NINDS Common Data Element (CDE) Project

Stroke Version 2.0 Public Review

Stroke Types and Subtypes Subgroup Materials

Guidance Document:

- Stroke Types and Subtypes

Case Report Form:

- Stroke Types and Subtypes

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Stroke Types and Subtypes Subgroup: Recommendations

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1. **Definition of Clinical Stroke (Symptomatic)**

- **"Time-based" Definition**: Stroke is a sudden focal neurological deficit of presumed vascular origin lasting ≥ 24 hours (or fatal within 24 hours).

  Source: ~~American Stroke Association (ASA) Scientific Statement~~ Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, Elkind MS, George MG, Hamdan AD, Higashida RT, Hoh BL, Janis LS, Kase CS, Kleindorfer DO, Lee JM, Moseley ME, Peterson ED, Turan TN, Valderrama AL, Vinters HV; American Heart Association Stroke Council, Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular and Stroke Nursing; Council on Epidemiology and Prevention; Council on Peripheral Vascular Disease; Council on Nutrition, Physical Activity and Metabolism. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013;44(7):2064-2089.

- **"Tissue-based" Definition:** Symptomatic stroke is a sudden focal neurological deficit, of any duration, due to focal brain, spinal cord, or retinal infarction or hemorrhage. Infarction or hemorrhage may be demonstrated either:
  - directly by imaging/laboratory/pathologic examination in patients with symptom duration less than 24 hours, or
  - inferred by symptoms lasting ≥ 24 hours (or fatal within 24 hours) that cannot be attributed to another cause.

  Source: ~~Easton JD, Saver JL, Albers GW, et al.~~ Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, Elkind MS, George MG, Hamdan AD, Higashida RT, Hoh BL, Janis LS, Kase CS, Kleindorfer DO, Lee JM, Moseley ME, Peterson ED, Turan TN, Valderrama AL, Vinters HV; American Heart Association Stroke Council, Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular and Stroke Nursing; Council on Epidemiology and Prevention; Council on Peripheral Vascular Disease; Council on Nutrition, Physical Activity and Metabolism. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013;44(7):2064-2089. Available at: Stroke Related Journals.

2. **Definitions for Clinical Stroke Types (Symptomatic)**

2.1. Ischemic Stroke

- **Time-based Definition:** Ischemic stroke is a sudden focal neurologic deficit of presumed vascular origin of ≥ 24 hours that is not due to hemorrhage as determined by imaging or is due an ischemic infarction that correlates with the clinical deficit as determined by imaging or autopsy.

  Source: ~~American Stroke Association (ASA) Scientific Statement~~. Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, Elkind MS, George MG, Hamdan AD, Higashida RT, Hoh BL, Janis LS, Kase CS, Kleindorfer DO, Lee JM, Moseley ME, Peterson ED, Turan TN, Valderrama AL, Vinters HV; American Heart Association Stroke Council, Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular and Stroke Nursing; Council on Epidemiology and Prevention; Council on Peripheral Vascular Disease; Council on Nutrition, Physical Activity and Metabolism. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013;44(7):2064-2089.

  ~~Source: Framingham Heart Study (with some adjustment of wording)~~

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- **Tissue-based Definition:** Ischemic stroke is defined as sudden, focal neurologic deficit secondary to an infarction of central nervous system tissue on brain imaging or autopsy.
- **Comment for ~~Ischemic Stroke new~~ tissue-based definition:** The recent definition is tissue-based and generally presumes imaging to rule in/out infarction. This definition indicates that both clinical and imaging provide important data to determine the presence of a clinical stroke. One useful operationalized definition of clinically symptomatic ischemic stroke using the tissue-based definition is: a symptomatic ischemic stroke is deemed present if either of the following criteria are met: 1) focal neurologic deficit of any duration due to an imaging or pathologically confirmed acute cerebral infarction, or 2) focal neurologic deficit of presumed vascular origin of ≥ 24 hours that is not due to hemorrhage or another cause as determined by imaging. Rare instances where tissue-based definition remains to be of limited utility ~~Examples~~ include patients with non-focal neurologic symptoms who have acute infarction by MR/CT imaging, and ~~patients with focal symptoms less than 24 hours who have MR imaging of diffusion-positive infarct, inability of CT scans to detect some very early ischemic damage in first hours after onset in patients with focal deficits/symptoms greater than 24 hours, and the rare occurrence of negative MR imaging of very small infarcts in patients with focal symptoms lasting more than 24 hours.~~ patients with focal deficits/symptoms greater than 24 hours where neuroimaging does not reveal any abnormality consistent with acute ischemic injury.
  Finally, cerebral infarctions with subsequent bleeding into the parenchyma, ventricles, or subarachnoid space, even if they involve hematomas, should be classified as cerebral infarctions, not intracerebral hemorrhage.

2.2. Transient Ischemic Attack (TIA)

- **Time-based Definition:** TIA is a sudden, focal neurological deficit (brain, spinal cord, or retina) of presumed vascular origin lasting <24 hours.

  Source: ~~American Stroke Association (ASA) Scientific Statement~~ Easton JD, Saver JL, Albers GW, Alberts MJ, Chaturvedi S, Feldmann E, Hatsukami TS, Higashida RT, Johnston SC, Kidwell CS, Lutsep HL, Miller E, Sacco RL; American Heart Association; American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; Interdisciplinary Council on Peripheral Vascular Disease. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. Stroke. 2009;40(6):2276-2293.

- **Comment for Time-based Definition:** Useful for longitudinal epidemiologic studies which applied this definition
- **Tissue-based Definition:** TIA is a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction.

  Source: ~~American Stroke Association (ASA) Scientific Statement~~ Easton JD, Saver JL, Albers GW, Alberts MJ, Chaturvedi S, Feldmann E, Hatsukami TS, Higashida RT, Johnston SC, Kidwell CS, Lutsep HL, Miller E, Sacco RL; American Heart Association; American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; Interdisciplinary Council on Peripheral Vascular Disease. Definition and evaluation of transient ischemic attack: a scientific statement for

healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. Stroke. 2009;40(6):2276-2293.

- **Comment for Tissue-based Definition:** The timing, sensitivity, and type of imaging modality are important in the tissue-based definition of TIA.

2.3. Acute Neurovascular Syndrome

For patients with relatively brief symptom duration (e.g., symptoms that persist several hours but less than a day), who do not receive a detailed diagnostic imaging evaluation, it may be difficult to determine whether stroke or TIA is the most appropriate diagnosis. For these patients, it would be reasonable that a term such as acute neurovascular syndrome should be chosen, analogous to the terminology used in cardiology (Class IIa, Level of Evidence).

Source: Easton JD, Saver JL, Albers GW, Alberts MJ, Chaturvedi S, Feldmann E, Hatsukami TS, Higashida RT, Johnston SC, Kidwell CS, Lutsep HL, Miller E, Sacco RL; American Heart Association; American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; Interdisciplinary Council on Peripheral Vascular Disease. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. Stroke. 2009;40(6):2276-2293.

2.4. Intracerebral hemorrhage (ICH)

- **Tissue-based Definition:** Intracerebral hemorrhage is defined as non-traumatic abrupt onset of severe headache, altered level of consciousness and/or focal neurologic deficit that is associated with a focal collection of blood within the brain parenchyma on imaging or at autopsy and is not due to trauma or hemorrhagic conversion of a cerebral infarction.

  Source: ~~Rochester/Cincinnati~~ Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, Elkind MS, George MG, Hamdan AD, Higashida RT, Hoh BL, Janis LS, Kase CS, Kleindorfer DO, Lee JM, Moseley ME, Peterson ED, Turan TN, Valderrama AL, Vinters HV; American Heart Association Stroke Council, Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular and Stroke Nursing; Council on Epidemiology and Prevention; Council on Peripheral Vascular Disease; Council on Nutrition, Physical Activity and Metabolism. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013;44(7):2064-2089.

2.5. Intraventricular hemorrhage (IVH)

- **Tissue-based Definition:** Intraventricular hemorrhage is non-traumatic acute onset of headache, altered level of consciousness and/or focal neurologic deficit that is associated with a focal

collection of blood that is isolated only to the ventricular system on CT, MRI or autopsy.

Source: ~~Cincinnati~~ Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, Elkind MS, George MG, Hamdan AD, Higashida RT, Hoh BL, Janis LS, Kase CS, Kleindorfer DO, Lee JM, Moseley ME, Peterson ED, Turan TN, Valderrama AL, Vinters HV; American Heart Association Stroke Council, Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular and Stroke Nursing; Council on Epidemiology and Prevention; Council on Peripheral Vascular Disease; Council on Nutrition, Physical Activity and Metabolism. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013;44(7):2064-2089.

2.6. Subarachnoid hemorrhage (SAH)

- **Tissue-based Definition:** Subarachnoid hemorrhage is defined as non-traumatic abrupt onset of severe headache or altered level of consciousness that is associated with blood in the subarachnoid space on CT or at autopsy, or a clinical history and exam consistent with SAH (sudden onset of severe headache or altered level of consciousness) with xanthochromia and many red blood cells in the cerebrospinal fluid. Cases that have both ICH and SAH are classified as SAH if an aneurysmal source of bleeding is documented or if the neuroradiologist suspects a subarachnoid origin of the bleeding. Cases are classified as ICH if a parenchymal source of bleeding seems most likely.

  Source: ~~Rochester/Cincinnati~~ Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, Elkind MS, George MG, Hamdan AD, Higashida RT, Hoh BL, Janis LS, Kase CS, Kleindorfer DO, Lee JM, Moseley ME, Peterson ED, Turan TN, Valderrama AL, Vinters HV; American Heart Association Stroke Council, Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular and Stroke Nursing; Council on Epidemiology and Prevention; Council on Peripheral Vascular Disease; Council on Nutrition, Physical Activity and Metabolism. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013;44(7):2064-2089.

2.7. Clinical Stroke of Uncertain Type

- **Time-based Definition:** Clinical Stroke of Uncertain type is a defined as acute onset of a focal neurological deficit that persists more than 24 hours or is fatal and that cannot be attributed to another cause. This category is used when radiographic or pathologic information is unavailable or insufficient to distinguish among cerebral infarction, ICH, and SAH.

  Source: ~~Rochester/Cincinnati~~

  Broderick J, Brott T, Kothari R, Miller R, Khoury J, Pancioli A, Gebel J, Mills D, Minneci L, Shukla R. The Greater Cincinnati/Northern Kentucky Stroke Study: preliminary first-ever and total incidence rates of stroke among blacks. Stroke. 1998;29(2):415-421.

  Brown RD, Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Stroke incidence, prevalence, and survival: secular trends in Rochester, Minnesota, through 1989. Stroke. 1996;27(3):373-380.

2.8. Silent Stroke (Clinically Asymptomatic)

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Under a tissue-based definition of stroke, ischemic strokes may be symptomatic or asymptomatic ("silent"). The definitions above refer to clinically symptomatic stroke and stroke subtypes or TIAs. A stroke is considered silent ~~Silent ischemic strokes occur~~ when there is evidence of cerebral infarction that is >=3mm on brain imaging or autopsy without a clinical correlate. Similarly, patients may have evidence of hemosiderin indicating prior micro-hemorrhages or asymptomatic hemorrhages (example small cavernous malformations) without a clinical correlate. These silent strokes, whether ischemic or hemorrhagic, are defined in the imaging CDEs.

Source: Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, Elkind MS, George MG, Hamdan AD, Higashida RT, Hoh BL, Janis LS, Kase CS, Kleindorfer DO, Lee JM, Moseley ME, Peterson ED, Turan TN, Valderrama AL, Vinters HV; American Heart Association Stroke Council, Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular and Stroke Nursing; Council on Epidemiology and Prevention; Council on Peripheral Vascular Disease; Council on Nutrition, Physical Activity and Metabolism. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013;44(7):2064-2089.

3. Ischemic Stroke Subtype Classification ~~Systems~~

3.1. Classification Based on Diagnostic Accuracy of Ischemic Stroke

3.1.1. Acute Ischemic Cerebrovascular Syndrome (AICS) Classification System

Source: Kidwell CS, Warach S. Acute ischemic cerebrovascular syndrome: diagnostic criteria. Stroke. 2003;34(12):2995-2998.

- **Subtypes:**
  - **Definite AICS:** Acute onset of neurologic dysfunction of any severity consistent with focal brain ischemia and imaging/laboratory confirmation.
  - **Probable AICS:** Acute onset of neurologic dysfunction of any severity suggestive of focal brain ischemic syndrome but without imaging/laboratory confirmation of acute ischemic pathology (diagnostic studies were negative but insensitive for ischemic pathology of the given duration, severity and location). Imaging, laboratory, and clinical data studies do not suggest non-ischemic etiology: possible alternative etiologies are ruled out.
  - **Possible AICS:** Acute neurologic dysfunction of any duration or severity possibly consistent with focal brain ischemia without imaging/laboratory confirmation of acute ischemic pathology (diagnostic studies were not performed or were negative and sensitive for ischemic pathology of the given duration, severity and location). Possible alternative etiologies are not ruled out. Symptoms may be non-focal or difficult to localize.

3.2. ~~Etiologic Classification Systems for Ischemic Stroke~~ Classification Based on Presumed Etiology of Ischemic Stroke

- Classification approaches:~~Important definitions in ischemic stroke classification:~~
  - **Phenotypic classification:** Categorizations are done according to abnormal test findings organized in major etiologic groups. Do not prioritize positive test finding for one etiology in the presence of positive test results for multiple etiologies. For instance, a patient with distal middle cerebral artery occlusion, evidence of concurrent renal embolism, moderate atherosclerotic stenosis in ipsilateral proximal internal carotid artery and atrial fibrillation would be classified "atherosclerosis + cardiac embolism". Phenotypic classification ~~does not~~ requires

minimal ~~any~~ judgment on the part of the clinician-investigator. No causal inferences are made. There are no trade-offs among positive test findings and thereby inadvertent loss of information. An important shortcoming of phenotypic approach is that it allows categorization of stroke patients into a ~~vast~~ number of possible subtypes (see below for the number of subtypes in each system). Baltimore-Washington Classification System, Causative Classification System, and ASCO(D) classification are examples for phenotypic approach.

- **Causative classification:** This approach integrates diagnostic test results into major etiologic categories to identify a single most likely causative subtype for each patient. Unlike phenotypic classification, designation of the causative subtype is a decision-making process. It requires integration of multiple aspects of ischemic stroke evaluation including symptom characteristics, vascular risk factors, diagnostic test findings, response to treatment, and prognosis. For instance, the probable causative subtype would be "cardiac embolism" in the example given above because of the presence of concurrent systemic embolism. The advantage of this approach is its ability to classify etiologies into a fewer number of subtypes. As a shortcoming, causative systems' ability to unambiguously assign the cause of stroke is limited because of the absence of a gold standard. Trial of ORG 10172 in Acute Stroke Treatment and Causative Classification of Stroke systems are examples for causative subtyping.
- **Comment:** It is important to explicitly acknowledge in a research study whether stroke etiologies are assigned based on their phenotypic characteristics (i.e. sole presence) or their potential to cause a stroke. Phenotypic classification is particularly well-suited for use for coding purposes as well as in large scale studies such as epidemiologic or genetic studies. Causative subtypes can be derived from phenotypic classification via a decision-making process. The rules employed for decision making should be explicitly described in research studies aiming to use phenotypic systems to generate causative subtypes.

3.2.1. Trial of ORG 10172 in Acute Stroke Treatment (TOAST) Classification System

Source: ~~Adams HP et al. Stroke 1993;24 :35~~ Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, Marsh EE 3rd. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke. 1993;24(1):35-41.

- **Approach:** Causative
- **Subtypes:**
  - Large artery atherosclerosis: Atherosclerotic lesion causing greater than 50% stenosis.
  - Cardioembolism: Divided into high-risk and medium-risk sources based on their relative potential to cause stroke
  - Small vessel occlusion: Lacunar syndrome with or without evidence of ischemic lesion less than 1.5 cm in diameter in the brain stem or subcortical white matter
  - Stroke of other determined etiology: Rare causes such as non-atherosclerotic vasculopathies, hematologic disorders, or hypercoagulable states
  - Stroke of undetermined etiology
    - Two or more causes
    - Negative evaluation (unknown)
    - Incomplete evaluation
- **Number of subtypes:** 11 [4 major subtypes, 2 possible states for each subtype (probable

and possible), and undetermined category broken into 3 subgroups]

- **Classification rules:** Based on clinical stroke features, CT/MRI, and ECG/TTE
- **Important features:**
  - ~~Carries on the long standing tradition of classifying stroke into 5 major subtypes.~~
  - Widely accepted and simple.
  - Validated by independent groups: Subtypes can *modestly* predict hard stroke outcomes (recurrence rate, survival, clinical disability).
  - Takes into account the degree of diagnostic certainty in subtype assignments (diagnoses could be either "probable" or "possible" depending on the availability of diagnostic tests for ~~other~~ alternative causes). ~~This allows an algorithmic approach to missing diagnostic tests such that, for instance, atrial fibrillation is classified as "possible" rather than "probable" cardioembolism if vascular imaging is not done.~~
- Weaknesses:
  - Lack of a gold standard to define the exact mechanism of stroke.
  - Formulations are based on clinical, imaging, and laboratory features that are sensitive but not ~~necessarily~~ specific to a particular etiology.
  - No decision rules are applied to identify the most likely mechanism in patients with multiple competing etiologies. Assigning every patient~~s~~ with more than one etiology into "~~unclassified~~ undetermined" group inflates the size of "undetermined" category.
  - The major limitation of the scale is that it includes, in the same category (undetermined category), patients with more than one defined cause, those with incomplete evaluation,as well as those without any defined cause after extensive evaluation, which are three different groups of patients.
  - ~~Most classification rules are opinion-based.~~
  - ~~Not all inclusive. For instance, cannot accommodate patients with complicated atheroma plaque causing less than 50% stenosis.~~
  - Poor to moderate inter-rater reliability
  - Independent assessment by 2 raters: kappa = 0.49
  - Independent assessment by multiple raters = 0.42-0.54
  - Requires revision to accommodate major advances in diagnostic technology (~~advanced~~ MRI, non-invasive angiography, TEE, Holter etc.) since 1993.
- **Comment:** TOAST is a simple and~~,~~ widely used ~~accepted, and validated~~ system. Nevertheless, it suffers from a poor to moderate reliability and validity ~~(misclassification error)~~. It is recommended for use in large studies where the impact of misclassification error becomes less important.

3.2.2. The Causative Classification System

Source: ~~Ay et al. Ann Neurol 2005;58:688;~~ Ay H, Furie KL, Singhal A, Smith WS, Sorensen AG, Koroshetz WJ. An evidence-based causative classification system for acute ischemic stroke. Ann Neurol. 2005;58(5):688-697.

~~Ay et al. Stroke 2007;38:2979;~~ Ay H, Benner T, Arsava EM, Furie KL, Singhal AB, Jensen MB, Ayata C, Towfighi A, Smith EE, Chong JY, Koroshetz WJ, Sorensen AG A computerized

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algorithm for etiologic classification of ischemic stroke: the Causative Classification of Stroke System. Stroke. 2007;38(11):2979-2984.

~~Ay et al. Stroke 2009;40:e203;~~ Ay H, Arsava EM, Johnston SC, Vangel M, Schwamm LH, Furie KL, Koroshetz WJ, Sorensen AG. Clinical- and imaging-based prediction of stroke risk after transient ischemic attack: the CIP model. Stroke. 2009;40(1):181-186.

~~Arsava et al. JAMA Neurol. 2017; 74(4):419;~~ Arsava EM, Helenius J, Avery R, Sorgun MH, Kim GM, Pontes-Neto OM, Park KY, Rosand J, Vangel M, Ay H. Assessment of the Predictive Validity of Etiologic Stroke Classification. JAMA Neurol. 2017;74(4):419-426.

- **Approach:** Causative and Phenotypic
- **Causative Subtypes:**
  - **Large artery atherosclerosis**: Either occlusive, or stenotic (≥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) vascular disease judged to be due to atherosclerosis in the clinically-relevant extracranial or intracranial arteries.
  - **Cardio-aortic embolism:** Cardiac sources of embolism are segregated into high- and low-risk categories with reference to an objective 2% primary stroke risk threshold
  - **Small artery occlusion**: 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 in the absence of any focal pathology in the parent artery at the site of the origin of the penetrating artery (focal atheroma, parent vessel dissection, vasculitis, vasospasm, etc.)
  - **Other uncommon causes:** Specific disease processes not included in the first 3 categories that involve clinically-appropriate brain arteries
  - **Undetermined causes**:
    - **Unknown-cryptogenic embolism**: Angiographic evidence of abrupt cut-off in an otherwise normal looking artery or subsequent complete recanalization of a previously occluded artery
    - **Unknown:** Other cryptogenic strokes that do not fulfill the criteria for cryptogenic embolism
    - **Unclassified**: Multiple competing etiologies
    - **Incomplete evaluation:** Failure to investigate for a relevant etiology in the absence of positive evidence
  - **Number of subtypes:** Standard causative: 5, extended causative: 16 [3 possible states for each major subtype (evident, probable, and possible), and undetermined category broken into 4 subgroups], phenotypic: 96
  - **Classification rules:** Based on clinical history, CT/MRI, CTA/MRA, ECG/TTE/TEE/Holter ~~Echo~~
  - **Important Features:**
    - ~~Provides stroke subtyping in two domains:~~
    - ~~Causative classification: identifies the most likely cause of stroke through a decision making process using objective, evidence-based rules (etiology specific stroke risks, sensitivity and specificity of stroke features for a given subtype).~~

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- ~~Phenotypic classification: provide a summary of positive test results organized in four major categories (large artery atherosclerosis, cardiac embolism, small artery disease, uncommon causes)~~
- Uses evidence- and rule-based criteria to establish causal associations.
- ~~The use of rule-based approach allows the system to a~~Assigns the most likely ~~mechanism~~ cause of stroke in the presence of ~~when~~ multiple ~~potential~~ competing causes ~~exist~~ based on associated stroke features that favor one mechanism over the others.
- Classifies~~y~~ subtypes with different confidence levels based on the weight of causal evidence. ~~as evident/probable/possible.~~
- ~~Uses objective criteria to stratify cardiac sources of embolism into high and low-risk groups (primary stroke risks associated with each individual source).~~
- ~~Requires the demonstration of brain lesion and its vascular cause (brain and vascular imaging are required)~~
- ~~Integrates depth and completeness of diagnostic evaluation into the level of confidence for subtype assignments.~~
- Automated, web-based interface that is free for academic use https://ccs.mgh.harvard.edu~~A web-based automated version is available~~ (~~Web-based Automated Version).~~Retains and standardizes individual etiology level data that underlie subtype classification.
- High to excellent reliability (kappa:0.75-0.90)
  - ~~Internal assessment by 2 raters: kappa = 0.90~~
  - ~~External assessment with 5 raters (multicenter-US study): kappa = 0.80-0.86~~
  - ~~External assessment with 20 raters (multicenter-international study): kappa = 0.80~~
  - ~~External assessment for intra-rater reliability: kappa = 0.86-0.90.~~

    ~~High reliability is achieved with small "unclassified" group.~~
- High discriminative validity: ability to generate distinct subtypes with discrete clinical features and hard stroke outcomes.
- ~~The design is flexible so modifications can be incorporated as new data accumulate.~~
- ~~CCS conflates complex aortic atheroma and low or uncertain risk cardiac sources into a single category.~~ Accommodates mild (<50%) atherosclerotic stenosis as a potential cause of stroke depending on associated clinical stroke features and the results of tests for other etiologies.

- **Weaknesses:**
  - Lack of a gold standard to define the exact mechanism of stroke.
  - Heavily depends on the availability of ~~MRI (DWI)~~brain and vascular imaging. The system may less favorably validate in settings where access to radiographic tests is limited.
  - The ~~basic~~ assumption that there is only one possible mechanism for each stroke event is ~~probably~~ an oversimplification.

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- ~~Based on evidence from diverse studies.~~ Classifying complex aortic atheroma as a proximal source of embolism in Causative and also as a large artery atherosclerosis in Phenotypic classification creates confusion.
- The number of phenotypic subtypes (~~54~~96) is too many for most research studies.

- **Comment**: ~~CCS allows stratification of stroke patients on the basis of their causative and phenotypic characteristics.~~ As compared to ~~TOAST~~ other classification methods, CCS is a more complex system but it provides ~~causative~~ etiologic stroke subtypes~~ assignments~~ with higher reliability and less misclassification error. ~~A web-based automated version is available. It is recommended for use in all venues of stroke research.~~

3.2.3. Baltimore-Washington Cooperative Young Stroke Study Classification System

Source: ~~Johnson CJ et al. Stroke 1995; 26:46~~ Johnson CJ, Kittner SJ, McCarter RJ, Sloan MA, Stern BJ, Buchholz D, Price TR. Interrater reliability of an etiologic classification of ischemic stroke. Stroke. 1995;26(1):46-51.

- **Approach:** Phenotypic
- **Subtypes:**
  - Atherosclerotic vasculopathy
  - Non-atherosclerotic vasculopathy
  - Vasculopathy of uncertain cause (lacunar)
  - Cardiac/transcardiac embolism
  - Hematologic/other
  - ~~Migraneous~~ Migrainous
  - Oral contraceptive and exogenous estrogen use
  - Other drug related
  - Indeterminate
- **Number of subtypes:** 257 (2 possible states for 8 major subtypes and hematologic/other)
- **Classification rules:** Based on CT/MRI, ECG/TTE, catheter angiography
- **Important features:**
  - Particularly suitable for young adults aged 15 to 44 years.
  - Takes into account the degree of causal certainty in subtype assignments (etiologies are classified as either “probable” or “possible” depending on their risk potential for causing stroke).
- **Weaknesses:**
  - Lack of a gold standard to define the exact mechanism of stroke.
  - Definitions and categorizations into probable and possible groups are not based on objective evidence.
  - Limited acceptance and use by the community.
  - No criteria to incorporate missing diagnostic tests into the decision-making algorithm.

- Limited inter-rater reliability
- Internal assessment by pairs of raters: kappa = 0.28-0.70.
- No independent reliability assessment.
- No validity assessment.

- **Comments:** Baltimore-Washington Cooperative Young Stroke Study System is particularly suited for etiologic subtype classification in young adult patients with ischemic stroke (15 - 44 years)

3.2.4. The A-S-C-O (Phenotypic) Classification of Stroke

Source: ~~Cerebrovasc Dis 2009;27:502~~ Amarenco P, Bogousslavsky J, Caplan LR, Donnan GA, Hennerici MG. New approach to stroke subtyping: the A-S-C-O (phenotypic) classification of stroke. Cerebrovasc Dis. 2009;27(5):502-508.

- **~~Type~~ Approach:** Phenotypic
- **Number of subtypes:** 625 (there are 4 subtypes and 5 possible states for each subtype)
- **Classification rules:** Based on CT/MRI, CTA/MRA, ECG/~~Echo~~ TTE/TEE/Holter
- **Important features:**
  - Classify positive test results according to completeness and quality of diagnostic evaluation into 3 levels of confidence (definite cause, causality uncertain, unlikely a direct cause).

  ~~a. Do not prioritize one mechanism in the presence of multiple competing mechanisms.~~

  ~~b. Integrates concurrent (causally-unrelated) conditions such as leukoaraiosis and contralateral atherosclerotic stenosis into subtype assignments.~~

  ~~o Final classification includes both causally-related and causally-unrelated factors.~~

  ~~o Itemize all diagnostic criteria required to identify or rule out a stroke etiology.~~

  - Moderate to excellent inter-rater reliability depending on the phenotypic subtype.

    Source: Chen N, Zhou M, Wang Y, Wang H, Yang M, Guo J, Yang X, Zheng H, Zhou D, He L. Inter-rater reliability of the A-S-C-O classification system for ischemic stroke. J Clin Neurosci. 2013;20(3):410-412.

    Marnane M, Duggan CA, Sheehan OC, Merwick A, Hannon N, Curtin D, Harris D, Williams EB, Horgan G, Kyne L, McCormack PM, Duggan J, Moore A, Crispino-O'Connell G, Kelly PJ. Stroke subtype classification to mechanism-specific and undetermined categories by TOAST, A-S-C-O, and causative classification system: direct comparison in the North Dublin population stroke study. Stroke. 2010;41(8):1579-1586.

    Wolf ME, Sauer T, Alonso A, Hennerici MG. Comparison of the new ASCO classification with the TOAST classification in a population with acute ischemic stroke. J Neurol. 2012;259(7):1284-1289.

  - High discriminative validity.
  - A newer version that incorporates 'D' for dissection (ASCOD) is available. ASCOD provides subtypes in 5 domains (A, S, C, O, D) where each domain can be defined in 5 possible states.

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Source: Amarenco P, Bogousslavsky J, Caplan LR, Donnan GA, Wolf ME, Hennerici MG. The ASCOD phenotyping of ischemic stroke (Updated ASCO Phenotyping). Cerebrovasc Dis. 2013;36(1):1-5.

- **Weaknesses:**
  - Lack of a gold standard to define the exact mechanism of stroke.
  - ~~This is a new system. There is no data on its reliability and validity yet.~~
  - Combination of causative and non-causative factors (leukoaraiosis, mild atherosclerosis, etc.) causes confusion ~~on~~ when ~~how to~~ interpreting the classification results.
  - ~~Most of the criteria used to define causal associations are not evidence based.~~
  - Relies on the availability of MRI brain and vascular imaging.
  - Too many subtypes for an average research project.
- **Comment:** ASCO(D) allows stratification of stroke patients on the basis of their phenotypic characteristics. ~~They~~ ASCO(D) would be particularly useful in large scale studies such as epidemiologic or genetic studies.

3.3. Classification Based on Syndromic Characteristics ~~Classification~~ of Ischemic Stroke

3.3.1. Oxfordshire Community Stroke Project Subtype Classification

Source: Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. Classification and natural history of clinically identifiable subtypes of cerebral infarction. Lancet. 1991 ~~Jun 22~~;337(8756):1521-1526.

- **Subtypes:**
  - Total anterior circulation infarcts (TACI)
  - Partial anterior circulation infarcts (PACI)
  - Lacunar infarcts (LACI)
  - Posterior circulation infarcts (POCI)
- **Classification rules:** Based on clinical stroke features.
- **Important features:**
  - Classifies stroke according to extent and site of brain infarction. This is not an etiologic classification system.
  - Classifications are easily done based on clinical grounds.
  - Subtypes modestly predict prognosis.
- **Weaknesses:**
  - Lack of a gold standard to define the exact mechanism of stroke.
  - Low inter-rater reliability
    - Internal assessment by 2 raters: kappa = 0.54
    - External assessments by 2 raters: kappa = 0.31-0.53
    - External assessments by 4 raters: kappa = 0.64

- The overall validity of the system seems to be mediated by only TACI and LACI subtypes. The clinical significance of PACI and POCI subtypes are not well defined.

- **Comments:** Oxfordshire Community Stroke Project Subtype Classification is a syndromic classification system and may be used in research settings where resources and quality of diagnostic investigations for stroke etiology are limited. It does not require technology; however, it does require a trained examiner. This classification system provides useful initial etiological, prognostic and anatomical information that helps triage stroke care and research.

3.4. Definition of Stroke of Unknown Cause

3.4.1. TOAST Definition

No likely etiology determined despite an extensive evaluation.

Comment: TOAST definition is a diagnosis of exclusion. Cryptogenic category excludes low-risk cardiac causes. TOAST leaves the depth and completeness of diagnostic investigations to the discretion of the rater.

3.4.2. CCS Definition

No identified etiology despite appropriate diagnostic evaluation.

Comment: The appropriateness and depth of diagnostic evaluation are determined on a case by case basis depending on the level of suspect from a particular etiology. Cryptogenic category excludes low-risk cardiac and vascular causes. CCS defines an additional subset called cryptogenic embolism where clinical and imaging evaluation suggests an embolic mechanism, but diagnostic evaluation does not reveal an embolic source.

3.4.3. ESUS Definition

Non-lacunar brain infarct without ≥50% luminal stenosis in the clinically relevant artery or major risk cardioembolic sources or other rare causes of stroke.

Comment: ESUS definition requires exclusion of major causes of stroke. ESUS accommodates certain low- but proven-risk cardiac and arterial sources resulting in identification of a population that is not truly cryptogenic. ESUS does not require any objective proof for embolism; the term "embolic" is based on the observation that embolism is a common mechanism of stroke. Caution should be exercised as some branch occlusions could be caused by non-embolic mechanisms such as atherosclerosis, arteritis, or those attributable to other vasculopathies such as CADASIL. The definition of lacunar infarction in ESUS [subcortical infarct ≤1.5 cm (≤2.0 cm on DWI) in largest dimension and in distribution of small, penetrating cerebral arteries of cerebral hemispheres and pons] may permit misclassification of embolic small subcortical infarcts within the territory of cortical penetrating arteries as non-embolic small vessel disease.

4. Intracerebral Hemorrhage Subtype Classification Systems

The etiology of the intracerebral hemorrhage should be recorded to the most detailed extent possible. Key issues include:

- Location: Deep (thalamic, putamen, globus pallidum, and deep white matter), lobar, cerebellar, and brainstem. For those ICHs that are large in size, distinction between lobar and deep will be judged by presumed origin of the bleeding.
- Presumed cause: hypertensive, amyloid angiopathy, arteriovenous malformation, cavernous hemangioma, venous angioma, aneurysm (if SAH and ICH – then classified as SAH), anti-coagulant related ICH, thrombolytic ICH (not hemorrhagic transformation of cerebral infarction), tumor,

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~~aneurysm~~, other (list), undetermined. Hypertensive ICH is defined as an ICH in the setting of known history of hypertension in a deep, cerebellar, or brainstem location without another defined structural cause. ICH presumed secondary to amyloid angiopathy is suggested by lobar ICH without another defined cause in the setting of prior lobar ICH, old cortical microhemorrhages on MRI, imaging of amyloid by PET, or biopsy/surgical specimen consistent with amyloid angiopathy. Patients with presumed amyloid angiopathy are generally older than age 60.

- Volume: This can be measured by formula for estimated ellipsoid volume = AX BXC/2 where A, B, and C represent diameter of ICH in centimeters in three dimensions.
- Presence of IVH -= yes or no. Patients with ICH and IVH are classified as ICH subtype.

5. Intraventricular Hemorrhage Subtype Classification Systems

The etiology of the intraventricular hemorrhage should be recorded to the most detailed extent possible. Key issues include:

- ~~Presumed cause: hypertensive, arteriovenous malformation, anti-coagulant related, IVH, tumor, other (list), or undetermined. Hypertensive ICH is defined as an IVH in the setting of known history of hypertension without another defined structural cause.~~
- Volume/location of IVH: This is defined by ventricles involved (2 lateral, third, and fourth ventricle). Several scales measure of volume of IVH. One example is the Graeb scale below.
- Patients with both ICH and IVH are classified as ICH.
- Patients with both ~~IVH~~ SAH and ~~SAH~~ IVH with aneurysmal cause are classified as SAH.
- Presumed cause: hypertensive, arteriovenous malformation, anti-coagulant related IVH, tumor, other (list), or undetermined. Hypertensive ICH is defined as an IVH in the setting of known history of hypertension without another defined structural cause.

5.1. Graeb: Intraventricular Hemorrhage Scale

Source: Graeb DA, Robertson WD, Lapointe JS, Nugent RA, Harrison PB. Computed tomographic diagnosis of intraventricular hemorrhage. Etiology and prognosis. Radiology. 1982;143(1):91-96.

- Scoring:
  - Lateral Ventricles
    - 1= Trace amount of blood or mild bleeding
    - 2= < Half of the ventricle filled with blood
    - 3= > Half of the ventricle filled with blood
    - 4= Ventricle expanded and filled with blood
  - Third and Fourth Ventricles
    - 1= Blood present without dilatation
    - 2= Ventricle expanded and filled with blood

Each ventricle is scored separately, including both lateral ventricles

Maximum score: 12

6. Subarachnoid Hemorrhage Subtype Classification Systems

6.1. Etiologic Classification of Subarachnoid Hemorrhage

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The etiology of the subarachnoid hemorrhage should be recorded to the most detailed extent possible. Key issues include:

- Is the SAH aneurysmal or non-aneurysmal: if due to saccular aneurysm, record details regarding the aneurysm including (at a minimum) location (parent artery) and maximum diameter. If it is a non-saccular aneurysm, record if it is mycotic or fusiform.
- If non-aneurysmal, if some other anatomical etiology is identified for SAH, then the etiology should be recorded. Some of the most likely disorders to be considered in etiologic subtyping include but are not limited to: 1) arteriovenous malformation or other vascular malformation, 2) tumor, 3) illicit drug use, 4) antithrombotic use, ~~5) non-saccular aneurysm (mycotic, fusiform)~~, ~~5~~6) spinal cord lesions including vascular malformation or tumor, and 6) amyloid angiopathy (cortical distribution of SAH).
- If no etiology is identified despite appropriate evaluation, then the imaging should be noted as either 1) pre-truncal/peri-mesencephalic localization for the hemorrhage, or 2) other.

6.2. Subarachnoid Hemorrhage Severity Classification

6.2.1. Hunt and Hess Scale

Source: Hunt W, Hess R. Surgical risk as related to time of intervention in the repair of intracranial aneurysms. J~~ournal of~~ Neurosurg~~ery~~.1968;28(1):14-20.

- **Comments:** This scale was initially proposed in 1968. The scale makes use of the degree of meningeal irritation, the severity of neurological deficit, and the level of arousal. This is a 5 level scale, the higher the score the lower the likelihood of survival. In 1974, a modification of the scale added a zero grade for unruptured aneurysms. It remains widely utilized. This scale is ~~highly~~ recommended for classifying the overall severity of SAH.

6.2.2. Fisher Scale

Source: Fisher CM, Kistler JP, Davis JM. Relation of cerebral vasospasm to subarachnoid hemorrhage visualized by computerized tomographic scanning. Neurosurgery.1980;6(1):1-9.

- **Comment:** Characterizing the appearance of subarachnoid hemorrhage on imaging. This scale was proposed to predict the occurrence of cerebral vasospasm after SAH. In this four grade scale, the lowest grade suggests no blood visualized on CT, and the other grades define varying amounts and locations of subarachnoid hemorrhage on CT scan. It is widely used. This scale is ~~highly~~ recommended for classifying the imaging severity of SAH.

6.2.3. Combination scale (Ogilvy)

Source: Ogilvy CS, Carter BS. A proposed comprehensive grading system to predict outcome for surgical management of intracranial aneurysms. Neurosurgery. 1998;42(5):959-968.

- **Comment:** The Hunt and Hess, and Fisher scales were combined with patient age, aneurysm size, and location to define a grading system which predicts outcome. The complexity of the scale has precluded it from being used on a widespread basis. This scale is recommended as another option when classifying severity of SAH.

6.2.4. SAH Volume Scale (Hijdra)

Source: Hijdra A, Brouwers PJ~~AM~~, Vermeulen M, van Gijn J. Grading the amount of blood on computed tomograms after subarachnoid hemorrhage. Stroke.1990;21(8):1156-1161.

- **Comment:** This scale also grades the degree of SAH on the initial CT scan. The volume of SAH is defined by measurement of the amount of blood in each of 10 basal cisterns and fissures. The scale does have high inter-observer reliability. Due to its complexity it is not used on a widespread basis. This scale is recommended as another option when

classifying the imaging severity of SAH.

6.2.5. The World Federation of Neurosurgeons Classification

Source: Drake CG, Hunt WE, Sano K, et al. Report of World Federation of Neurological Surgeons Committee on a universal subarachnoid hemorrhage grading scale. J Neurosurg.1988; 68(6):985–986.

- **Comments:** This commonly used five grade scale is based on the Glasgow coma scale, and presence of a focal neurological deficit. This scale is ~~highly~~ recommended for classifying the overall severity of SAH.

7. Cerebral ~~V~~venous thrombosis (CVT) ~~occlusive disease~~ and stroke

Thrombosis of the dural sinuses and/or cerebral veins (CVT) is an unusual cause of stroke, but should be considered as a potential cause of cerebral infarction and of intracerebral hemorrhage. CVT causes approximately 0.5-1% of all strokes. The diagnosis of cerebral venous thrombosis is based on clinical suspicion, along with imaging confirmation. The clinical features of CVT are in part dependent on the location of the thrombosis. Cerebral infarction, often with hemorrhagic transformation, most commonly occurs with thrombosis of the superior sagittal sinus or lateral sinus. Thrombosis of the deep venous sinuses is less common but can lead to diencephalic, thalamic, or basal ganglial infarction. Cortical vein thrombosis is also uncommon, and specific clinical syndromes related to the larger cortical veins are rarely seen. Imaging is of great importance in confirming the diagnosis of CVT. For CVT associated with cerebral infarction, the following should be recorded, at a minimum: venous structures involved in the thrombotic process, any presence of hemorrhagic transformation of the infarct, and potential etiology of the CVT.

8. Pediatric Stroke

Note: Time-based and tissue-based definitions as previously discussed for adults in Sections 1 and 2 also apply to pediatric strokes.

8.1. Definitions for Pediatric Stroke Types

8.1.1. ~~Childhood Stroke~~ Definitions of vascular disease in childhood

- **Childhood arterial ischemic stroke** is a condition occurring in a person between 29 days of life through 18 years of life. Arterial ischemic stroke in a child presents with a deficit consistent with ischemia in an arterial distribution, or acute non-localizing encephalopathy (including new-onset symptomatic seizures), with confirmation of infarction on imaging or autopsy. ~~conforming to an arterial territory and corresponding in age and location to the clinical symptoms.~~ This is the same as ischemic stroke in adults (as previously defined see Section 2.1).
- **Childhood TIA** is a TIA (as previously defined for adults see Section 2.2~~1~~) occurring in a person between 29 days of life through 18 years of life.
- ~~**Childhood cerebral sinovenous ischemic stroke** is a condition that presents with acute or chronic encephalopathy manifest as headache, lethargy, seizures, altered mental status and/or focal neurologic deficit with neuroimaging confirmation of: 1) thrombotic occlusion in the cerebral venous system, 2) venous infarction on imaging or autopsy conforming to a venous territory, and 3) ischemia corresponding in age and location to the clinical symptoms.~~
- **Childhood intracerebral hemorrhage** is an intracerebral hemorrhage (as previously defined for adults see Section 2.4~~1~~) occurring in a person between 29 days of life through 18 years of life.

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- **Childhood subarachnoid hemorrhage** is a subarachnoid hemorrhage (as previously defined for adults see Section 2.6~~I~~) occurring in a person between 29 days of life through 18 years of life.
- **Childhood intraventricular hemorrhage** is an intraventricular hemorrhage (as previously defined for adults see Section 2.5~~I~~) occurring in a person between 29 days of life through 18 years of life.
- ~~**Childhood TIA** is a TIA (as previously defined for adults see Section 2.2I) occurring in a person between 29 days of life through 18 years of life.~~
- **Childhood Silent Stroke** is an asymptomatic ischemic infarct or hemorrhagic ~~or ischemic~~ stroke (as previously defined for adults see Section 2.8~~II, H~~) occurring in a person between 29 days of life through 18 years of life.
  - Silent cerebral infarct is a silent stroke defined in studies of sickle cell anemia as an MRI signal abnormality at least 3 mm in one dimension visible in two planes in the setting of normal neurologic examination without a history or physical finding associated with symptomatic stroke.

    Source: DeBaun MR, Gordon M, McKinstry RC, Noetzel MJ, White DA, Sarnaik SA, Meier ER, Howard TH, Majumdar S, Inusa BP, Telfer PT, Kirby-Allen M, McCavit TL, Kamdem A, Airewele G, Woods GM, Berman B, Panepinto JA, Fuh BR, Kwiatkowski JL, King AA, Fixler JM, Rhodes MM, Thompson AA, Heiny ME, Redding-Lallinger RC, Kirkham FJ, Dixon N, Gonzalez CE, Kalinyak KA, Quinn CT, Strouse JJ, Miller JP, Lehmann H, Kraut MA, Ball WS Jr, Hirtz D, Casella JF. Controlled trial of transfusions for silent cerebral infarcts in sickle cell anemia. N Engl J Med. 2014;371(8):699-710.
- **Childhood cerebral venous thrombosis (CVT) and stroke** is a condition that presents with acute or chronic encephalopathy manifest as headache, lethargy, seizures, altered mental status and/or focal neurologic deficit with neuroimaging confirmation of: 1) thrombotic occlusion in the cerebral venous system, 2) venous infarction or hemorrhage on imaging or autopsy conforming to a venous territory, corresponding in age and location to the clinical symptoms.

8.1.2. ~~Perinatal Stroke~~ Definitions of vascular disease in perinatal period

- ~~**Ischemic perinatal stroke (IPS) (or**~~ **Perinatal arterial ischemic stroke (PAIS)**~~)~~ is defined as a group of heterogeneous conditions in which there is focal disruption of cerebral blood flow secondary to arterial ~~or cerebral venous thrombosis or embolization~~ occlusion, between 20 weeks of fetal life and before ~~through~~ the 29~~8~~th postnatal day, confirmed by neuroimaging or neuropathologic studies. Precise timing of the vascular event leading to IPS is generally not known therefore additional classification of PAIS is based on the gestational or postnatal age at diagnosis.~~[1]~~
  - ~~**Neonatal**~~ **Acute perinatal** ~~**arterial**~~ **ischemic stroke** ~~**(AIS)**~~ is a subset of PAIS and presents ~~condition~~ with an acute encephalopathy, manifest as seizures, altered mental status and/or neurological deficit ~~occurring before~~ in a newborn infant after birth and before the 29th postnatal day (including preterm infants). AIS in neonates

~~[1] Raju TN, Nelson KB, Ferriero D, Lynch JK. Ischemic perinatal stroke: summary of a workshop sponsored by the National Institute of Child Health and Human Development and the National Institute of Neurological Disorders and Stroke. Pediatrics 2007; 120: 609-16.~~

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is confirmed by brain imaging showing parenchymal infarct(s) corresponding to arterial territory(ies).

- **Presumed pre- or perinatal ischemic stroke** is a subset of PAIS presenting after the neonatal period (usually with hemiparesis or a seizure) found to have a chronic, focal infarction on neuroimaging from a presumed arterial source. The history and imaging are consistent with a prenatal or perinatal onset of stroke presumed to have occurred between the 20th week of fetal life and before the 29th postnatal day. This group represents a group of heterogeneous conditions, which are discussed further in the referenced articles[~~1~~2~~3~~].

Source: Raju TN, Nelson KB, Ferriero D, Lynch JK, NICHD-NINDS Perinatal Stroke Workshop Participants. Ischemic perinatal stroke: summary of a workshop sponsored by the National Institute of Child Health and Human Development and the National Institute of Neurological Disorders and Stroke. Pediatrics. 2007;120(3):609-616.

Kirton A, DeVeber G, Pontigon AM, MacGregor D, Shroff M. Presumed perinatal ischemic stroke: vascular classification predicts outcomes. Ann.Neurol.2008;63(4):436-443.

Ferriero DM, Fullerton HJ, Bernard TJ, Billinghurst L, Daniels SR, DeBaun MR, deVeber G, Ichord RN, Jordan LC, Massicotte P, Meldau J, Roach ES, Smith ER; American Heart Association Stroke Council and Council on Cardiovascular and Stroke Nursing. Management of Stroke in Neonates and Children: A Scientific Statement From the American Heart Association/American Stroke Association. Stroke. 2019;50(3):e51-e96.

- ~~**Neonatal cerebral sinovenous ischemic stroke** is a condition with acute encephalopathy, manifest as seizures, altered mental status and/or neurological deficit occurring before the 29th postnatal day (including preterm infants). Cerebral sinovenous ischemic stroke in a neonate is confirmed by brain imaging showing: 1) thrombotic occlusion in the cerebral venous system, 2) venous infarction on imaging or autopsy conforming to a venous territory, and 3) ischemia corresponding in age and location to the clinical symptoms.~~
- ~~**Presumed pre- or perinatal stroke** is a condition with a chronic presentation of a focal deficit corresponding to a chronic/remote infarct on neuroimaging in children. The history and imaging are consistent with a prenatal or perinatal onset of infarction. This group represents a group of heterogeneous conditions, which are discussed further in the referenced articles.[13]~~
- **Perinatal intracerebral hemorrhage (ICH)** is a condition in a term (>36 weeks) neonate with encephalopathy, manifest as seizures, altered mental status and/or neurological deficit occurring before the 29th postnatal day. ICH in a term neonate is confirmed by

~~[2] Kirton A, DeVeber G, Pontigon AM, MacGregor D, Shroff M. Presumed perinatal ischemic stroke: vascular classification predicts outcomes. *Ann.Neurol.* 2008; 63: 436-43~~

~~[3] Ferriero DM, Fullerton HJ, Bernard TJ, Billinghurst L, Daniels SR, DeBaun MR, deVeber G, Ichord RN, Jordan LC, Massicotte P, Meldau J, Roach ES, Smith ER; American Heart Association Stroke Council and Council on Cardiovascular and Stroke Nursing. Management of Stroke in Neonates and Children: A Scientific Statement From the American Heart Association/American Stroke Association. Stroke. 2019;50(3):e51-e96.~~

neuroimaging or autopsy showing a focal collection of blood within the brain parenchyma that is not secondary to hemorrhagic transformation of an ischemic infarct. Hemorrhagic stroke in premature (gestational age <36 weeks) infants refers to germinal matrix hemorrhage, periventricular white matter hemorrhage and intraventricular hemorrhage. Etiologies, clinical manifestations and determinants of outcome in this population are distinct from that in term infants. As this disorder is distinct and has been extensively described in the neonatology literature, it is not included in the scope of this project.

- **Perinatal subarachnoid hemorrhage (SAH)** is a condition in a term (>36 weeks) neonate with encephalopathy, manifest as seizures, altered mental status and/or neurological deficit occurring before the 29th postnatal day. SAH in a term neonate is confirmed by neuroimaging or autopsy showing blood in the subarachnoid space. Cases that have both ICH and SAH are classified as SAH if an aneurysmal source of bleeding is documented. In perinatal cases with both ICH and SAH the cause of bleeding may not be clear and patients should be classified as having both ICH and SAH. Preterm hemorrhagic stroke is extensively defined in the neonatology literature, and beyond the scope of this project.
- **Perinatal intraventricular hemorrhage (IVH)** is condition in a term (>36 weeks) neonate with encephalopathy, manifest as seizures, altered mental status and/or neurological deficit occurring before the 29th postnatal day. IVH in a term neonate is confirmed by neuroimaging or autopsy showing a focal collection of blood that is isolated only to the ventricular system. Preterm hemorrhagic stroke is extensively defined in the neonatology literature, and beyond the scope of this project.
- **Perinatal cerebral venous thrombosis (CVT) and stroke** is a condition with an acute encephalopathy, manifest as seizures, altered mental status and/or neurological deficit in a newborn infant after birth and before the 29th postnatal day (including preterm infants) with neuroimaging confirmation of: 1) thrombotic occlusion in the cerebral venous system, 2) venous infarction or hemorrhage on imaging or autopsy conforming to a venous territory, corresponding in age and location to the clinical symptoms. As previously discussed for adults, the following should be recorded, at a minimum: venous structures involved in the thrombotic process, any presence of hemorrhagic transformation of the infarct, and potential etiology of the CVT.
- **Periventricular venous infarction (PVI)** criteria includes unilateral injury presumed to occur in utero or in the perinatal period with at least four of the following conditions: (1) focal periventricular encephalomalacia, (2) internal capsule T2 prolongation, (3) cortical and (4) relative basal ganglia sparing, and (5) remote hemorrhage.

  Source: Kirton A, Deveber G, Pontigon AM, Macgregor D, Shroff M. Presumed perinatal ischemic stroke: vascular classification predicts outcomes. Ann Neurol. 2008;63(4):436-443.

8.2. Etiologic Classification System for Childhood Arterial Ischemic Stroke

8.2.1. Trial of ORG 10172 in Acute Stroke Treatment (TOAST) Classification System

Source: Williams LS, Garg BP, Cohen M, Fleck JD, Biller J. Subtypes of ischemic stroke in children and young adults. Neurology. 1997~~ December~~;49(6):1541-1545.

Wraige E, Hajat C, Jan W, Pohl KR, Wolfe CD, Ganesan V. Ischaemic stroke subtypes in children and adults. Dev Med Child Neurol 2003~~ April~~;45(4):229-232.

- **Comments:** The first attempt at classification of childhood AIS was by Williams, who in the late 1990s found that the majority of children with AIS did not meet criteria for atherothrombotic, cardioembolic or small-vessel disease, as seen in adults.[1] Wraige and colleagues performed a similar study, seeking to classify children with AIS using the adult

TOAST criteria, and found a significant difference between the percentage of children that were able to be classified (8%), as compared to adults (54%) [p<0.01].[3] The TOAST classification system is rarely used in pediatric stroke studies.

8.2.2. Pediatric Stroke Classification (PSC) System Trial

Source: Wraige E, Pohl KR, Ganesan V. A proposed classification for subtypes of arterial ischaemic stroke in children. Dev Med Child Neurol 2005~~ April~~;47(4):252-256.

- **Subtypes:**
  - Sickle cell disease
  - Cardioembolic
  - Moyamoya Syndrome
  - Cervical arterial dissection
  - Steno-occlusive cerebral arteriopathy
  - Other determined aetiology
  - Multiple probable/ possible aetiologies
  - Undetermined aetiology
- **Number of subtypes:** 8
- **Classification rules:** Based on clinical stroke features, CT/MRI, CTA/MRA/CA and echocardiogram
- **Important features:**
  - Specific to childhood onset stoke
  - Includes all patients with childhood stroke
  - Reliability confirmed (ICC=0.92)
  - Based upon literature review
- **Weaknesses:**
  - Lack of a gold standard to define the exact mechanism of stroke.
  - Not consensus based
  - Has not been evaluated for prognostic validity or generalizability in prospective cohort studies
  - Overlaps with International Paediatric Stroke Study (IPSS) nomenclature
  - Does not describe the progression or regression of arteriopathy over time
  - Excludes perinatal and presumed perinatal ischemic stroke (see separate section on Perinatal Stroke Classification)
- **Comments:** This system has been widely used in existing literature on pediatric stroke, and is the basis for clinical decision-making in many centers. It may be a reasonable approach in selected studies. Additional prospective studies are needed to further evaluate validity and reliability, and its value for prognosis.

8.2.3. Sebire/ IPSS Classification of Arteriopathic Stroke Subtypes

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Stroke Types and Subtypes Subgroup: Recommendations

Source: Sebire G, Fullerton H, Riou E, deVeber G. Toward the definition of cerebral arteriopathies of childhood. Curr Opin Pediatr. 2004~~ December~~;16(6):617-622.

- **Subtypes:**
  - Arteriopathy associated with sickle cell disease
  - Transient cerebral arteriopathy
  - Moyamoya Syndrome
  - Arterial dissection
  - Chronic inflammatory vasculitis
  - Neurofibromatosis type 1 (NF1)
  - Metabolic arteriopathies
  - Fibromuscular dysplasia
  - Post irradiation arteriopathy
  - Cryptogenic arteriopathy
- Number of subtypes: ~~9~~ 10
- **Classification rules:** Based on clinical stroke features and CT/MRI, CTA/MRA/CA
- Important features:
  - Specific to childhood onset AIS
  - Very specific definitions for arteriopathy
  - Nomenclature utilized in the literature
  - Adopted by IPSS consensus
- **Weaknesses:**
  - Lack of a gold standard to define the exact mechanism of stroke.
  - No validity or reliability testing
  - Overlaps with PSC nomenclature
  - Does not incorporate all types of pediatric stroke--- cardioembolic for example
  - Excludes perinatal and presumed perinatal ischemic stroke (see separate section on Perinatal Stroke Classification)
  - No system for acute classification
- **Comments:** This system has been used in existing literature on pediatric stroke. It may be useful in studies focused specifically on cerebral arteriopathy. Additional prospective studies are needed to further evaluate validity and reliability, and its value for prognosis.

8.2.4. Childhood AIS Standard Classification and Diagnostic Evaluation Criteria (CASCADE criteria)

- **Acute Subtypes:**
  - Small vessel arteriopathy of childhood
    - definitive
    - biopsy proven

    - radiographically proven
    - probable
  - Unilateral focal cerebral arteriopathy of childhood (FCA)
    - anterior circulation with collaterals
    - anterior circulation without collaterals
    - posterior circulation
    - other
  - Bilateral cerebral arteriopathy of childhood
    - with collaterals
    - without collaterals
    - other
  - Aortic/ cervical arteriopathy
    - dissection
    - takayasu arteritis
    - other
  - Cardio- embolic
    - definitive
    - probable
  - Other
  - Undetermined Etiology
  - Multi-factorial
- Chronic Subtypes:
  - Progressive Arteriopathy
  - Stable Arteriopathy
  - Reversible Arteriopathy
  - Indeterminate Arteriopathy
- **Number of subtypes:** Acute: 7 major, 18~~5~~ minor; Chronic: 4
- **Classification rules:** Based on clinical stroke features CT/MRI, CTA/MRA/CA.
- **Important features:**
  - Specific to childhood onset AIS
  - Unifies Nomenclature utilized in the literature
  - Inclusive to all childhood onset AIS stroke
  - Created by IPSS working group via modified Delphi method
  - Uses “site of disease” as basis for classification
  - Demonstrates a moderate-substantial inter-rater reliability (κ=0.53-0.78) when employed by trained and experience raters *Bernard, 2012; Bernard, 2016

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Stroke Types and Subtypes Subgroup: Recommendations

~~Preliminary Kappa 0.54-0.81~~

- **Weaknes**ses:
  - Lack of a gold standard to define the exact mechanism of stroke.
  - Inter-rater reliability is only fair in cases of aortic/cervical arteriopathy (κ=0.36) *Bernard, 2012; Bernard, 2016

    ~~This system is in early stages of development (is not yet published as of Feb 2010)~~

    ~~Does not include inflammatory definitions such as vasculitis~~
  - Excludes perinatal and presumed perinatal ischemic stroke (see separate section on Perinatal Stroke Classification)
- **Comments:** This system has been ~~is currently being~~ used on a trial basis in ~~two active~~ prospective pediatric stroke cohort studies ~~of pediatric. a solid classification of childhood stroke,~~ but has only fair ~~does not have good~~ inter-rater reliability for childhood arteriopathies. In multicenter prospective trials of childhood stroke specifically targeted at children with arteriopathy, newer classification schemes should be considered (below)~~stroke in North America (Validation of the NIH Stroke Scale in Children, and Vascular Effects of Infection in Pediatric Stroke), and is in early stages of development. Additional prospective studies are needed to further evaluate validity and reliability, and its value for prognosis.~~

  Source:

  Bernard TJ, Beslow LA, Manco-Johnson MJ, Armstrong-Wells J, Boada R, Weitzenkamp D, Hollatz A, Poisson S, Amlie-Lefond C, Lo W, deVeber G, Goldenberg NA, Dowling MM, Roach ES, Fullerton HJ, Benseler SM, Jordan LC, Kirton A, Ichord RN. Inter-Rater Reliability of the CASCADE Criteria: Challenges in Classifying Arteriopathies. Stroke. 2016;47(10):2443-2449.

  Bernard TJ, Manco-Johnson MJ, Lo W, MacKay MT, Ganesan V, DeVeber G, Goldenberg NA, Armstrong-Wells J, Dowling MM, Roach ES, Tripputi M, Fullerton HJ, Furie KL, Benseler SM, Jordan LC, Kirton A, Ichord R. Towards a consensus-based classification of childhood arterial ischemic stroke. Stroke. 2012;43(2):371-377.

8.2.5. Vascular effects of Infection in Pediatric Stroke (VIPS) arteriopathy classification system and subtype definitions

- Source: Wintermark M, Hills NK, DeVeber GA, Barkovich AJ, Bernard TJ, Friedman NR, Mackay MT, Kirton A, Zhu G, Leiva-Salinas C, Hou Q, Fullerton HJ; VIPS Investigators. Clinical and Imaging Characteristics of Arteriopathy Subtypes in Children with Arterial Ischemic Stroke: Results of the VIPS Study. AJNR Am J Neuroradiol. 2017;38(11):2172-2179.

  Wintermark M, Hills NK, deVeber GA, Barkovich AJ, Elkind MS, Sear K, Zhu G, Leiva-Salinas C, Hou Q, Dowling MM, Bernard TJ, Friedman NR, Ichord RN, Fullerton HJ; VIPS Investigators. Arteriopathy diagnosis in childhood arterial ischemic stroke: results of the vascular effects of infection in pediatric stroke study. Stroke. 2014;45(12):3597-3605.
- **Subtypes:**
  - No arteriopathy: an isolated arterial occlusion in the context of clinical history and/or parenchymal imaging that typifies cardioembolism
  - Possible arteriopathy: an isolated arterial occlusion that could be attributable to either cardioembolism or an in situ arterial abnormality

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Stroke Types and Subtypes Subgroup: Recommendations

- Definite arteriopathy: the imaging appearance of an in situ arterial abnormality (stenosis, irregularity, occlusion, banding, pseudoaneurysm, dissection flap) not attributable to an exogenous thrombus (e.g., cardioembolism) and not considered a normal developmental variant.
  - Focal cerebral arteriopathy (FCA): a unifocal and unilateral stenosis or irregularity of the large intracranial arteries of the anterior circulation (distal internal carotid arteries and/or its proximal branches). FCA refers to an imaging appearance rather than a pathophysiological entity. It may be presumed inflammatory (FCA-i) or presumed dissection (FCA-d). FCA-i is also known in older literature as "transient cerebral arteriopathy", a term that has been updated in recognition that the arteriopathy is often persistent.
  - Intracranial arterial dissection. This subtype overlaps with FCA-d (above) when dissection occurs in the large intracranial arteries of the anterior circulation.
  - Extracranial arterial dissection
  - Bilateral cerebral arteriopathy of childhood: primary moyamoya disease (idiopathic form) and secondary moyamoya syndromes (due to radiation injury, neurofibromatosis, trisomy 21, sickle cell anemia or other condition)
  - Diffuse/multifocal vasculitis: including both primary (idiopathic) and secondary (due to infection, autoimmune disorders or other entities.
  - Genetic or syndromic arteriopathy
  - Other

- **Number of subtypes:** 3 major, 7 minor
- **Classification rules:** Based on clinical stroke features, parenchymal imaging and vascular imaging (MRI/MRA/CTA/DSA).
- **Important features:**
  - Demonstrated substantial inter-rater reliability (κ=0.77)
  - Specific to childhood onset AIS, focusing on arteriopathy

    Provides new definition for Focal Cerebral Arteriopathy (FCA): unifocal and unilateral stenosis/irregularity of the large intracranial arteries of the anterior circulation (distal internal carotid artery [ICA] and/or its proximal branches).
  - Introduces the concept of FCA-i and FCA-d
  - Utilizes a multistep process for classification among highly trained raters
- **Weaknesses:**
  - Lack of a gold standard to define the exact mechanism of stroke.
  - Focuses on arteriopathy
  - May be expensive to employ or difficult for non-experts to apply
  - Often requires follow-up vascular imaging over time and/or arterial wall imaging to distinguish between minor subtypes
  - Overlap between minor subtypes of intracranial dissection and FCA-d.

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Stroke Types and Subtypes Subgroup: Recommendations

- Overlap between minor subtypes of secondary moyamoya and genetic/syndromic arteriopathy in some cases.
- No separate classification for sickle cell arteriopathy.

- Comments: This system of classification is likely the best method for subclassifying arteriopathies in prospective clinical studies in childhood stroke. The complexity of this system, and its reliance upon trained raters in a multistep process may not make it feasible for all studies. This system provides an updated definition of FCA.

8.2.6. Focal Cerebral Arteriopathy Severity Score (FCASS)

Source: Fullerton HJ, Stence N, Hills NK, Jiang B, Amlie-Lefond C, Bernard TJ, Friedman NR, Ichord R, Mackay MT, Rafay MF, Chabrier S, Steinlin M, Elkind MSV, deVeber GA, Wintermark M; VIPS Investigators. Focal Cerebral Arteriopathy of Childhood: Novel Severity Score and Natural History. Stroke. 2018;49(11):2590-2596.

Comment: The FCASS was designed for the scoring of the severity of Focal Cerebral Arteriopathy. The FCASS score is generated by individually scoring the appearance of five arterial segments (the supracliniod internal carotid artery; M1 and M2 segments of the middle cerebral artery; A1 and A2 segments of the anterior cerebral artery) on MRA, CTA or conventional angiography and then summing the five individual scores. An additional "delta point" applies only to follow-up imaging to indicate progression or improvement not captured by other aspects of the score. The baseline scoring range is 0-20. Scoring range of follow-up imaging is 0-21.

8.3. Etiologic Classification System for Perinatal Stroke

8.3.1. NIH Ischemic Perinatal Stroke Workshop Classification

Source: Raju TN, Nelson KB, Ferriero D, Lynch JK, NICHD-NINDS Perinatal Stroke Workshop Participants. Ischemic perinatal stroke: summary of a workshop sponsored by the National Institute of Child Health and Human Development and the National Institute of Neurological Disorders and Stroke. Pediatrics. 2007~~ September~~;120(3):609-616.

- **Subtypes:**
  - Ischemic Perinatal Stroke:
    - Fetal ischemic stroke: diagnosed before birth by using fetal imaging methods or in stillbirths on the basis of neuropathologic examination
    - Neonatal ischemic stroke: diagnosed after birth and on or before the 28th postnatal day (including in preterm infants)
    - Presumed perinatal ischemic: diagnosed in infants >28 days of age in whom it is presumed (but not certain) that the ischemic event occurred sometime between the 20th week of fetal life through the 28th postnatal day.
- **Number of subtypes: 3**
- **Classification rules:** Based on gestational or postnatal age at diagnosis, clinical stroke features, CT/MRI

NINDS Stroke Common Data Element (CDE) Project

Stroke Types and Subtypes Subgroup: Recommendations

- **Important features:**
  - Specific for perinatal AIS
  - Consensus based
  - Inclusion of all ischemic perinatal strokes
- **Weaknesses/Challenges:**
  - Lack of a gold standard to define the exact mechanism of stroke.
  - Distinguished hemorrhagic stroke from hemorrhagic transformation of an ischemic infarct
  - Does not address perinatal hemorrhagic stroke
  - Established timing of event
  - Inter-rater reliability untested
- **Comments:** This system is a reasonable option for very simple classification based on timing of onset in large scale or broadly inclusive studies of perinatal ischemic stroke, and to distinguish cases of presumed vascular occlusive causation from other types of neonatal cerebral ischemic injury such as global hypoxia-ischemia or periventricular leukomalacia. Additional prospective studies are needed to further evaluate validity and reliability, and its value for prognosis.

8.3.2. Sophia Classification

Source: Govaert P, Ramenghi L, Taal R, de Vries L, Deveber G. Diagnosis of perinatal stroke I: definitions, differential diagnosis and registration. Acta Paediatr. 2009~~ Oct~~;98(10):1556-1567.

- **Classification mechanisms:**
  - Classification of stroke subtypes by vessel affected
    - Neonatal arterial isch~~a~~emic stroke
    - Neonatal cerebral sinovenous thrombosis
    - Haemorrhagic stroke
  - Classification by timing of stroke
    - Fetal stroke
    - Neonatal stroke
    - Presumed fetal or neonatal stroke
  - Composite diagnostic classification
    - Gestational age at birth, by week
    - Birth weight
    - Gender
    - Delivery mode
    - Time of detection
    - Presentation
    - ~~Type of stroke~~

- Vessel (s) affected

- **Number of classification mechanisms:** 3
- **Classification rules:** Based on anatomic location, timing of stroke and clinical stroke features
- **Important Features:**
  - Specific for perinatal cerebrovascular syndromes
  - Inclusive of arterial, venous and hemorrhagic perinatal stroke
  - Simultaneously uses multiple classification mechanisms
- **Weaknesses/Challenges:**
  - Lack of a gold standard to define the exact mechanism of stroke.
  - Difficulty of distinguishing hemorrhagic stroke from hemorrhagic transformation of an ischemic infarct
  - Establishing timing of event
  - Inter-rater reliability untested
- **Comments:** This system is the preferred approach among IPSS investigators for studies of perinatal stroke syndromes. Additional prospective studies are needed to further evaluate validity and reliability, and its value for prognosis.

8.4. Etiologic Classification System for Pediatric Hemorrhagic Stroke

The creation of pediatric specific classification mechanisms for pediatric hemorrhagic stroke is urgently needed. The Sophia classification addresses this need for neonates, but there is little literature about classification of childhood-onset hemorrhagic stroke. Initial work in this area will likely adopt versions of adult classification systems described above.

~~9. References~~

~~Raju TN, Nelson KB, Ferriero D, Lynch JK. Ischemic perinatal stroke: summary of a workshop sponsored by the National Institute of Child Health and Human Development and the National Institute of Neurological Disorders and Stroke. Pediatrics 2007; 120: 609-16.~~

~~Kirton A, DeVeber G, Pontigon AM, MacGregor D, Shroff M. Presumed perinantal ischemic stroke: vascular classification predicts outcomes. Ann.Neurol. 2008, 63: 436-43.~~

~~International Paediatric Stroke Study Definitions~~

Note: Some of the CDE discussed on this document are Supplemental – Highly Recommended. Please see Start-Up document for details.

[Study Name/ID pre-filled]

Site Name:

Subject ID:

Stroke Types and Subtypes CRF Module

Definition of Clinical Stroke (Symptomatic)

"Time-based" Definition: Stroke is a sudden focal neurological deficit of presumed vascular origin lasting >= 24 hours (or fatal within 24 hours).

"Tissue-based" Definition: Symptomatic stroke is a sudden focal neurological deficit, of any duration, due to focal brain, spinal cord, or retinal infarction or hemorrhage. Infarction or hemorrhage may be demonstrated either 1) directly by imaging/laboratory/pathologic examination in patients with symptom duration less than 24 hours, or 2) inferred by symptoms lasting >= 24 hours (or fatal within 24 hours) that cannot be attributed to another cause.

**Has the patient suffered a stroke according to the "time-based" definition?

☐Yes ☐No ☐Unknown

**Has the patient suffered a clinical stroke according to the ~~following~~ tissue-based" definition?

☐Yes ☐No ☐Unknown

Definitions for Clinical Stroke Types (Symptomatic)

**Indicate the type of clinical stroke suffered by the adult patient, using the duration of symptoms to distinguish between ischemic stroke and TIA.

☐Ischemic Stroke

Laterality:

☐ Right

☐ Left

☐Transient Ischemic Attack (TIA)

☐Intracerebral hemorrhage (ICH)

Laterality:

☐ Right

☐ Left

☐Intraventricular hemorrhage (IVH)

☐Subarachnoid hemorrhage (SAH)

☐Clinical Stroke of Uncertain Type

☐Silent Stroke (Clinically Asymptomatic)

Stroke Types and Subtypes CRF Module ~~Subgroup~~

[Study Name/ID pre-filled]

Site Name:

Subject ID:

**Indicate the type of clinical stroke suffered by the adult patient, using tissue status to distinguish between ischemic and TIA.

☐Ischemic Stroke

Laterality:

☐ Right

☐ Left

☐Transient Ischemic Attack (TIA)

☐Intracerebral hemorrhage (ICH)

Laterality:

☐ Right

☐ Left

☐Intraventricular hemorrhage (IVH)

☐Subarachnoid hemorrhage (SAH)

☐Clinical Stroke of Uncertain Type

☐Silent Stroke (Clinically Asymptomatic)

Date information collected:

Ischemic Stroke Subtype Classification Systems

Identify the ischemic stroke subtype based on the acute Ischemic cerebrovascular syndrome (AICS) classification system.

☐Definite AICS

☐Probabl~~ey~~ AICS

☐Possible AICS

☐Not AICS

Identify the Ischemic Stroke Subtype based on the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) Classification System.

☐Large artery atherosclerosis

☐Cardioembolism

☐Small ~~vessel~~ artery occlusion

☐Stroke of other determined etiology

Stroke Types and Subtypes CRF Module ~~Subgroup~~

[Study Name/ID pre-filled]

Site Name:

Subject ID:

☐Stroke of undetermined etiology

Identify the Ischemic Stroke Subtype based on The Causative Classification System's – standard causative subtypes.

☐Large artery atherosclerosis

☐Cardioaortic embolism

☐Small artery occlusion

☐Other uncommon causes

☐Undetermined causes

Identify the Ischemic Stroke Subtype based on The Causative Classification System's – standard phenotypic subtypes.

Evaluate the patients for the predefined phenotype of large artery atherosclerosis.

☐ Major ☐ Minor ☐ Absent ☐ Incomplete evaluation

Evaluate the patients for the predefined phenotype of cardiac embolism.

☐ Major ☐ Minor ☐ Absent ☐ Incomplete evaluation

Evaluate the patients for the predefined phenotype of small artery occlusion.

☐ Major ☐ Absent ☐ Incomplete evaluation

Evaluate the patients for the predefined phenotype of other uncommon causes.

☐ Major ☐ Absent

Identify the Ischemic Stroke Subtype based on the Baltimore-Washington Cooperative Young Stroke Study (BWCYSS) Classification System.

☐Atherosclerotic vasculopathy

☐Nonatherosclerotic vasculopathy

☐Vasculopathy of uncertain cause (lacunar)

☐Cardiac/transcardiac embolism

☐Hematologic/Other

☐ ~~Migraneous~~ Migrainous

☐Oral contraceptive and exogenous estrogen use

☐Other drug related

☐Indeterminate

Stroke Types and Subtypes CRF Module ~~Subgroup~~

[Study Name/ID pre-filled]

Site Name:

Subject ID:

Identify the Ischemic Stroke Subtype based on ASCOD System's – standard phenotypic subtypes.

Evaluate the patients for the predefined phenotype of atherosclerosis (A).

☐0 ☐1 ☐2 ☐3 ☐9

Evaluate the patients for the predefined phenotype of small vessel disease (S).

☐0 ☐1 ☐2 ☐3 ☐9

Evaluate the patients for the predefined phenotype of cardiac source (C).

☐0 ☐1 ☐2 ☐3 ☐9

Evaluate the patients for the predefined phenotype of other cause (O).

☐0 ☐1 ☐2 ☐3 ☐9

Evaluate the patients for the predefined phenotype of dissection (D)

☐0 ☐1 ☐2 ☐3 ☐9

Identify the levels of diagnostic evidence for the ASCO grades.

☐Level A

☐Level B

☐Level C

Identify the Stroke Subtype as defined by the A-S-C-O pattern (e.g., A1-S3-C1-O3)

☐

Identify the Oxfordshire Community Stroke Project (OCSP) subtype classification.

☐Partial anterior circulation infarcts (PACI)

☐Lacunar infarcts (LACI)

☐Posterior circulation infarcts (POCI)

~~☐ Cerebral infarction~~

☐Total anterior circulation infarcts (TACI)

Identify Embolic Stroke of Undetermined Significance (requires all items below to be checked)

☐Non-lacunar stroke

Stroke Types and Subtypes CRF Module ~~Subgroup~~

[Study Name/ID pre-filled] Site Name:

Subject ID:

☐Absence of extracranial or intracranial atherosclerosis causing ≥50% luminal stenosis in arteries supplying the area of ischemia

☐No major risk cardioembolic source of embolism

☐No other specific cause of stroke identified (eg, arteritis, dissection, migraine/vasospasm, and drug abuse)

Intracerebral Hemorrhage Subtype Classification Systems

Indicate the presumed cause(s) of the intracerebral hemorrhage (ICH). Choose all that apply.

☐Hypertensive

☐Amyloid angiopathy

☐Arteriovenous malformation

☐Cavernous hemangioma

☐Venous angioma

☐Aneurysm (if SAH and ICH – then classified as SAH)

☐Anti-coagulant related ICH

☐Thrombolytic ICH (not hemorrhagic transformation of cerebral infarction)

☐Tumor

~~☐Aneurysm~~

☐Other, specify:

☐Undetermined

Intraventricular Hemorrhage Subtype Classification Systems

Indicate the presumed cause(s) of the intraventricular hemorrhage (IVH). Choose all that apply.

☐Hypertensive – Hypertensive ICH is defined as an IVH in the setting of known history of hypertension without another defined structural cause.

☐Arteriovenous malformation

☐Anti-coagulant related IVH

☐Tumor

☐Other, specify (list):

☐Undetermined

Stroke Types and Subtypes CRF Module ~~Subgroup~~

[Study Name/ID pre-filled]

Site Name:

Subject ID:

Indicate Graeb IVH Scale

Table 1 Graeb IVH Scale

Measurement method	Observed Score
Left lateral ventricle score	☐1 ☐2 ☐3 ☐4
Right lateral ventricle score	☐1 ☐2 ☐3 ☐4
Third ventricle score	☐1 ☐2
Fourth ventricle score	☐1 ☐2
Total score	

Subarachnoid Hemorrhage Subtype Classification Systems

Indicate the presumed cause(s) of the subarachnoid hemorrhage (SAH). Choose all that apply.

☐Saccular aneurysm
☐Fusiform aneurysm
☐Mycotic aneurysm
☐Cerebral AVM or other vascular malformation
☐Cerebral tumor
☐Illicit drug use
☐Antithrombotic use
☐Spinal cord AVM
☐Spinal cord tumor
☐Presumed amyloid angiopathy
☐Other, specify:
☐Undetermined

Stroke Types and Subtypes CRF Module ~~Subgroup~~

[Study Name/ID pre-filled]

Site Name:

Subject ID:

SAH Volume Scale ~~(Hijdra)~~

Table 2 SAH Volume Scale

Scale	Observed Score
Hunt Hess scale	☐1 ☐2 ☐3 ☐4 ☐5
Fisher scale	☐1 ☐2 ☐3 ☐4
Modified Fisher scale	☐0 ☐1 ☐2 ☐3 ☐4
Ogilvy subarachnoid hemorrhage (SAH) grading system	☐1 ☐2 ☐3 ☐4 ☐5
Column scale (Hijdra) for the interhemispheric fissure score **Specify laterality: ☐	☐0 ☐1 ☐2 ☐3
Sylvian fissure lateral part left score	☐0 ☐1 ☐2 ☐3

Commented [KG1]: Curation for Hijdra Scale CDEs across Stroke and SAH requires review.

Stroke Types and Subtypes CRF Module ~~Subgroup~~

[Study Name/ID pre-filled]

Site Name:

Subject ID:

Scale	Observed Score
Basal part left score	☐0 ☐1 ☐2 ☐3
Suprasellar cistern left score	☐0 ☐1 ☐2 ☐3
Ambient cistern left score	☐0 ☐1 ☐2 ☐3
Quadrigeminal cistern score	☐0 ☐1 ☐2 ☐3
Total amount of subarachnoid blood. Sum of the scores of the 10 basal cisterns and fissures.	

World Federation of Neurological Surgeons (WFNS) Grading System for subarachnoid hemorrhage scale.

☐1 ☐2 ☐3 ☐4 ☐5

Pediatric Stroke

**Indicate the type of clinical stroke suffered by the child.

☐Childhood arterial ischemic stroke

☐Childhood TIA

~~☐Childhood cerebral sinovenous ischemic stroke~~

☐Childhood intracerebral hemorrhage

☐Childhood subarachnoid hemorrhage

☐Childhood intraventricular hemorrhage

☐Childhood cerebral venous thrombosis

Stroke Types and Subtypes CRF Module ~~Subgroup~~

[Study Name/ID pre-filled] Site Name:

Subject ID:

☐~~Childhood TIA~~

☐Childhood Silent Stroke

**Indicate the type of clinical stroke suffered by the neonate.

☐~~Ischemic perinatal stroke (IPS)~~ **Perinatal arterial ischemic stroke (PAIS)

- ☐~~Neonatal~~ Acute perinatal arterial ischemic stroke ~~(AIS)~~
- ☐Presumed pre- or perinatal stroke
- ☐~~Neonatal cerebral sinovenous ischemic stroke~~

☐~~Presumed pre- or perinatal stroke~~

☐Perinatal intracerebral hemorrhage (ICH)

☐Perinatal subarachnoid hemorrhage (SAH)

☐Perinatal intraventricular hemorrhage (IVH)

☐Perinatal cerebral venous thrombosis (CVT)

☐Periventricular venous infarction (PVI)

Indicate the Pediatric Stroke Classification (PSC) system subtype.

☐Sickle cell disease

☐Cardioembolic

☐Moyamoya Syndrome

☐Cervical arterial dissection

☐Steno-occlusive cerebral arteriopathy

☐Other determined etiology

☐Multiple probable/ possible etiologies

☐Undetermined etiology

Indicate the subtype as related to the Sebire/International Pediatric Stroke Study (IPSS) classification.

☐Arteriopathy associated with sickle cell disease

☐Transient cerebral arteriopathy

☐Moyamoya Syndrome

☐Arterial dissection

☐Chronic inflammatory vasculitis

☐Neurofibromatosis type 1 (NF1)

☐Fibromuscular dysplasia

☐Post irradiation arteriopathy

Stroke Types and Subtypes CRF Module ~~Subgroup~~

[Study Name/ID pre-filled] Site Name:

Subject ID:

☐Metabolic arteriopathies

☐Cryptogenic arteriopathy

Childhood AIS Standardized Classification and Diagnostic ~~Evaulation~~ Evaluation (CASCADE)

Primary Classification: Acute – All patients with defined childhood arterial ischemic stroke will be classified into a single acute primary category, at the time of initial diagnosis (within 1 month of presentation).

☐Small vessel arteriopathy of childhood (SVA)

☐Unilateral focal cerebral arteriopathy of childhood (FCA)

☐Bilateral cerebral arteriopathy of childhood

☐Aortic/ cervical arteriopathy

☐Cardio- embolic

☐Other

☐Undetermined etiology

☐Multi-factorial

Primary Classification: Chronic – Patients with an initial vascular diagnosis (at 0-1 month) for "Primary Classification: Acute" are given a follow-up diagnosis based on studies obtained at or after 3-6 months that will capture any progression, stability or regression of the arteriopathy.

☐Progressive Arteriopathy

☐Stable Arteriopathy

☐Reversible Arteriopathy

☐Indeterminate Arteriopathy

~~Secondary Classification: There may be genetic, inflammatory or other factors which further distinguish groups within the primary disease classifications. These modifying variables will be included in a secondary etiologic or syndromic classification (i.e. varicella, trisomy 21, PHACES syndrome). The diagnoses given here are not a complete list. These are examples. A complete list of secondary classifications is yet to be developed, and is open to suggestions.~~

~~☐Genetic – vasculopathy~~

~~☐Infectious~~

~~☐Hematologic/thrombotic~~

~~☐Inflammatory~~

~~☐Genetic – metabolic~~

~~☐Drug/toxin exposure~~

~~☐ Other, specify:~~

Stroke Types and Subtypes CRF Module ~~Subgroup~~

[Study Name/ID pre-filled]

Site Name:

Subject ID:

Indicate the subtype based on the Vascular effects of Infection in Pediatric Stroke (VIPS) arteriopathy classification system.

Primary diagnosis:

☐No arteriopathy

☐Possible arteriopathy

☐Definite arteriopathy

If definite arteriopathy, indicate secondary diagnosis:

☐Focal cerebral arteriopathy (FCA)

- ☐Focal cerebral arteriopathy - dissection type (FCA-d)
- ☐Focal cerebral arteriopathy - inflammatory type (FCA-i) (includes transient cerebral arteriopathy (TCA))

☐Intracranial arterial dissection This subtype overlaps with FCA-d (above) when dissection occurs in the large intracranial arteries of the anterior circulation.

☐Extracranial arterial dissection

☐Bilateral cerebral arteriopathy of childhood (primary moyamoya disease and secondary moyamoya syndromes)

☐Diffuse/multifocal vasculitis

☐Genetic or syndromic arteriopathy

☐Other

Focal Cerebral Arteriopathy Severity Score (FCASS)

Score supraclinoid ICA:

☐0=no involvement

☐1=irregularity or banding with no stenosis

☐2=stenosis, <50% reduction in diameter

☐3=stenosis, >50% reduction in diameter

☐4=occlusion

Score M1:

☐0=no involvement

☐1=irregularity or banding with no stenosis

☐2=stenosis, <50% reduction in diameter

☐3=stenosis, >50% reduction in diameter

☐4=occlusion

Stroke Types and Subtypes CRF Module ~~Subgroup~~

[Study Name/ID pre-filled]

Site Name:

Subject ID:

Score A1:

☐0=no involvement

☐1=irregularity or banding with no stenosis

☐2=stenosis, <50% reduction in diameter

☐3=stenosis, >50% reduction in diameter

☐4=occlusion

Score M2:

☐0=no involvement

☐1=irregularity or banding with no stenosis

☐3=stenosis

☐4=occlusion

Score A2:

☐0=no involvement

☐1=irregularity or banding with no stenosis

☐3=stenosis

☐4=occlusion

Baseline score: sum the five individual scores (without weighting); the maximum baseline score is 20 (maximum individual segment score of 4 multiplied by 5 arterial segments).

Score Delta Point (only for Follow-up score):

☐+1 if interval worsening (progression) not otherwise captured by the follow-up FCASS

☐-1 if interval improvement not otherwise captured by the follow-up FCASS

Follow-up score: For follow-up imaging, sum the five individual scores (without weighting) and apply the delta point if applicable. The maximum follow-up score is 21 (20 plus the delta point).

Indicate the subtype based on the Ischemic Perinatal Stroke (IPS) Workshop sponsored by NIH in 2007.

☐Fetal ischemic stroke

☐Neonatal ischemic stroke

☐Presumed perinatal ischemic

Stroke Types and Subtypes CRF Module ~~Subgroup~~

[Study Name/ID pre-filled] Site Name:

Subject ID:

Identify the Sophia classification of stroke subtype by vessel affected.

☐Neonatal arterial ischemic stroke (AIS)

☐Neonatal cerebral sinovenous thrombosis (CST)

☐Hemorrhagic stroke

Identify the Sophia classification of stroke subtype by timing of stroke.

☐Fetal stroke

☐Neonatal stroke

☐Presumed fetal or neonatal stroke

Gestational age at birth:

Birth weight:

~~Gender C00035~~

~~☐Female~~

~~☐Male~~

~~☐Unknown~~

~~☐Unspecified~~

~~☐Not reported~~

*Sex assigned at birth:

☐Female

☐Male

☐Intersex

☐Unknown

☐Other, specify:

*Gender identity:

☐Female

☐Male

☐Unknown

☐Other, specify:

Stroke Types and Subtypes CRF Module ~~Subgroup~~

[Study Name/ID pre-filled] Site Name:

Subject ID:

Identify the mother's mode of delivery of the neonate.

☐Spontaneous cephalic vaginal

☐Cephalic vaginal with instrumental traction (vacuum, forceps or both)

☐Breech vaginal

☐Elective caesarean

☐Emergency caesarean

Identify the time of detection of the stroke event in the participant/subject.

☐Fetal

☐Neonatal early/late (day after birth)

☐Presumed fetal or perinatal

Identify the signs and symptoms exhibited by the neonate at presentation.

☐Seizures

☐Other neurological signs, specify:

☐Focal EEG changes

☐Chance findings during routine imaging, specify:

Identify the vessel affected by the stroke event.

☐Arterial cortical

☐Arterial perforator

☐Brainstem or spinal cord arteries

☐Sinus

☐Deep or Pial Vein

☐Lobar or Subarachnoid

Identify the imaging method at detection.

☐Ultrasound

☐MRI/MRA/MRV

☐CT

☐Other, specify:

Stroke Types and Subtypes CRF Module ~~Subgroup~~

[Study Name/ID pre-filled] Site Name:

Subject ID:

General Instructions

This CRF contains data to define clinical stroke, stroke types, ischemic stroke subtypes, intracerebral hemorrhage subtypes, intraventricular hemorrhage subtype, subarachnoid hemorrhage subtype and pediatric stroke types.

Note: Some of the CDE discussed on this document are Core and Supplemental – Highly Recommended as indicated by asterisks below. Please see Start-Up document for details.

*Element is classified as Core

**Element is classified as Supplemental – Highly Recommended

The remaining data elements are Supplemental and should only be collected if the research team considers them appropriate for their study.

Specific Instructions

Please see the Recommendations document above and Data Dictionary for definitions for each of the data elements included in this CRF Module.