will be provided to the CCNs and  
3510 the MPQC for review.  
3511

3512 In collaboration with each CCN participating in the MRI study, the MRI Reading Center  
3513 will identify an MRI site which is located in geographic proximity to the CCN's clinical  
3514 sites. The MRI Reading Center will develop a detailed protocol and manual of  
3515 procedures to ensure that the MRIs taken over time are of the highest quality with the  
3516 smallest variation due to changes in technique and to allow the most precise estimate of  
3517 change over time. The MRI Reading Center will provide training and certification for MRI  
3518 site staff in order to ensure uniformity of methods, and will monitor carefully the quality of  
3519 their work. Working with the CC, the MRI Reading Center will develop an analytical plan  
3520 to estimate as precisely as possible the change in brain MRI over time for each SPRINT-  
3521 MIND-MRI participant. Periodic reports will be generated to address MRI quality for each  
3522 scanning site, and these will be provided to the CCNs and the MPQC for review.  
3523

3524 The Drug Distribution Center will be responsible for developing and implementing plans  
3525 for cost-effective drug acquisition; packaging, labeling, and dispensing drugs according  
3526 to the study protocol; and providing data to the CC for further analyses. The DDC will  
3527 design the technical aspects of drug packaging and labeling to facilitate participants'  
3528 ability to understand and adhere to the drug regimen. The DDC will work with the  
3529 clinical sites and CCNs to develop cost-effective inventory management procedures.  
3530

#### 3531 **13.4 NHLBI Project Office and Other Government Representatives** 3532

3533 The NHLBI Project Office will be responsible for the scientific conduct and administration  
3534 of SPRINT. Representatives from the Project Office participate in the scientific, general  
3535 organizational and fiscal management of the trial. NHLBI staff includes scientific  
3536 representation from the Project Office team and members of the Office of Acquisitions

3537 and the Office of Biostatistics Research. In addition, the NIH SPRINT team includes  
3538 scientific staff from the NIDDK, the NINDS and the NIA.

3539

### 3540 **13.5 The SPRINT Steering Committee, Executive Committee, Conflict of Interest** 3541 **Committee and the Subcommittees of the Steering Committee**

3542

3543 The SPRINT Steering Committee provides the overall leadership for the study and  
3544 establishes scientific and administrative policy. It is composed of the Principal  
3545 Investigators from the five Clinical Center Networks, the Principal Investigator from the  
3546 Coordinating Center, the NHLBI Project Officer, representatives from NIDDK, NINDS,  
3547 NIA, the Steering Committee Chair, and the Steering Committee Vice-Chair. This  
3548 committee oversees the overall conduct of the trial throughout all phases, develops the  
3549 trial design, prepares the final protocol, and approves the study forms and manual of  
3550 operations. During the data collection phases of the trial, this committee oversees data  
3551 collection practices and procedures to identify and correct deficiencies. The Steering  
3552 Committee also will consider and adopt changes in the study protocol or procedures as  
3553 necessary during the course of the trial.

3554

3555 The SPRINT Steering Committee is chaired by the Steering Committee Chair, who  
3556 serves as the senior executive officer of the investigative group. A Vice-Chair assists  
3557 the Chair with Steering Committee responsibilities. Voting Steering Committee members  
3558 are the Principal Investigators from the five CCNs, the Principal Investigator from the  
3559 Coordinating Center, and the NHLBI Project Officer. If a CCN PI or the CC PI cannot  
3560 make a meeting at which a vote is taken, then the Co-Principal Investigator may vote  
3561 (with the understanding that the Co-PI is fully informed about the issue). The Steering  
3562 Committee Chair, or Vice-Chair in his/her absence, votes only to break a tie. CCN and  
3563 Site Co-investigators and Coordinators, CC staff, NIH staff, consultants, and opinion  
3564 leaders may also be invited to attend meetings.

3565

3566 The SPRINT Executive Committee will oversee the day-to-day operations of the trial as  
3567 an extension of the Steering Committee to ensure efficient and quality performance. The  
3568 members include the Steering Committee Chair, Steering Committee Vice-Chair,  
3569 Coordinating Center personnel, Project Office personnel, and one CCN PI (rotated  
3570 annually so that each PI has the opportunity to serve). Other key study personnel (e.g.,  
3571 Chair of the Operations/Project Coordinators Subcommittee, Director of the DDC) may  
3572 be asked to participate as either ad hoc or regular members.

3573

3574 The SPRINT Conflict of Interest Committee reviews potential conflict of interest issues.  
3575 The NIH Project Office, Steering Committee Chair, and CC PI comprise this committee,  
3576 which has the overall responsibility for the trial's ethical oversight policy and procedures.

3577

3578 There are a number of standing subcommittees and working groups which report to the  
3579 Steering Committee. These subcommittees and groups and their charges are detailed  
3580 in Appendix 5.

3581

### 3582 **13.6 The Data and Safety Monitoring Board**

3583

3584 An independent Data and Safety Monitoring Board will be established to monitor data  
3585 and oversee participant safety. Members will be appointed by the NHLBI to provide  
3586 oversight of the trial and its ancillary studies. The SPRINT DSMB may include experts in  
3587 cardiovascular medicine (particularly hypertension), kidney disease, clinical trials,

3588 geriatrics, biostatistics, bioethics, quality of life, cost effectiveness, cognitive function and  
3589 other areas as needed. DSMB participants include the Steering Committee Chair (who  
3590 is unblinded) and Vice-Chair (who is blinded), CC PI and senior staff, and  
3591 representatives from the NHLBI and other NIH sponsors. The DSMB normally meets  
3592 twice a year to monitor safety, to advise the NHLBI about study progress, including  
3593 contractor performance, and to make recommendations to the NHLBI regarding study  
3594 continuation and protocol changes. In addition, the CC may provide data to the DSMB  
3595 Chair to ensure early identification of any major adverse outcomes of therapy. The  
3596 DSMB has the responsibility to recommend to the NHLBI whether the trial should  
3597 continue, whether the protocol should be modified, or whether there should be early  
3598 termination. The DSMB will provide reports to the NHLBI through the Executive  
3599 Secretary, who will be appointed by the NHLBI. Recommendations by the DSMB must  
3600 be approved by the NHLBI prior to implementation.

### 3601 3602 **13.7 Role of Industry**

3603  
3604 Industry may contribute resources to the study and will be acknowledged appropriately.  
3605 However, the scientific decisions and governance of the trial will be determined by the  
3606 Steering Committee, as per NHLBI Policy.

### 3607 3608 **13.8 Conflict of Interest Policy**

3609  
3610 The SPRINT investigators have established a policy regarding Conflict of Interest, which  
3611 is presented in the MOP. This policy was developed to meet two goals. First, the  
3612 investigators wished to maintain the confidence that advice was being given, and  
3613 decisions made, in as unbiased and fully informed manner as possible. Second, the  
3614 investigators wished that the processes and results of the trial would meet public  
3615 standards of conduct.

### 3616 3617 **13.9 Timeline**

3618  
3619 SPRINT will begin recruiting and randomizing during the fall of 2010. Recruitment will  
3620 continue for approximately two years. The minimum length of participant planned follow-  
3621 up will be four years, and maximum length of follow-up will be approximately six years,  
3622 so the final study visits will occur in late 2016 or early 2017. If the event rate in the  
3623 standard therapy arm is substantially less than 2.2%, we may ask that the DSMB  
3624 consider recommending a two year extension of the trial.

### 3625 3626 **13.10 Ancillary Studies**

#### 3627 3628 **13.10.1 Introduction**

3629  
3630 In addition to the main SPRINT protocol, investigators may wish to perform Ancillary  
3631 Studies using the SPRINT population, blood or urine samples, or other collected data.  
3632 An ancillary study is an investigation not initiated by the SPRINT Steering Committee,  
3633 with objectives that are not within the main SPRINT specific objectives and not part of  
3634 the SPRINT protocol but uses SPRINT participants, samples, and/or data collected by  
3635 SPRINT. In most cases, an ancillary study will involve acquisition of additional data that  
3636 are not compiled as part of the SPRINT data set. An ancillary study may or may not use  
3637 all randomized participants. Investigators are encouraged to propose and conduct  
3638 ancillary studies. Such studies enhance the value and productivity of SPRINT and help

3639 ensure the continued interest of the diverse group of investigators who are critical to the  
3640 success of the trial as a whole. These studies provide an exceptional opportunity for  
3641 investigators, either within or outside of SPRINT, to conduct additional projects at  
3642 relatively low cost. In general, ancillary studies will require additional funding from the  
3643 NIH or other sources.

### 3644 3645 **13.10.2 Application Review Process**

3646  
3647 To protect the integrity of SPRINT, all ancillary studies must be reviewed and approved  
3648 by the SPRINT Steering Committee before access to SPRINT data, samples, or  
3649 participants is permitted. Investigators will not be allowed access to the SPRINT  
3650 participants, samples, or database without approval. New ancillary study proposals will  
3651 be submitted to the SPRINT Ancillary Science (AS) Subcommittee, which will review all  
3652 ancillary study proposals and make a recommendation to the Steering Committee. In  
3653 the event that investigators wish to modify an ancillary science protocol that has already  
3654 been approved by the SPRINT SC, they will need to first obtain AS Subcommittee and  
3655 SC approval. Ancillary study forms can be obtained by contacting the Coordinating  
3656 Center or accessing the SPRINT website.

3657  
3658 Studies submitted for approval less than four months prior to a funding application  
3659 deadline may not receive timely approval. When the application is complete, the study  
3660 proposal will be sent to the AS Subcommittee for review. The AS Subcommittee will  
3661 have monthly calls to discuss proposals, which will be circulated at least one week prior  
3662 to the calls. After review and approval by the AS Subcommittee, approval/disapproval  
3663 will be made by the Steering Committee. Ancillary Science investigators must include  
3664 one or more SPRINT investigators in their ancillary study proposals.

3665  
3666 The Coordinating Center will usually be responsible for all data management and  
3667 analysis for all ancillary studies. Specialized expertise external to the coordinating  
3668 center (e.g., processing of images) may be needed at the coordinating center's  
3669 discretion. Costs associated with ancillary study data management and analysis must  
3670 be budgeted into each ancillary study, even if the applicants have the necessary  
3671 expertise in data management and analysis.

3672  
3673 Prior to grant submission (or study initiation if no external funding is required), the CCN  
3674 PI must approve participation of sites in her/his network. This is required as the CCN PI  
3675 is responsible for the conduct of all aspects of SPRINT within her/his network. Part of  
3676 this is management and oversight of clinic and participant burden. As needed, the CCN  
3677 will include funding for oversight (e.g., investigator, coordinator, and fiscal personnel  
3678 time, travel). The SPRINT Steering Committee also reserves the right to review the  
3679 burden of ancillary studies on an on-going basis and take appropriate actions as  
3680 necessary. Investigators with approved ancillary studies will report the status of the  
3681 studies annually to the Chair of the AS Subcommittee.

3682  
3683 Additional detail on the review process and criteria for judging proposals can be found in  
3684 the MOP.

### 3685 3686 **13.10.3 Additional Requirements of Ancillary Science Investigators**

3687  
3688 All ancillary study investigators will be required to budget adequately for all necessary  
3689 resources for their studies. This includes, but may not be limited to, costs for data

3690 collection, sample collection, sample shipping, sample extraction, sample analysis, data  
3691 entry, website development, data analysis, dataset preparation, data storage and  
3692 publication of results. The final budget may be determined after AS and SC approval.  
3693

3694 Each ancillary study will cause an increase in utilization of main SPRINT study  
3695 resources, particularly by the SPRINT Presentations and Publications (P&P)  
3696 Subcommittee. To help with study operations, each ancillary science proposal team  
3697 should budget for and may be asked to contribute efforts to the main SPRINT study by,  
3698 for example, assigning a person to serve as a reviewer for the P&P Subcommittee.  
3699

3700 Investigators proposing the use of laboratory measurements are encouraged to use the  
3701 SPRINT Central Laboratory if at all possible. This will facilitate sample processing and  
3702 shipping and may reduce the amount of sample required.  
3703

3704 All images (e.g., MRI) or tracings (e.g., ECG) must be available for other investigators to  
3705 use in the spirit of the NIH policy available at <http://grants.nih.gov/grants/sharing.htm>.  
3706 To achieve this goal, ancillary studies must budget for the costs associated with  
3707 archiving these images and making them available to others. If there are legitimate  
3708 reasons why this cannot be accomplished, this can be discussed on a case-by-case  
3709 basis by the investigators, the funding agency, and the SPRINT SC.  
3710

### 3711 **13.11 Publication Policy**

3712

3713 The purpose of the policy is to encourage and facilitate the presentation and publication  
3714 of SPRINT Study background, rationale, design, and analyses; ensure appropriate use  
3715 of the SPRINT data, timely completion of manuscripts and presentations, equitable  
3716 access to authorship, and adherence to established principles of authorship; and  
3717 coordinate the reporting of trial results. The policy applies to all investigators analyzing,  
3718 presenting, and publishing data from main SPRINT, SPRINT-MIND, SPRINT-Senior  
3719 (hereafter collectively called “SPRINT”) and ancillary studies, except for those using the  
3720 NHLBI Data Repository data (see <https://biolincc.nhlbi.nih.gov/home/>).  
3721

3722 There are several principles underlying this policy:  
3723

- 3724 1. Research questions and hypotheses to be addressed using SPRINT Study data  
3725 should be formulated *a priori* and clearly stated in a manuscript proposal to reduce  
3726 the likelihood that study results are attributable to type I error.  
3727
- 3728 2. Publication of scientific findings from the SPRINT Study should proceed in a timely  
3729 fashion once relevant analyses are complete.  
3730
- 3731 3. The publications arising from the SPRINT Study should avoid overlap and conflicting  
3732 representation of SPRINT Study findings. Overlaps are, however, acceptable for  
3733 review articles.  
3734
- 3735 4. Recognition through authorship will be distributed among the SPRINT investigators  
3736 so that:
  - 3737 i) all SPRINT investigators and team members have equitable opportunity to  
3738 lead and co-author SPRINT publications and, if appropriate, publications from  
3739 ancillary studies;

- 3740           ii) all Ancillary Study investigators have the opportunity to lead and be co-  
3741           authors on publications resulting from their ancillary studies.  
3742  
3743       5. The SPRINT Study should promote the career development of trainees and junior  
3744       faculty by providing them the opportunity to lead and be recognized as co-authors of  
3745       SPRINT publications, as appropriate.  
3746  
3747       6. Standards for authorship on SPRINT publications will adhere to the Uniform  
3748       Requirements for Manuscripts Submitted to Biomedical Journals of the International  
3749       Committee of Medical Journal Editors (NEJM 1997;336:309-315) and those  
3750       established by the destination journals.  
3751  
3752       7. The concept, in the form of a proposal, for all manuscripts must be approved by the  
3753       P&P Subcommittee prior to preparation.  
3754

3755       There are three categories of manuscripts and anticipated authorship:

- 3756           i) Main results developed based on core SPRINT data and study  
3757           aims/hypotheses (which will bear the corporate authorship, “The SPRINT  
3758           Research Group”). The design and main baseline papers will also be  
3759           corporate authored.  
3760  
3761           ii) Manuscripts developed and authored by investigators using data that are not  
3762           considered to be main SPRINT results.  
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3765           iii) Ancillary study results led by investigators bringing external funding or  
3766           resources into SPRINT for a specific project.  
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3768           (1) Unless specific justifications and alternative arrangements are made, all  
3769           SPRINT analyses will be performed by the Coordinating Center (CC), with  
3770           specialized expertise external to the Coordinating Center as needed at  
3771           the Coordinating Center’s discretion. Ancillary study budgets should  
3772           include funds allocated to the CC for that purpose.  
3773  
3774           (2) Ancillary study manuscripts are subject to similar review and tracking  
3775           procedures as other SPRINT manuscripts.  
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3777       During the operational phase of the trial, manuscripts proposing to use data other than  
3778       baseline data will be reviewed closely to ensure that the SPRINT study objectives are  
3779       not compromised. In general, the following will not be allowed:

- 3780           (1) Publication of follow-up data according to randomized group  
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3782           (2) Longitudinal analyses of outcomes pre-specified in the main protocol  
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3785       All such proposals will be considered on a case-by-case basis.

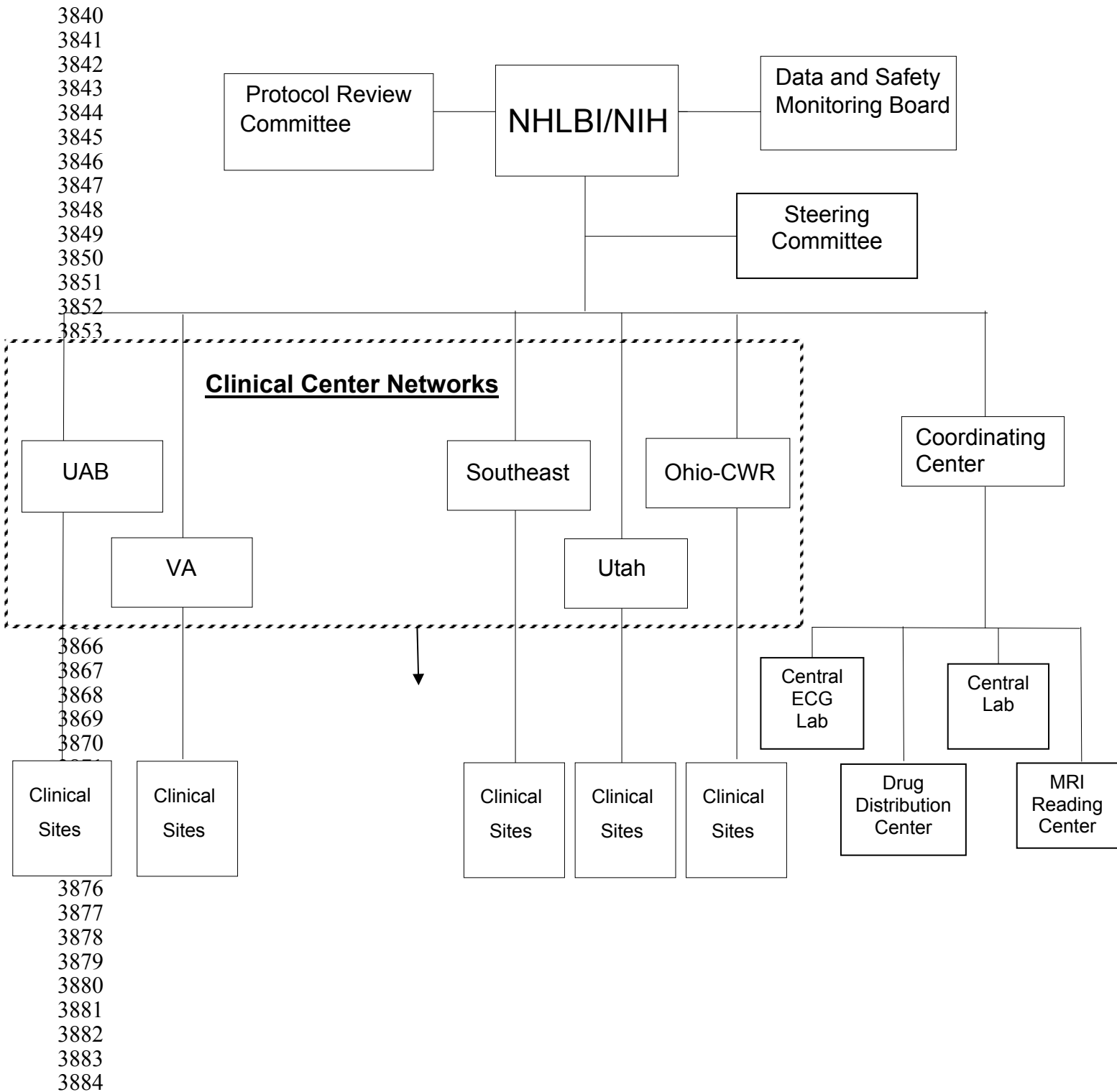
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3787       The final responsibility for review and approval of manuscript proposals, including  
3788       composition of writing committees, readiness for submission, and abstracts and material

3789 for presentations at meetings and conferences, rests with the Steering Committee. The  
3790 P&P Subcommittee will oversee and facilitate these processes, assisted by a  
3791 Publications Coordinator based at the Coordinating Center.

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**Figure 13.1: SPRINT Organizational Chart**



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4550	<b>APPENDIX 1: Abbreviations Used</b>		4604	
4551			4605	
4552	AAA:	Abdominal Aortic Aneurysm	4606	DASH: Dietary Approaches to Stop Hypertension
4553	AASK:	African American Study of Kidney Disease and Hypertension	4607	
4554			4608	DBP: Diastolic Blood Pressure
4555			4609	DDC: Drug Distribution Center
4556	ABI:	Ankle Brachial Index	4610	DHP: Dihydropyridine
4557	ACC:	American College of Cardiology	4611	DQ: Dementia Questionnaire
4558			4612	DSC: Digit Symbol Coding test
4559	ACCORD:	Action to Control Cardiovascular Risk in Diabetes	4613	DSMB: Data Safety Monitoring Board
4560			4614	
4561			4615	DSM-IV: Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition
4562	ACE:	Angiotensin Converting Enzyme	4616	
4563			4617	
4564	ACR:	Albumin to Creatinine Ratio	4618	DSST: Digit Symbol Substitution Test
4565	ACS:	Acute Coronary Syndrome	4619	
4566	AD:	Alzheimer's Disease	4620	DST: Digit Span Test
4567	AE:	Adverse Event	4621	ECG: Electrocardiogram
4568	AHA:	American Heart Association	4622	ED: Erectile Dysfunction
4569	ALLHAT:	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial	4623	eGFR: Estimated Glomerular Filtration Rate
4570			4624	
4571			4625	EnaC Inhibitor: Epithelial Sodium Channel Inhibitor
4572	ARB:	Angiotensin Receptor Blocker	4626	
4573	ARIC:	Atherosclerosis Risk in Communities	4627	EPICARE: Epidemiological Cardiology Research Center
4574			4628	
4575	AS:	Ancillary Science	4629	EQ-5D: EuroQol 5 Dimensional Descriptive System
4576	ASCOT:	Anglo-Scandinavian Cardiac Outcomes Trial	4630	
4577			4631	ESRD: End Stage Renal Disease
4578	BID:	Twice Daily	4632	EUROPA: European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease
4579	BNT:	Boston Naming Test	4633	
4580	BP:	Blood Pressure	4634	
4581	BPH:	Benign Prostatic Hyperplasia	4635	
4582	CABG:	Coronary Artery Bypass Grafting	4636	FAQ: Functional Activities Questionnaire
4583			4637	
4584	CAD:	Coronary Artery Disease	4638	FDA: Food and Drug Administration
4585	CAMELOT:	Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis Trial	4639	
4586			4640	FES-I: Falls Self-Efficacy Scale International
4587			4641	
4588	CC:	Coordinating Center	4642	FRS: Framingham Risk Score
4589	CCB:	Calcium Channel Blockers	4643	FSFI: Female Sexual Function Assessment
4590	CCN:	Clinical Center Network	4644	
4591	CE:	Carotid Endarterectomy	4645	GCP: Good Clinical Practice
4592	CEA:	Cost-Effectiveness Analysis	4646	GEMS: Gingko Evaluation of Memory Study
4593	CHD:	Coronary Heart Disease	4647	
4594	CHF:	Chronic Heart Failure	4648	GFR: Glomerular Filtration Rate
4595	CHS:	Cardiovascular Health Study	4649	GXT: Graded Exercise Test
4596	CKD:	Chronic Kidney Disease	4650	HDFFP: Hypertension Detection and Follow-up Program
4597	Co-PI:	Co-Principal Investigator	4651	
4598	CPT:	Current Procedural Terminology	4652	HF: Heart Failure
4599			4653	HIPAA: Health Information Portability and Accountability Act
4600	CUA:	Cost-Utility Analysis	4654	
4601	CV:	Cardiovascular	4655	HOPE: Hospital Outcomes Project for the Elderly
4602	CVD:	Cardiovascular Disease	4656	
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4657	HOT:	Hypertension Optimal	4710	NINDS:	National Institute of
4658		Treatment trial	4711		Neurological Disorders and
4659	HRQL:	Health Related Quality of Life	4712		Stroke
4660	HTN:	Hypertension	4713	OH:	Orthostatic Hypotension
4661	HVLT:	Hopkins Verbal Learning Test	4714	P&P:	Publications and
4662	HYVET:	Hypertension in the Very	4715		Presentations
4663		Elderly Trial	4716	PAD:	Peripheral Artery Disease
4664	HYVET COG:	Hypertension in the Very	4717	PCI:	Percutaneous Coronary
4665		Elderly Trial – cognitive	4718		Intervention
4666		function assessment	4719	PEACE:	Prevention of Events with
4667	ICER:	Incremental Cost-Effectiveness	4720		Angiotensin Coverting
4668		Ratio	4721		Enzyme
4669	ID:	Identification	4722	PHI:	Private Health Information
4670	IIEF:	International Index of Erectile	4723	PHQ:	Patient Health Questionnaire
4671		Function	4724	PI:	Principal Investigator
4672	IRB:	Institutional Review Board	4725	PKD:	Polycystic Kidney Disease
4673	ISH:	Isolated Systolic Hypertension	4726	PROGRESS:	Perindopril Protection
4674	JNC:	Joint National Committee	4727		Against Recurrent Stroke
4675	JNC-7:	The Seventh Report of the	4728		Study
4676		Joint National Committee on	4729	PTS:	Participant Tracking System
4677		Prevention, Detection,	4730	QALY:	Quality Adjusted Life Years
4678		Evaluation, and Treatment of	4731	QC:	Quality Control
4679		High Blood Pressure	4732	RAAS:	Renin-angiotensin-
4680	LMT:	Logical Memory Test	4733		aldosteribe system
4681	LVH:	Left Ventricular Hypertrophy	4734	RAS:	Renin Angiotensin System
4682	MAP:	Mean Arterial Pressure	4735	SAE:	Serious Adverse Event
4683	MAR:	Missing-at-Random Analyses	4736	SBP:	Systolic Blood Pressure
4684	MCI:	Mild Cognitive Impairment	4737	SCOPE:	Study on Cognition and
4685	MDRD:	Modification of Diet in Renal	4738		Prognosis in the Elderly
4686		Disease Study	4739	SHEP:	Systolic Hypertension in the
4687	MI:	Myocardial Infarction	4740		Elderly Program
4688	MIND:	Memory and Cognition In	4741	SPRINT:	Systolic Blood Pressure
4689		Decreased Hypertension	4742		Intervention Trial
4690	MoCA:	Montreal Cognitive	4743	SPRINT MIND:	SPRINT Memory and
4691		Assessment	4744		Cognition In Decreased
4692	MOP:	Manual of Procedures	4745		Hypertension
4693	MPQC:	Measurement Procedures and	4746	SSL:	Secure Socket Layer
4694		Quality Control	4747	SVID:	Small Vessel Ischemic
4695	mRey-O:	Modified Rey-Osterrieth	4748		Disease
4696		Complex Figure	4749	Syst-Eur:	Systolic Hypertension in
4697	MRI:	Magnetic Resonance Imaging	4750		Europe Trial
4698	NEJM:	New England Journal of	4751	TICS-M:	Modified Telephone Interview
4699		Medicine	4752		for Cognitive Status
4700	NKF:	National Kidney Foundation	4753	TMT:	Trail Making Test
4701	NHANES:	National Health and Nutrition	4754	UKPDS:	United Kingdom Prospective
4702		Examination Survey	4755		Diabetes Study
4703	NHLBI:	National Heart, Lung, and	4756	WHI:	Women’s Health Initiative
4704		Blood Institute	4757	WHIMS:	Women’s Health Initiative
4705	NIA:	National Institute on Aging	4758		Memory Study
4706	NIDDK:	National Institute of Diabetes	4759	WWW:	World Wide Web
4707		and Digestive and Kidney	4760		
4708		Diseases			
4709	NIH:	National Institutes of Health			

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## **APPENDIX 2: Computational Details and Sensitivity Analyses for the CVD outcome**

Power computations were developed using event rates observed in ALLHAT. The ALLHAT Coordinating Center provided us with summary data across all three arms allowing us to calculate event rates using different combinations of baseline characteristics. Event rates were calculated using a composite outcome including fatal CVD, non-MI acute coronary syndrome, and nonfatal MI, stroke, and heart failure. For ALLHAT participants without diabetes, the annual event rate was 4.39 %/yr. (Note: ALLHAT used hospitalized angina rather than non-MI acute coronary syndrome.)

This rate of 4.39 %/yr provides a starting point for the estimation of event rates we will expect in SPRINT. Several factors can be considered which suggest that these rates should be either increased or decreased. Factors arguing for an increased event rate include (1) SPRINT will have an older cohort of participants than did ALLHAT, (2) SPRINT will use the Framingham risk score of  $\geq 15\%$  10-year CVD risk as an inclusion criterion, and (3) inclusion of a substantial group of participants with Stage 3 or Stage 4 CKD. Factors that are expected to reduce the event rate include (1) the temporal trend towards a reduction in CVD event rates in the U.S. and (2) a more rigorous definition of non-MI acute coronary syndrome that will be used in SPRINT. It is difficult to precisely estimate the impact that these five factors will have on the SPRINT event rate.

In ALLHAT, event rates increased substantially with age. The event rate for participants 70 to <75 years old was 5.19 %/yr; for participants  $\geq 75$  years old, the event rate was 6.99 %/yr. In ALLHAT 17.7% of the participants were 70 to <75 years old, while 18.5% were  $\geq 75$  years old. We expect that participants in these age categories will represent a greater fraction of the SPRINT cohort. Approximately 50% (4625 participants) are expected to be at least 70 years old, while 35.1% (3250 participants) are expected to be  $\geq 75$  years old. This will likely yield a higher event rate in SPRINT, compared to ALLHAT.

The event rate in ALLHAT among participants with 10-year Framingham risk  $\geq 15\%$  at baseline was 4.67 %/yr. Our including people with  $\geq 15\%$  10-year risk will help to ensure a higher event rate.

We expect that 4300 SPRINT participants will have eGFR 20 to <60 mL/min/1.73m<sup>2</sup> with equal numbers above and below 45 mL/min/1.73m<sup>2</sup>. In ALLHAT, the event rate was 5.89 %/yr for those with eGFR 45 to <60 mL/min/1.73m<sup>2</sup>. Among those <45, the event rate was 8.24 %/yr. In ALLHAT, 18.6% had eGFR <60 mL/min/1.73m<sup>2</sup> as compared with the expected 46.7% in SPRINT. Increasing the numbers of participants with CKD in SPRINT will help increase the event rates.

We compared ALLHAT participants with diabetes to participants in the ACCORD BP trial (all of whom have diabetes) using outcome variables that are as similar as possible. In ALLHAT the event rate was 5.90 %/yr. The corresponding event rate in ACCORD was 3.43 %/yr. The reduction in event rates between ALLHAT and ACCORD could be due to a temporal trend (ALLHAT was 1994—1999, ACCORD was 2001—2009), because ALLHAT participants were older (mean 67 years) than ACCORD (mean 62.2 years), or for other reasons.

Exactly how we should use the ALLHAT data to estimate the event rates for SPRINT is unclear. Since the rates in ACCORD were approximately half of those in ALLHAT, *for the purposes of*

4812 power we will assume that the SPRINT rates will also be half of the ALLHAT rates. This  
 4813 assumption balances the possibility of a further temporal trend in event rate reduction with the  
 4814 fact that participants recruited for SPRINT will be older, have lower kidney function, and have  
 4815 greater Framingham CVD risk scores than those recruited in either ALLHAT or ACCORD. We  
 4816 expect that this may be slightly conservative. Thus, we assume that the event rate in SPRINT  
 4817 will be approximately 2.2 %/yr for the composite outcome including non-fatal MI, non-fatal  
 4818 stroke, cardiovascular death, hospitalized heart failure, and non-MI acute coronary syndrome.  
 4819

4820 We have assumed a 2-year uniform accrual period, 3 years 10 months minimum follow-up  
 4821 (assumes that closeout visits occur uniformly over a 4-month period), and a 2 sided significance  
 4822 level of 0.05. The effect size for the primary outcome is assumed to be 20% in the entire  
 4823 sample and the CKD subsample, and 25% in the Senior subsample. Loss to follow-up and  
 4824 events are assumed to follow an exponential model. We expect that the annual rate of loss to  
 4825 follow-up will be approximately 2% but have included rates up to 3% to be conservative.  
 4826 Calculations made using two methods (Lachin and Foulkes, 1986;Lakatos, 1988) were similar.  
 4827 Power for the primary outcome for a range of event rates and annual loss rates is presented in  
 4828 Table 1 for the assumed effect size of 20%.  
 4829

Table 1. Power for the primary outcome in entire sample of 9250 participants for a 20% effect (Hazard Ratio of 0.8).					
Annual Loss Rate (%/yr)	Annual Standard Arm Event Rate (%/yr)				
	1.8	2.0	2.2	2.4	2.6
1	82.9	86.5	89.4	91.7	93.5
2	82.0	85.7	88.7	91.0	93.0
3	81.1	84.8	87.9	90.4	92.4

4830 In ALLHAT the event rates were 5.89 %/yr and 8.24 %/yr for people whose eGFR was 45 to  
 4831 <60 or <45 mL/min/1.73m<sup>2</sup>. We will assume that the event rate for the primary outcome in  
 4832 SPRINT will be 4 %/yr among participants with eGFR <60 mL/min/1.73m<sup>2</sup>. Power for the  
 4833 primary outcome among SPRINT participants with CKD for a range of event rates and annual  
 4834 loss rates is presented in Table 2 for the assumed effect size of 20%.  
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Table 2. Power for the primary outcome in CKD subsample (eGFR < 60 mL/min/1.73m <sup>2</sup> ) of 4300 participants for a 20% effect (Hazard Ratio of 0.8).					
Annual Loss Rate (%/yr)	Annual Standard Arm Event Rate (%/yr)				
	3.5	3.75	4.0	4.25	4.5
1	77.9	80.5	82.7	84.8	86.6
2	76.9	79.5	81.9	83.9	85.8
3	75.9	78.6	80.9	83.1	85.0

4837 In ALLHAT, the event rate was 6.99 %/yr among participants at least 75 years old. Applying the  
 4838 same halving as was done above for the entire sample, we will assume that the event rate in  
 4839 SPRINT will be 3.5 %/year among participants ≥75 years old. Power for the primary outcome  
 4840 among SPRINT Senior for a range of event rates and annual loss rates is presented in Table 3  
 4841 for the assumed effect size of 25%.  
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Table 3. Power for the primary outcome in Senior subsample ( $\geq 75$ years old) of 3250 participants for a 25% effect (Hazard Ratio of 0.75).					
Annual Loss Rate (%/yr)	Annual Standard Arm Event Rate (%/yr)				
	3.0	3.25	3.5	3.75	4.0
1	79.9	82.8	85.3	87.5	89.4
2	79.0	81.9	84.5	86.7	88.6
3	78.0	81.0	83.6	85.9	87.9

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**APPENDIX 3: Computational Details and Sensitivity Analyses for the MIND outcomes**

*Dementia.* The primary outcome for SPRINT MIND is all-cause dementia. Table 1 summarizes dementia rates from HYVET-COG (Peters, 2008), the Ginkgo Evaluation of Memory Study (GEMS) (DeKosky, 2008), the Cardiovascular Health Study (CHS) (Fitzpatrick, 2004) and the Women’s Health Initiative Memory Study (WHIMS) (Shumaker, 2004). In HYVET-COG, there was a 14% non-significant decline in dementia. Overall annual dementia rate varied from 0.13% to 3.86%. The Women’s Health Initiative Memory Study (WHIMS) (Shumaker, 2004) recruited women 65 and older with a mean age of 69 in two hormone replacement therapy interventions. Both trials were stopped early because of unexpected increased health risks in women receiving the hormone therapy. Of the studies reported here, WHIMS may be the least similar to SPRINT.

Table 1. Annual rates of dementia from previous studies.

Age	eGFR	HYVET-COG	GEMS	CHS	WHIMS
<75				1.29	0.08
75+	<45		3.09 (3.86) <sup>1</sup>	4.55	0.81
	45-59.9		4.87 (6.39)		
	60-89.9		3.02 (3.20)		
	90+		2.87 (3.70)		
80+		3.50			
ALL		3.50	3.09 (3.86)	2.62	0.13

<sup>1</sup> With prior CVD

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Based on these data and the expected number of SPRINT participants 75 or older, and with CKD or MCI at baseline, we expect the annual event rate in SPRINT to be 3.1%-3.5%. In meta-analyses performed by the HYVET investigators, three of the four trials had hazard ratios ranging from 0.84 to 0.90. A reasonable goal for SPRINT MIND is to detect a relative difference between arms expressed by a hazard ratio of 0.5 to 0.8 for dementia. Using a 2-sided proportional hazards regression test of time until first incidence of dementia, we can expect at least 79% power for annual dementia rates of 3.1%-3.5% and an effect size of 0.15 and 96% power for annual dementia rates of 3.2%-3.5% and an effect size of 0.20.

*Cognitive Function.* SPRINT will include 2,800 participants receiving the extended cognitive battery at baseline, and years 2 and 4 post randomization. We obtained the standard deviations for several of the tests included in the SPRINT battery to determine detectable differences. The standard deviation for the Digit Symbol Substitution Test is from actual ACCORD MIND data 40 months post randomization adjusted for baseline and stratifying factors. Actual means were not available so we used the ACCORD MIND assumptions in their sample size calculations based on CHS data. GEMS provided us with standard deviations and means for Trails A & B, Digit Span and the Boston Naming Test. Table 2 shows that we can detect mean differences for



4883 each test of 5.1% or less between the two SPRINT treatment groups at year 4, with 90%  
 4884 statistical power, assuming 3%/year loss to follow-up. The statistical power will even be  
 4885 increased when combining the scores for these tests in each domain.  
 4886

4887 Table 2. Means, standard deviations and power for cognitive tests.

Cognitive Test	Mean (STD)	Power	
		80%	90%
Effect Size		0.114	0.132
Digit Symbol Substitution Test	39.5 <sup>1</sup> (7.9) <sup>2</sup>	0.90 (2.4%)	1.05 (2.7%)
Trails A <sup>3</sup>	47.5 (18.1)	2.07 (4.4%)	2.40 (5.1%)
Trails B <sup>3</sup>	124.4 (40.6)	4.65 (3.7%)	5.38 (4.3%)
Digit Span <sup>3</sup>	13.9 (2.6)	0.30 (2.2%)	0.34 (2.4%)
Boston Naming Test <sup>3</sup>	26.2 (2.6)	0.30 (1.1%)	0.34 (1.3%)

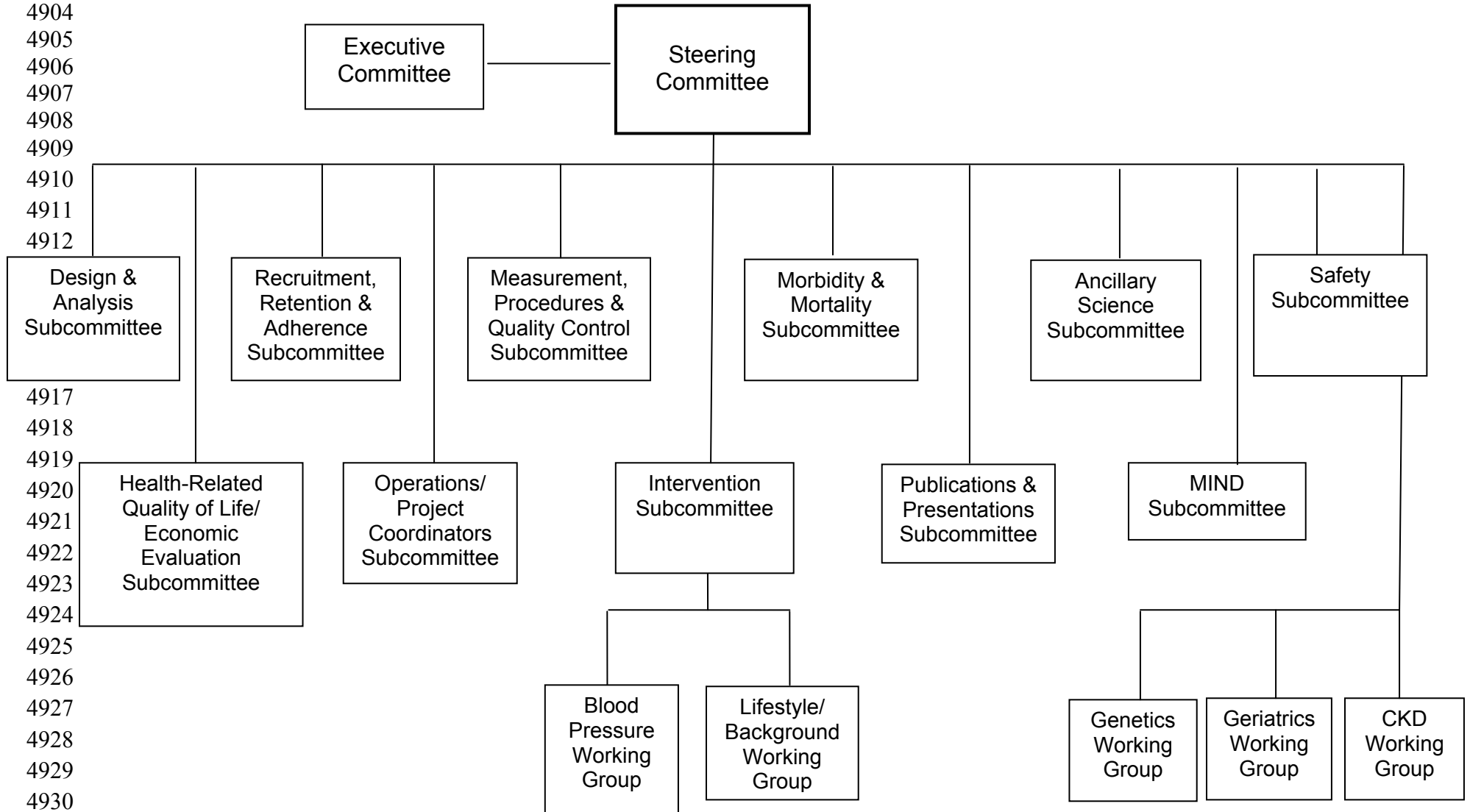
4888 <sup>1</sup> From ACCORD MIND assumptions in sample size calculations based on CHS data

4889 <sup>2</sup> From actual ACCORD MIND data at 40 months post randomization

4890 <sup>3</sup> From GEMS at 48 months post randomization

4891  
 4892 *MRI.* We will perform MRI in 640 of SPRINT MIND participants. The standard deviations for  
 4893 total abnormal tissue volume and total brain volume from the ACCORDMIND study 40 months  
 4894 post randomization adjusted for baseline and cranial size are 2.77 cm<sup>3</sup> and 16.45 cm<sup>3</sup>. The final  
 4895 analysis of the MRI data collected in SPRINT MIND will compare the mean total abnormal  
 4896 tissue and mean total brain volumes between the groups, controlling for the baseline MRI value  
 4897 and cranial side. With 640 participants (320 participants in each treatment group), after  
 4898 accounting for a 3%/yr loss to-follow-up, and assuming a 0.05 two-sided significance level, we  
 4899 will be able to detect group differences in total abnormal vascular lesion volumes of 0.65 cm<sup>3</sup>  
 4900 and 0.76 cm<sup>3</sup>, and in total brain volumes of 3.9 cm<sup>3</sup> and 4.5 cm<sup>3</sup> over 4 years, with 80% and  
 4901 90% power, respectively.

4902 **APPENDIX 4: SPRINT Organizational Chart**  
 4903 **Committees and Subcommittees**



4932 **APPENDIX 5**

4933 **SPRINT Charges & Membership of Committees & Subcommittees**

4934

4935 Below are the charges of the committees and subcommittees to the Steering Committee. Each  
4936 subcommittee will assume additional responsibilities as deemed necessary by the SPRINT  
4937 Steering or Executive Committee.

4938

4939 SPRINT Steering Committee (SC) provides the overall leadership for the trial and establishes  
4940 the scientific and administrative policies. It will be led by the independent Study Chair, who is  
4941 also the Chair of the Steering Committee. The Vice Chair of the Steering Committee, who may  
4942 be a CCN or a clinical site PI, will be a permanent SC member and also will be the Vice Chair of  
4943 the Executive Committee. Other members of the Steering Committee include the Principal  
4944 Investigators (PIs) from the Clinical Center Networks (CCNs), NIH representatives (from the  
4945 NHLBI, NIDDK, NIA and NINDS), Coordinating Center (CC) staff, and other subcommittee  
4946 chairs as needed. This committee oversees the overall conduct of the trial throughout all  
4947 phases. The SC provides the leadership for the trial design, the protocol, Manual of Procedures  
4948 (MOP), and study forms, all of which require final SC approval. This committee oversees  
4949 recruitment, intervention, follow-up, and data collection practices and procedures to identify and  
4950 correct deficiencies. They will consider adopting changes in the study protocol or procedures as  
4951 necessary during the course of the SPRINT trial. Voting members will include the CCN PIs, the  
4952 CC PI, and the NIH Project Office (which includes the joint interests of the four NIH funding  
4953 institutions – NHLBI, NIDDK, NIA, and NINDS). The Steering Committee Chair will vote in the  
4954 case of a tie.

4955

4956 SPRINT Executive Committee (EC) is the operational arm of the Steering Committee and  
4957 makes decisions on behalf of the Steering Committee (SC) on day-to-day operational issues  
4958 that require immediate action. This committee will consist of the Study Chair, SC Vice Chair,  
4959 CC PI, NIH Project Office staff, Drug Distribution Center director, Project Coordinators/  
4960 Operations Subcommittee Chair, one rotating CCN PI, CC Program Coordinator, CC staff, and  
4961 other subcommittee chairs as needed. This committee will meet by conference call every other  
4962 week or as needed. The Executive Committee will develop the SC meeting agenda and  
4963 timeline for completion of tasks. Important study issues, protocol changes, and other items will  
4964 be discussed by the EC prior to presentation to the full SC for review and approval.

4965

4966 SPRINT Conflict of Interest Committee: This committee reviews potential conflict of interest  
4967 issues. The NIH Project Office, Steering Committee Chair, and CC Chair comprise this  
4968 committee, which has the overall responsibility for the trial's ethical oversight policy and  
4969 procedures.

4970

4971 **Subcommittees:**

4972

4973 In general, each subcommittee will have representative(s) from the Coordinating Center, from  
4974 each CCN, and from the NIH Project Office. Together the Steering Committee and each  
4975 subcommittee should determine the expertise required for the given subcommittee. For  
4976 example, the Intervention Subcommittee should include experts in hypertension, nephrology,  
4977 neurology, and geriatrics. In addition, the various subcommittees may form working groups to  
4978 address major issues within their charge (e.g., Genetics Working Group, CKD Working Group).  
4979 The subcommittee and the CC will decide what periodic reports the subcommittee needs to  
4980 perform its charge.

4981

4982 Ancillary Science Subcommittee (AS): This subcommittee is charged with developing  
4983 procedures for review and approval by the SC for ancillary studies and substudies. The AS will  
4984 review proposals for feasibility and compatibility with the main study protocol and aims. Specific  
4985 evaluation criteria include participant and study burden. There will be substantial statistical  
4986 support to the development of ancillary studies through this committee. It is suggested to have  
4987 all 5 CCNs represented on this committee.  
4988

4989 Design and Analysis Subcommittee (D&A): This subcommittee will review the currently  
4990 proposed and alternative designs for the trial, including the analysis plan, the impact on sample  
4991 size, statistical power and patient recruitment, as well as sequential monitoring, subgroup  
4992 monitoring, and adjustments for multiple comparisons. This subcommittee will work closely with  
4993 the Intervention Subcommittee and the Recruitment, Retention and Adherence Subcommittee  
4994 on the development of analysis plans for recruitment and adherence monitoring.  
4995

4996 Economic Evaluation/Health Related Quality of Life Subcommittee: This subcommittee will  
4997 develop the protocol for the economic evaluation of the SPRINT interventions and the protocol  
4998 for assessing the impact of these interventions on health-related quality of life. This will allow the  
4999 study to estimate overall costs, cost effectiveness and cost utility for the SPRINT interventions.  
5000 This subcommittee also will train the CCNs regarding collection of human resource costs,  
5001 quality of life data and plans for analyses of these data, and provide interim reports to the SC.  
5002

5003 Intervention Subcommittee: This subcommittee is charged with generating all of the blood  
5004 pressure (BP) intervention plans for the trial, including materials, medications, titration  
5005 algorithms and schedules, visit schedules, adherence strategies to the medications protocol and  
5006 all BP monitoring including reports. This committee will consider issues concerning the SPRINT  
5007 intervention on high-risk groups such as the elderly, CKD patients, and groups at highest risk for  
5008 heart failure. The Intervention Subcommittee will provide guidelines on the standard of care for  
5009 both treatment arms, as well as lifestyle choices, such as exercise, limiting salt, smoking  
5010 cessation and medical management strategies. An additional charge for this subcommittee is to  
5011 monitor the safety of the interventions and to make recommendations regarding any possible  
5012 changes to the protocol and MOP for patient safety reasons. This subcommittee will likely have  
5013 working groups such as a Medications Working Group and Lifestyle/Background Working Group  
5014 to provide plans for standard of care.  
5015

5016 Measurements, Procedures and Quality Control Subcommittee (MPQC): This subcommittee is  
5017 charged with developing and implementing the quality assurance and control mechanisms for  
5018 the study. The MPQC Subcommittee will work with the Central Lab in developing procedures  
5019 for biological sample collection, processing, shipping, storage, and analysis – as well as a blood  
5020 drawing and aliquoting scheme to reflect the storage of specimens for future use. This  
5021 subcommittee will work with the ECG Reading Center to develop quality control procedures to  
5022 ensure high quality data. Initially, this subcommittee will establish criteria under which the study  
5023 will be expected to perform. This subcommittee will require communication with the CC in  
5024 overseeing the quality assurance procedures, such as the standardized collection of data at all  
5025 CCNs and clinical sites. They will monitor all quality control as well, and will work closely with  
5026 the CC in producing quality control reports. The CC will provide the necessary information to  
5027 the subcommittee, such as data entry quality control and missing data reports. If quality control  
5028 is an issue based on site visits reports, the MPQC Subcommittee will be alerted and requested  
5029 to provide recommendations to the Steering Committee, as all site visit reports are reviewed by  
5030 this subcommittee to determine if any action is warranted. This subcommittee will develop site  
5031 visit protocols and CCN “report cards.” Clear definitions of the boundaries for the CC and CCN  
5032 monitoring responsibilities will be drafted.

5033 Mortality and Morbidity Subcommittee (M&M): This subcommittee will initially be responsible for  
5034 developing event definitions and classifications and coding guidelines, then subsequent  
5035 adjudication procedures. The M&M Subcommittee will be responsible for establishing the  
5036 guidelines for cause of death; diagnosis of MI, stroke, and heart failure; and evaluating other  
5037 cardiac events and the trial endpoints. They will jointly monitor all classifications of events,  
5038 oversee the data collection of events, including forms design, and will serve as the liaison  
5039 between the CCNs, clinical sites and the CC for the events ascertainment data collection. This  
5040 subcommittee will require expertise in neurology, nephrology, and cardiology. The M&M  
5041 subcommittee will function as an adjudication subcommittee once the trial gets underway.  
5042

5043 Presentations and Publications Subcommittee (P&P): This subcommittee is charged with  
5044 developing procedures for review and approval by the SC, and will review all publications,  
5045 presentations, abstracts, and slides of the SPRINT trial and substudy results. The CC and this  
5046 subcommittee will develop procedures to track the development of publications and  
5047 presentations (P&P), as well as strategies for stimulating P&P productivity. Additionally, the CC  
5048 will provide analyses for publications and presentations, and the study web site will provide P&P  
5049 tracking reports and study presentations and publications.  
5050

5051 Project Coordinators/Operations Subcommittee: This subcommittee facilitates communication  
5052 and collaboration among clinical sites, the CCNs, and the Coordinating Center. It focuses on  
5053 recruitment, retention, adherence, and implementation issues, identifying problems early to  
5054 promptly implement solutions. In addition, the Operations subcommittee addresses specific  
5055 CCN and clinic requests for tracking and scheduling reports, missed appointment reports, data  
5056 entry updates or issues requiring attention, and coordinates certification updates and numerous  
5057 data management issues. This subcommittee will include representatives from the CC (e.g.,  
5058 project managers) and from the MRI and ECG Reading Centers, Central Laboratory and Drug  
5059 Distribution Center. The CCN Coordinator Chair of this committee can be rotated annually as  
5060 needed and will serve as a member of the Executive Committee.  
5061

5062 Recruitment, Retention and Adherence Subcommittee: This subcommittee will be charged with  
5063 developing the eligibility criteria, recruitment, retention and adherence to the protocol and  
5064 procedural strategies. Generation of the SPRINT template informed consent and HIPAA  
5065 authorizations will be done in conjunction with other subcommittees, such as PC/Operations,  
5066 MPQC, and Intervention subcommittees. Recruitment and retention strategies will be  
5067 developed with special emphasis on issues pertinent to recruitment of ethnic groups, women,  
5068 those with CKD and the elderly. The subcommittee will develop educational and recruitment  
5069 materials and will provide the culture-specific central training in recruitment strategies. During  
5070 the follow-up phase, this subcommittee will monitor all aspects of retention, including visit and  
5071 procedure adherence, and will provide input on necessary retention tracking reports. This  
5072 subcommittee will collaborate with the Intervention subcommittee to develop strategies and  
5073 tactics to enhance and monitor intervention adherence. This subcommittee also will assist the  
5074 Coordinating Center in monitoring recruitment at the CCNs and clinical sites in order to identify  
5075 recruitment difficulties.  
5076

5077 Safety Subcommittee: This subcommittee is charged with responding to concerns about the  
5078 safety of study participants that may arise during the course of the SPRINT study. Concerns  
5079 related to safety of study intervention, study medication or study procedures will be reviewed by  
5080 the committee and either by addressed directly or referred to another subcommittee/ working  
5081 group as appropriate. Additionally, this committee will help triage issues raised by clinic IRBs  
5082 that are related to safety and review any clinical practice issues that may arise. They may also  
5083 review summaries of study data related to the overall safety of study participation, but not

5084 reported by treatment assignment, and develop related reports for or respond to concerns from  
5085 the Data and Safety Monitoring Board. The Safety Committee will include the Safety Officer,  
5086 representatives from the Intervention Committee, the CKD working group, the MIND Committee,  
5087 the Geriatrics working group, and may be joined by other experts for specific issues as needed.  
5088

5089 SPRINT-MIND Subcommittee: This subcommittee will provide the scientific leadership for  
5090 SPRINT-MIND and will include cognitive functioning, dementia and MRI representatives from  
5091 the CC, CCNs, the NIH (NINDS, NHLBI, NIDDK, and NIA) and the site PI of the MRI Reading  
5092 Center. This subcommittee will monitor all 3 areas of MIND: dementia, cognitive functioning and  
5093 MRI scans, as well as selection of the data collection instruments and training of clinical staff.  
5094 The SPRINT-MIND Subcommittee will serve as the adjudicators for cognition outcomes as  
5095 members of the M&M subcommittee. This subcommittee may utilize working groups as needed,  
5096 such as MIND Operations or MIND Geriatrics Working Group.  
5097

5098 **APPENDIX 6**

5099 **Participating Sites**

5100

5101 **SPRINT CLINICAL CENTER NETWORKS**

5102

5103 **Ohio/Case Western Reserve CCN**

5104 Network Hub: Case Western Reserve (PI: Jackson Wright, MD)

5105 Bolwell Suite 2200

5106 11100 Euclid Ave

5107 Cleveland, OH 44106-6053

5108

5109 **Southeast CCN**

5110 Network Hub: Wake Forest University Health Sciences (PI: Michael Rocco, MD)

5111 Wake Forest University Health Sciences

5112 Section on Nephrology

5113 Medical Center Blvd

5114 Winston-Salem, NC 27157-1063

5115

5116 **University of Alabama – Birmingham CCN**

5117 Network Hub: University of Alabama, Birmingham (PI: Suzanne Oparil, MD)

5118 703 19<sup>th</sup> St South

5119 ZRB 1034

5120 Birmingham, AL 35294

5121

5122 **Utah CCN**

5123 Network Hub: University of Utah (PI: Alfred Cheung, MD)

5124 Dialysis Program/University of Utah

5125 Ezekiel R & Edna Dunke Bldg

5126 84 N Medical Dr East, Room 201

5127 Salt Lake City, UT 84108

5128

5129 **Veteran's Administration (VA) CCN**

5130 Network Hub: Memphis, TN (PI: Bill Cushman, MD)

5131 Hypertension and Lipids Research

5132 111Q/1030 Jefferson Ave

5133 Memphis, TN 38104-2193

5134

5135 **SPRINT COORDINATING CENTER**

5136 (PI: David M Reboussin, PhD)

5137 Wake Forest University Health Sciences

5138 Division of Public Health Sciences

5139 Department of Biostatistical Sciences

5140 Medical Center Blvd, Wells Fargo-21

5141 Winston-Salem, NC 27157

5142

5143

5144

5145

5146 **SPRINT CENTRAL RESOURCE CENTERS**

5147 Drug Distribution Center (PI: Mike Sather, Rob Ringer)

5148 VA Cooperative Studies Program  
5149 Clinical Research Pharmacy Coordinating Center  
5150 2401 Centre Ave SE  
5151 Albuquerque, NM 87106  
5152  
5153 ECG Reading Center (PI: Elsayed Soliman)  
5154 EPICARE  
5155 Wake Forest University Health Sciences  
5156 Medical Center Blvd, Wells Fargo-13  
5157 Winston-Salem, NC 27157  
5158  
5159 MRI Reading Center (PI: R. Nick Bryan)  
5160 Brain Magnetic Resonance Imaging Reading Center  
5161 University of Pennsylvania  
5162 Section of Biomedical Image Analysis  
5163 3400 Spruce St  
5164 Philadelphia, PA 19104  
5165  
5166 Central Lab (PI: Tony Killeen)  
5167 University of Minnesota Collaborative Studies Clinical Lab  
5168 420 Delaware St SE  
5169 Minneapolis, MN 55455  
5170  
5171  
5172 **FEDERAL SPONSORS**  
5173  
5174 National Institutes of Health (NIH)  
5175 National Heart, Lung, and Blood Institute (NHLBI)  
5176 National Institute of Neurological Disorders and Stroke (NINDS)  
5177 National Institute on Aging (NIA)  
5178 National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)  
5179