

## Section 2. Inclusion and Exclusion Criteria

### 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  $\geq$  130 mm Hg on 2 visits within 3 months prior to the randomization visit in order to be eligible for the trial.
  4. Risk (one or more of the following):
    - a) Presence of clinical\* or subclinical\*\* cardiovascular disease other than stroke
    - b) CKD, defined as eGFR 20 – 59 ml/min/1.73m<sup>2</sup> based on the 4-variable Modification of Diet in Renal Disease (MDRD) equation and latest lab value, within the past 6 months. (If the serum creatinine is unstable within the last 6 months, enrollment into SPRINT could be delayed until the serum creatinine has been stabilized and the eGFR is still within the allowed range.)
    - c) Framingham Risk Score for 10-year CVD risk  $\geq$  15% based on laboratory work done within the past 12 months for lipids
    - d) Age  $\geq$  75 years.
- \* Clinical CVD (other than stroke)
- a) Previous myocardial infarction (MI), percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), carotid endarterectomy (CE), carotid stenting
  - b) Peripheral artery disease (PAD) with revascularization
  - c) Acute coronary syndrome with or without resting ECG change, ECG changes on a graded exercise test (GXT), or positive cardiac imaging study
  - d) At least a 50% diameter stenosis of a coronary, carotid, or lower extremity artery
  - e) Abdominal aortic aneurysm (AAA)  $\geq$  5 cm with or without repair
- \*\* Subclinical CVD
- a) Coronary artery calcium score  $\geq$  400 Agatston units within the past 2 years.
  - b) Ankle brachial index (ABI)  $\leq$  0.90 within the past 2 years.
  - c) Left ventricular hypertrophy (LVH) by ECG (based on computer reading), echocardiogram report, or other cardiac imaging procedure report within the past 2 years.

### b) Exclusion Criteria

1. An indication for a specific BP lowering medication (e.g., beta-blocker following acute myocardial infarction) that the person is not taking and the person has not been documented to be intolerant of the medication class. (If a screenee has a non-hypertension indication for a BP-lowering medication (e.g., beta-blocker post-MI, renin angiotensin system (RAS) blocker for CVD prevention, or alpha blocker for benign prostatic hypertrophy (BPH)), the screenee should be on the appropriate dose of such medication before assessing whether he/she meets the SPRINT inclusion criteria. If the investigator believes that a potential participant has such an indication but is not receiving appropriate treatment, he/she should encourage the potential participant's primary care provider to consider placing the patient on the appropriate therapy prior to proceeding with the screening process.)
2. Known secondary cause of hypertension that causes concern regarding safety of the protocol.
3. One minute standing SBP < 110 mm Hg. Not applicable if unable to stand due to wheelchair use.
4. Proteinuria in the following ranges (based on a measurement within the past 6 months)
  - (a) 24 hour urinary protein excretion  $\geq 1$  g/day, or
  - (b) If measurement (a) is not available, then 24 hour urinary albumin excretion  $\geq 600$  mg/day, or
  - (c) If measurements (a) or (b) are not available, then spot urine protein/creatinine ratio  $\geq 1$  g/g creatinine, or
  - (d) If measurements (a), (b), or (c) are not available, then spot urine albumin/creatinine ratio  $\geq 600$  mg/g creatinine, or
  - (e) If measurements (a), (b), (c), or (d) are not available, then urine dipstick  $\geq 2+$  protein
5. Arm circumference too large or small to allow accurate blood pressure measurement with available devices
6. Diabetes mellitus. Participants taking medications for diabetes at any time in the last 12 months are excluded. Participants are also excluded if there is documentation of: FPG at or above 126 mg/dL, A1C  $\geq 6.5$  percent, a two-hour value in an OGTT (2-h PG) at or above 200 mg/dL or a random plasma glucose concentration  $\geq 200$  mg/dL. The diagnosis of diabetes must be confirmed on a subsequent day by repeat measurement, repeating the same test for confirmation. However, if two different tests (eg, FPG and A1C) are available and are concordant for the diagnosis of diabetes, additional testing is not needed. If two different tests are discordant, the test that is diagnostic of diabetes should be repeated to confirm the diagnosis.
7. History of stroke (not CE or stenting)
8. Diagnosis of polycystic kidney disease
9. Glomerulonephritis treated with or likely to be treated with immunosuppressive therapy
10. eGFR < 20 ml/min /1.73m<sup>2</sup> or end-stage renal disease (ESRD)
11. Cardiovascular event or procedure (as defined above as clinical CVD for study entry) or hospitalization for unstable angina within last 3 months
12. Symptomatic heart failure within the past 6 months or left ventricular ejection fraction (by any method) < 35%
13. A medical condition likely to limit survival to less than 3 years, or a cancer diagnosed and treated within the past two years that, in the judgment of clinical study staff, would compromise a participant's ability to comply with the protocol and complete the trial. Exceptions to the exclusion for diagnosed cancer would include, for example, non-melanoma skin cancer, early-stage prostate cancer, localized breast cancer.
14. Any factors judged by the clinic team to be likely to limit adherence to interventions. For example,

- (a) Active alcohol or substance abuse within the last 12 months
  - (b) Plans to move outside the clinic catchment area in the next 2 years without the ability to transfer to another SPRINT site, or plans to be out of the study area for more than 3 months in the year following enrollment.
  - (c) Significant history of poor compliance with medications or attendance at clinic visits
  - (d) Significant concerns about participation in the study from spouse, significant other, or family members
  - (e) Lack of support from primary health care provider
  - (f) Residence too far from the study clinic site such that transportation is a barrier including persons who require transportation assistance provided by the SPRINT clinic funds for screening or randomization visits
  - (g) Residence in a nursing home. Persons residing in an assisted living or retirement community are eligible if they meet the other criteria.
  - (h) Clinical diagnosis of dementia, treatment with medications for dementia, or in the judgment of the clinician cognitively unable to follow the protocol
  - (i) Other medical, psychiatric, or behavioral factors that in the judgment of the Principal Investigator may interfere with study participation or the ability to follow the intervention protocol
15. Failure to obtain informed consent from participant
  16. Currently participating in another clinical trial (intervention study). Note: Patient must wait until the completion of his/her activities or the completion of the other trial before being screened for SPRINT.
  17. Living in the same household as an already randomized SPRINT participant
  18. Any organ transplant
  19. Unintentional weight loss > 10% in last 6 months
  20. Pregnancy, currently trying to become pregnant, or of child-bearing potential and not using birth control

### Section 3. Definition of Study Outcomes

The primary outcome measure for SPRINT will be major CVD events, defined as the composite endpoint comprised of the first occurrence of a myocardial infarction (MI), non-MI acute coronary syndrome (non-MI ACS), stroke, heart failure (HF), or death attributable to cardiovascular disease (CVD).

**MI DEFINITION:** Generally defined as death of part of the myocardium due to an occlusion of a coronary artery from any cause, including spasm, embolus, thrombus or rupture of a plaque. The definition includes MI that occurred during surgery/procedure and MI aborted by thrombolytic therapy or procedure, as well as due to demand ischemia (1,2). MI will be ascertained both from adjudication of hospital records for clinical events and also from the finding of new significant Q waves from the standardized interpretation of the study visit-obtained ECG (silent or unrecognized MI).

**Table 1. SPRINT Classification of MI (1)**

	Positive biomarker findings							
	Cardiac symptoms or signs present				Cardiac symptoms or signs absent			
ECG Findings**	Diagnostic <sup>+</sup>	Equivocal <sup>+</sup>	Missing <sup>+</sup>	Normal <sup>+</sup>	Diagnostic	Equivocal	Missing	Normal
Evolving diagnostic	Def	Def	Def	Def	Def	Def	Def	Def
Positive	Def	Prob	Prob	No	Def	Prob	Poss	No
Nonspecific	Def	Poss	No	No	Def*	Poss	No	No
Negative for evolving ischemia	Def	Poss	No	No	Def*	No	No	No

\*In absence of diagnostic troponin, downgrade to possible.

\*\*Def = Definite indicates definite MI; Prob = Probable, probable MI; Poss = Possible, possible MI; and No, no MI. Classification of case is at highest level allowed by combinations of 3 characteristics (cardiac signs and symptoms, ECG findings, biomarkers).

#### **Biomarker criteria** (1-3):

<sup>+</sup>Diagnostic = At least 1 positive biomarker (at least 1 value at least twice the upper limit of normal) in an adequate set of biomarkers showing a rising or falling pattern in the setting of clinical cardiac ischemia and the absence of noncardiac causes of biomarker elevation. An adequate set is at least 2 measurements of the same marker taken at least 6 hours apart. Equivocal = Present but not diagnostic. Missing = Not available for the time of the event. Normal = Normal. Troponin will take precedence over CK-MB, and CK-MB will take precedence over CK if both are available. Enzymes following CPR are non-interpretable; cardiac ablation, pacing and defibrillator shocks are causes of myocardial injury not related to ischemia (2).

The 2003 AHA Scientific Statement (1) and the Universal Definition (4) define positive biomarkers as “the 99<sup>th</sup> percentile of the distribution in healthy populations, or the lowest level at which a 10% coefficient of variation can be demonstrated for that laboratory” assay.

#### **Cardiac symptoms and signs**

**Cardiac symptoms.** Cardiac symptoms include symptoms suggestive of an ischemic cause and include (but are not limited to) acute chest, neck, jaw, arm pain, or epigastric pain, or discomfort or pressure without apparent non-cardiac cause. More general, atypical symptoms, such as fatigue, nausea, vomiting, diaphoresis, faintness, and back pain, should not be used.

**Cardiac signs.** These can be used for determination of MI, and include acute HF or cardiogenic shock in the absence of non-CHD causes. These can be especially helpful when the patient is unable to provide a history on presentation.

### **ECG Criteria**

**Evolving:** evolution of a new diagnostic Q wave; OR equivocal Q wave and evolution of major ST depression or elevation or T wave inversion

**Positive:** evolving ST elevation alone; OR evolving equivocal Q wave and evolving ST or T wave depression or inversion; OR new left bundle branch block

**Nonspecific:** evolving minor Q wave alone or evolving non-ST elevation non-Q wave pattern (including evolving ST depression alone)

**Negative for evolving ischemia:** Normal ECG(s), or findings other than those described in the above categories

### **Aborted MI**

Aborted MI is defined as positive signs/symptoms and positive ECG, but enzymes remain below the upper limit of normal and the participant received emergent treatment for cardiac ischemia (thrombolytic or revascularization).

### **Procedure Related MI**

**For PTCA,** levels of CK- MB or troponin above 3 times the ULN within 48 hours of the procedure will be characterized as positive (4). Similarly for **CABG**, levels of troponin or MB above 5 times the ULN within 48 hours of the procedure will be categorized as positive. Total CK will not be used for post-CABG enzymes (4).

A revascularization procedure performed for the treatment of acute ischemia (e.g., angioplasty following the presentation of acute coronary syndrome/MI) should *not* be considered as procedure-related (1); however, the occurrence of a second MI with the revascularization procedure will be recorded. The procedure-related MI category is intended to identify MIs that occurred only after the procedure, and were not already in evolution.

**NON-MI ACS Definition:** Defined as hospitalization for evaluation and treatment of an accelerating or new symptom pattern consistent with coronary artery insufficiency without meeting the definition of MI, but requiring evaluation to rule-out MI on clinical presentation. Non-MI ACS will also require objective findings of coronary ischemia.

Non MI ACS will be defined by one of 3 clinical presentations:

1. New cardiac symptoms and positive ECG findings with normal biomarkers not meeting criteria for MI, or
2. A changing symptom pattern and positive ECG findings with normal biomarkers not meeting criteria for MI, or
3. New or changing cardiac symptoms with normal biomarkers and ECGs but with further confirmatory evidence of CAD (eg 70% cross-sectional obstruction in at least one major coronary artery or branch on angiography at or near the time of admission, treatment with revascularization; prior documented CAD – prior CABG, PTCA, etc- positive exercise test

at or near the time of admission, perfusion defect documented on stress scintigraphy or echo). Stress testing within approximately one month prior to admission or occurring during admission will be accepted as related to a particular hospital admission for possible non-MI ACS.

Non-MI ACS requires an **unscheduled admission** that must have begun **within 24 hours** of the most recent symptoms. Escalation of pharmacotherapy such as intravenous nitrates or increasing dosages of  $\beta$ -blockers, should be considered supportive but not diagnostic of non-MI ACS.

**STROKE DEFINITION:** Stroke is generally defined as neurological deficit of cerebrovascular cause that persists beyond 24 hours or is interrupted by death within 24 hours (5). Stroke will be classified as brain infarction, subarachnoid hemorrhage, intraparenchymal hemorrhage, other hemorrhage, other type, or unknown type.

Brain infarction (ischemic stroke) is defined as a new lesion detected by computed tomography or magnetic resonance imaging or, in the absence of a new lesion on available imaging, clinical findings consistent with the occurrence of stroke that lasted for more than 24 hours (6). Brain infarctions will be further sub-typed large artery atherosclerosis, cardio-aortic embolism, small artery occlusion, other causes, and undetermined causes (7, 8).

Strokes following invasive cardiovascular interventions will also be classified as such. Strokes after cardiovascular invasive interventions will be defined as those associated with the intervention within 7 days. Stroke post non-cardiovascular surgery will be defined as occurring within 7 days of non-cardiovascular surgery or other invasive procedure

Case definitions are based on the World Health Organization definition of stroke, and the updated definition of TIA that is imaging, rather than time, based (9).

Stroke is defined as a rapid onset of focal neurological symptoms, headache, or meningismus

**AND**

Deficit not due to closed head injury, intracranial neoplasm, coma due to metabolic disorders or disorders of fluid or electrolyte balance, peripheral neuropathy, or central nervous system infections (encephalitis or meningitis – subacute bacterial endocarditis would be counted as stroke), or other non-vascular cause

**AND**

Lesion on brain imaging consistent with symptoms

**OR**

Evidence of central or branch retinal artery occlusion

**OR**

Death within 24 hours without resolution of symptoms

**Subarachnoid Hemorrhage (SAH)**

Sudden onset of severe headache, meningismus, depressed consciousness or coma, or focal neurological symptoms

**AND**

Bloody spinal fluid within a few minutes or hours of onset

**OR**

Xanthochromic spinal fluid after 12 hours

**OR**

CT or MRI findings indicating a blood clot in the Sylvian fissure, between the frontal lobes, in the basal cisterns, or in a ventricle (without associated intraparenchymal hematoma)

**AND**

SAH is spontaneous and did not occur as a result of trauma or other process.

**OR**

Angiographic identification of a saccular aneurysm as a source of bleeding WITH bloody or xanthochromic spinal fluid

**OR**

Surgical or autopsy evidence of saccular aneurysm in the appropriate clinical setting or with evidence of SAH

Intraparenchymal Hemorrhage (IPH): A focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma (10).

Sudden onset of focal neurological symptoms or coma

**AND**

An area of increased density indicative of IPH identified by CT or MRI

**OR**

Demonstration of an IPH at autopsy or, surgery

**OR**

Cerebral angiographic, surgical, or autopsy evidence of a vascular mass without evidence of aneurysm or arteriovenous malformation

Other Hemorrhage (OH): subdural and epidural hematomas are *not* considered strokes (10).  
Insufficient data to classify SAH or IPH

**AND**

Imaging shows blood in the parenchyma, subarachnoid space, ventricle, or any combination of the above

**OR**

Bloody (nontraumatic) or xanthochromic spinal fluid

**OR**

Surgical or autopsy evidence of blood in the parenchyma, subarachnoid space, ventricle, or any combination

Brain Infarction (INF): An episode of neurological dysfunction caused by focal cerebral or retinal infarction.

Not meeting criteria for SAH, IPH, or OH

**AND**

Sudden onset of focal neurological symptoms or coma leading to death or lasting > 24 hours

**AND**

Consistent imaging findings (i.e. no SAH, IPH), or clinically consistent lesion compatible with infarction or hemorrhagic infarction

**OR**

Autopsy or surgical evidence of a nonhemorrhagic (ischemic) infarct of the brain (cerebral thrombosis or cerebral embolism)

### **Brain Infarct Subtypes**

#### **Large artery atherosclerosis**

##### **Evident**

Either occlusive, or stenotic vascular disease judged to be due to atherosclerosis in the clinically-relevant extracranial or intracranial arteries

[ $\geq 50\%$  diameter reduction *or*  $< 50\%$  diameter reduction with plaque ulceration or thrombosis, or plaque with  $< 50\%$  diameter reduction that is seated at the site of the origin of the penetrating artery supplying the region of an acute lacunar infarct]

##### **AND**

The absence of acute infarction in vascular territories other than the stenotic or occluded artery

##### **Probable**

Prior history of one or more transient monocular blindness (TMB), TIA, or stroke in the territory of index artery affected by atherosclerosis within the month preceding the index stroke

##### ***OR***

Evidence of thrombosis, near-occlusive stenosis, or non-chronic complete occlusion judged to be due to atherosclerosis in the clinically-relevant extracranial or intracranial arteries (except for the vertebral arteries)

##### ***OR***

The presence of ipsilateral and unilateral acute internal watershed infarctions or multiple, temporally separate, infarctions exclusively within the territory of the affected artery

##### **Possible**

The presence of an atherosclerotic plaque protruding into the lumen and causing mild stenosis ( $< 50\%$ ) in the absence of any detectable plaque ulceration or thrombosis in a clinically-relevant extracranial or intracranial artery and prior history of two or more TMB, TIA, or stroke from the territory of index artery affected by atherosclerosis, at least one event within the last month

#### **Cardio-aortic embolism**

##### **Evident**

The presence of a high-risk cardiac source of cerebral embolism (left atrial or ventricular thrombus, atrial fibrillation, sick sinus, atrial flutter, recent MI, rheumatic aortic or mitral disease, prosthetic valve, chronic MI plus EF $< 28\%$ , symptomatic CHF with EF $< 30\%$ , dilated cardio myopathy, non-bacterial endocarditis, SBE, papillary elastoma, myxoma)

##### **Probable**

Evidence of systemic embolism

##### ***OR***



The presence of multiple temporally related acute infarctions within both right and left anterior, or both anterior and posterior, circulations in the absence of non-embolic occlusion or near occlusive stenosis of all relevant vessels

**AND**

Other diseases that can cause multifocal ischemic brain injury such as vasculitides, vasculopathies, and haemostatic or hemodynamic disturbances must not be present

**Possible**

The presence of a cardiac condition with low or uncertain primary risk of cerebral embolism (mitral calcification, PFO, PFO/ASA, left ventricular aneurysm without thrombus, left atrial stroke, aortic athero, other arrhythmias)

**Small artery occlusion**

**Evident**

Imaging evidence of a single and clinically relevant acute infarction less than 20 mm in greatest diameter within the territory of basal or brainstem penetrating arteries

**AND**

Absence of any focal other pathology in the parent artery at the site of the origin of the penetrating artery (focal atheroma, parent vessel dissection, vasculitis, vasospasm, etc.)

**Probable**

The presence of stereotypic lacunar transient ischemic attacks within the last week

**OR**

The presence of a lacunar syndrome (pure motor, pure sensory, sensorimotor, ataxic hemiparesis, dysarthria-clumsy hand)

**Possible**

Presenting with a classical lacunar syndrome in the absence of imaging that is sensitive enough to detect small infarctions

**Other uncommon etiology**

**Evident**

The presence of a specific disease process that involves clinically-appropriate brain arteries

**Probable**

A specific disease process that has occurred in clear and close temporal or spatial relationship to the onset of brain infarction such as arterial dissection, cardiac or arterial surgery, and cardiovascular interventions

**Possible**

Evidence for an evident other cause in the absence of complete diagnostic investigation for mechanisms listed above

**Undertermined Cause**

**Unknown**

Cryptogenic embolism:

Angiographic evidence of abrupt cut-off consistent with a blood clot within otherwise angiographically normal appearing intracranial arteries

**OR**

Imaging evidence of complete recanalization of previously occluded artery

**OR**

Presence of multiple acute infarctions that have occurred closely-related in time without detectable abnormality in the relevant vessels

Other cryptogenic

Those not fulfilling the criteria for cryptogenic embolism

Incomplete evaluation

The absence of diagnostic tests that, up to the examiner's judgment, their presence would have been essential to uncover the underlying etiology

### **Unclassified**

The presence of more than one possible or evident mechanism where there is either probable evidence for each, or no probable evidence to be able to establish a single cause

Other Stroke (OS)

Not meeting criteria for SAH, IPH, OH, or INF (e.g. cerebral sinus thrombosis with IPH, dissection)

Unknown Stroke Type (UNK)

Insufficient data to classify as SAH, IPH, OH, INF, or OS (e.g. no data available)

**HEART FAILURE DEFINITION:** Defined as hospitalization, or emergency department visit requiring treatment with infusion therapy, for a clinical syndrome that presents with multiple signs and symptoms consistent with cardiac decompensation/inadequate cardiac pump function. Adjudication will use the ARIC study adjudication system (11). The SPRINT HF outcome will include definite or possible acute decompensation, including HF with preserved left ventricular ejection fraction as well as HF with reduced ejection fraction. HF cases may also be adjudicated as chronic stable HF but this is not considered a SPRINT outcome. No identification of HF should rely on a single piece of data such as the presence of dyspnea or of edema, a low ejection fraction, or an increased brain natriuretic peptide (BNP) value.

In order to consider an ED only visit as either definite or possible decompensated HF, the medical record must contain specific, clear, and unequivocal documentation that IV therapy was administered, regardless of the strength of the history, physical exam, and evaluations. Intravenous therapy must consist of a loop diuretic or an inotropic agent.

Right sided heart failure due to lung disease with no component of left sided heart failure is very unlikely to respond to SPRINT interventions. Right sided heart failure will not be considered a SPRINT outcome and will not be adjudicated as such.

Evidence of signs and symptoms that may indicate new or decompensated heart failure include evidence of increasing or new onset shortness of breath, increasing or new onset edema, increasing or new onset paroxysmal nocturnal dyspnea, increasing or new onset orthopnea,

increasing or new onset hypoxia; and evidence in the doctor's notes that the reason for this hospitalization, or ED visit, was heart failure. Avoid assigning a classification of definite or possible decompensated heart failure if the symptoms include edema without respiratory symptoms unless there is other compelling evidence of heart failure.

**Definite decompensated heart failure**, i.e., decompensation clearly present based on available data (satisfies criteria for decompensation).

**Possible decompensated heart failure**, i.e., decompensation possibly but not definitively present. A typical case of "possible" rather than "definite" would be due to the presence of co-morbidity that could account for the acute symptoms (COPD exacerbation, for example). In general, prefer "possible" whenever the evidence for decompensation (symptoms, signs, imaging) is subtle.

**Chronic stable heart failure** i.e., no decompensation but participant has chronic heart failure. "Stable" also denotes "compensated" heart failure (not necessarily asymptomatic, but that patient's chronic HF symptoms are controlled with therapy and there is no evidence of augmentation of therapy for worsening HF during the hospitalization.) Note: This includes participants with asymptomatic LV dysfunction (evidence of LV systolic dysfunction, i.e.,  $EF \leq 50\%$ , and no heart failure symptoms).

HF unlikely should generally be chosen if the patient is on chronic dialysis and symptoms are due to inadequate dialysis with no evidence of cardiac systolic or diastolic dysfunction or history of clinical heart failure. Patients with ESRD on dialysis may be classified as "possible decompensated HF" (or possibly "definite") when there is appropriate supporting evidence for heart failure and the primary cause of the exacerbation is unlikely due to inadequate or missed dialysis. Patients with ESRD and low LVEF who had inadequate dialysis as the cause of volume overload should be classified as HF unlikely.

**DEATH DEFINITIONS:** Causes of death include:

- **Underlying cause** of death is the disease or injury that initiated the event resulting in death
- **Contributory causes** of death include other conditions that contributed to the fatal process, but were not the underlying cause.
- **Immediate cause** of death is the final disease or condition resulting in death and if different from the underlying cause is not recorded.

In SPRINT the adjudicator will only record the main underlying cause of death.

### **SPRINT-related outcomes**

Definite CVD death events will be defined based on temporal relationship to a documented event (e.g., hospitalization for MI or for stroke), or postmortem findings of an acute CVD event. Probable coronary heart disease (CHD) death (1) will be defined based on autopsy findings consistent with chronic CHD, prior history of CHD or documented symptoms consistent with CHD prior to death, and the absence of another likely cause of death. Possible fatal CHD will be adjudicated based on death certificate information consistent with an underlying CHD cause and no evidence of a non-coronary cause.

Case classification of fatal CHD events for hospitalized patients (1):

Definite fatal MI

1. Death within 28 days of hospital admission in definite MI cases

2. Postmortem findings consistent with MI within 28 days

Probable fatal MI

1. Death within 28 days of hospital admission in cases defined in probable MI cases
2. Death within 6 hours of hospital admission with cardiac symptoms and/or signs.

Other confirmatory data (biomarkers, ECG) are absent or not diagnostic.

Possible fatal coronary event

1. Death within 28 days of hospital admission for possible MI, unstable angina or chronic stable angina
2. Postmortem findings show old infarct and/or  $\geq 50\%$  atherosclerotic narrowing of coronary arteries.

Case classification of out-of-hospital CHD death (1):

Definite fatal MI:

1. Documented definite or probable MI in the previous 28 days and
2. No evidence of a noncoronary cause of death, or
3. Autopsy evidence of recent coronary occlusion or MI <28 days old.

Definite fatal CHD:

1. A history of CHD and/or documented cardiac pain within 72 hours before death and
2. No evidence of a noncoronary cause of death, or
3. Autopsy evidence of chronic CHD, including coronary atherosclerosis and myocardial scarring.

Possible fatal CHD:

An ICD code (underlying cause) for CHD death (ICD 9\*: 410 to 414, 427.5, 429.2; ICD 10: I20 to I25 and I46) and no evidence of a noncoronary cause of death

Stroke: Death occurring or following cases meeting criteria for stroke.

Sudden cardiac death: death occurring within 1 hour of onset of symptoms, and suggestive of an arrhythmic event

\* Sudden cardiac death must occur within one hour of symptom onset of a cardiac etiology and witnessed loss of consciousness with no other lethal non-atherosclerotic cause. Do not select this choice for unwitnessed deaths.

CHF: Death due to clinical, radiologic, or postmortem evidence of CHF without clinical or postmortem evidence of an acute ischemic event (cardiogenic shock included)

Not cardiac but other cardiovascular (e.g. ruptured aortic aneurysm): this category is intended for classifications of cardiovascular diseases for which hypertension is a risk factor that are not included in other causes listed above. It includes death due to ruptured thoracic or abdominal aortic aneurysm, and intestinal ischemia due to rupture of atherosclerotic plaque or due to cardioembolic phenomena (e.g. atrial fibrillation). This classification can be selected for participants who die of complications of attempted surgical repair of an aneurysm that did not rupture. Do not select this criterion for pulmonary embolism. Do not select this choice for an acute traumatic rupture of an otherwise normal artery (no aneurysm found), or for complications of arteritis due to known inflammatory conditions. Prefer definitive evidence, such as CT scan showing a ruptured aortic aneurysm, of the presence of this condition.

Death from kidney disease: In the absence of other causes, death within 30 days of withdrawal from chronic dialysis, death from hyperkalemia, death in ESRD patient in whom dialysis not initiated.

It is important to rule out other causes of death. For example, if a patient has terminal cancer and decides to withdraw from dialysis, the cause of death should be classified as death from malignancy, rather than uremia.

Death related to dialysis: Death related to the dialysis procedure, not the result of impaired kidney function. Examples are intradialytic hemolysis or air embolism as a result of extracorporeal circuit malfunctioning, and sepsis as a result of infected hemodialysis catheters or peritoneal dialysis catheters.

Adjudicators will also use specific information available to them in the case to record whether deaths occurred in relationship to an invasive procedure. There are two categories of intervention related events:

Death after invasive cardiovascular intervention. Death within 28 days of cardiovascular surgery or within 7 days of cardiac cath, arrhythmia ablation, angioplasty, atherectomy, stent deployment, or other invasive coronary vascular intervention. Cardiovascular procedures include PAD procedures, including amputation for ischemia.

**Non-SPRINT related outcomes:** Require documentation of a specific underlying cause in medical records and/or autopsy. Categories include:

Other cardiac/non-ischemic (eg, myocarditis)

Cancer

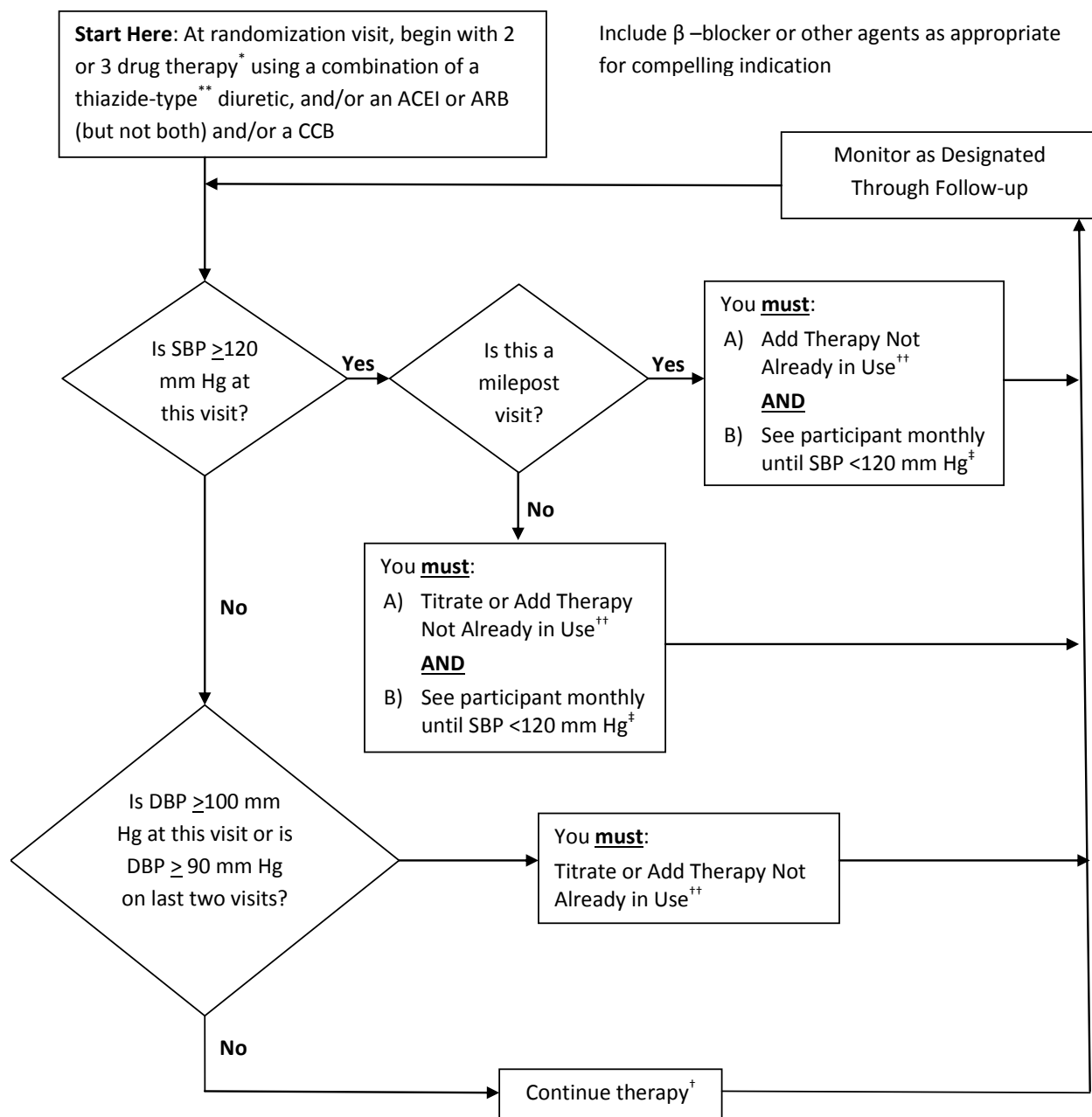
Accident/injury/homicide

Other non-cardiac, non-stroke death: requires evidence of a non-coronary and non-stroke cause of death exclusive of categories above. Deaths included in this category include those due to specific pulmonary diseases (eg, COPD), infection (eg, sepsis, pneumonia), and gastrointestinal disease (eg, gastrointestinal hemorrhage, pancreatitis).

Unclassifiable: insufficient information to determine whether the death was a CHD death (at any certainty level) or a non-cardiac death. Includes other ill-defined and unknown cause of morbidity and mortality and no evidence of a non-coronary cause

**END STAGE RENAL DISEASE DEFINITION:** One of the clinical outcomes of interest in SPRINT is the initiation of renal replacement therapy for ESRD. In order to meet criteria for SPRINT, a participant must have been on chronic dialysis for at least 3 months and/or received a renal transplant. The adjudicator will examine medical records to confirm whether the participant was currently on dialysis (any modality(ies)), and had received RRT for at least 3 months continuously, and if so, enter the date of initiation of dialysis (date of first treatment). The adjudicator will also confirm whether the participant received a transplant, and if so, the date of the transplant. Acute dialysis for management of acute kidney injury will not be considered a SPRINT ESRD outcome.

Figure S1. 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.

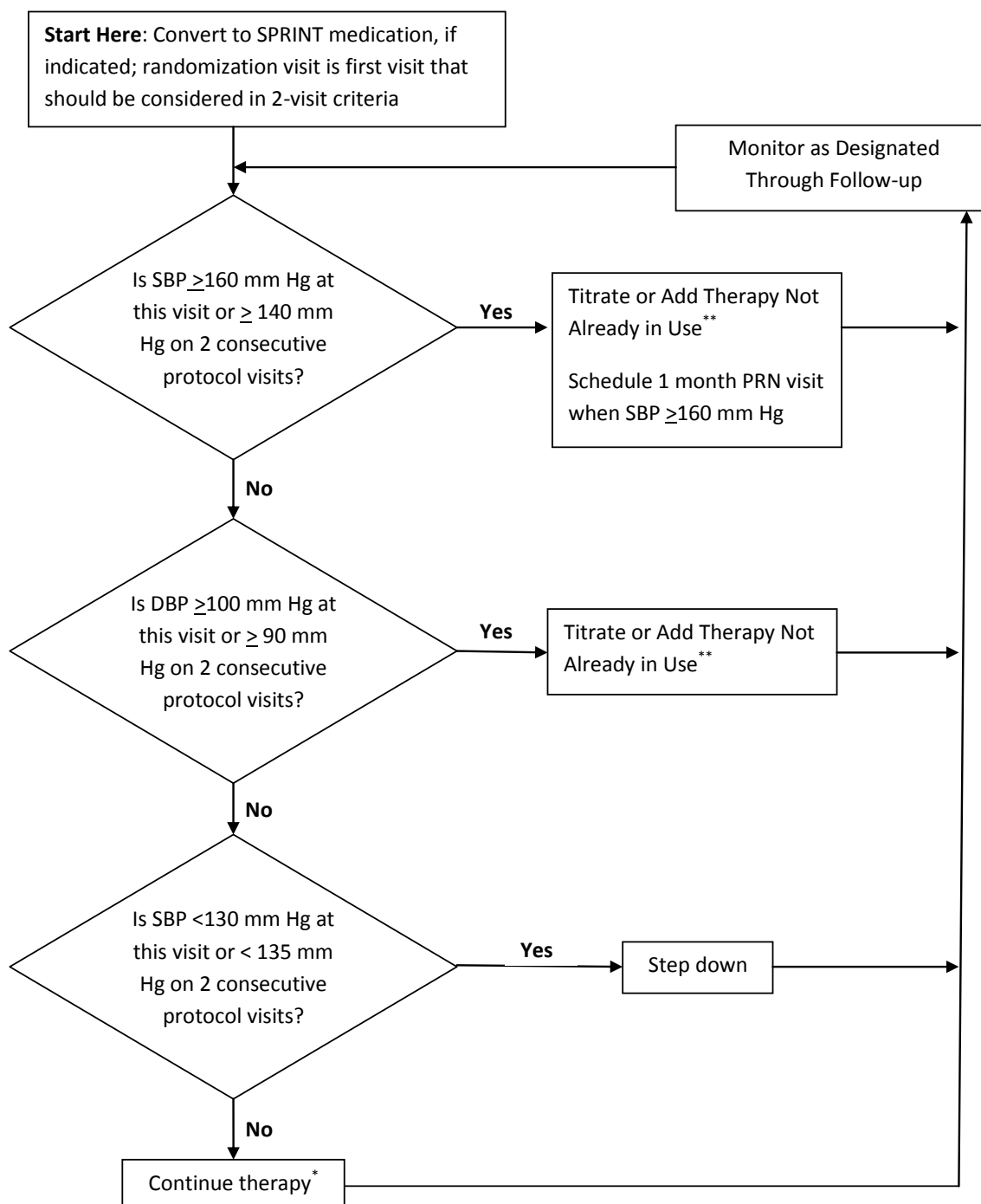
\*\* May use loop diuretic for participants with advanced CKD

† 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

Figure S2. 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