Workshop Materials

Discussion Paper: "Acute Ischemic Stroke Medical Device Trials Workshop"

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I. Introduction

The United States Food and Drug Administration (FDA) is releasing this discussion paper in preparation for the "Acute Ischemic Stroke Medical Device Trials" public workshop, which will be held at the Bethesda Marriott (5151 Pooks Hill Road, Bethesda, Maryland 20814) on October 6, 2015. The Agency is holding this workshop to open discussion among stakeholders (e.g., manufacturers, health care professionals, patients, patient advocates, academia, and other government agencies) and obtain their feedback on scientific and clinical considerations associated with challenges in the development of medical device trials for acute ischemic stroke.

The FDA will use information from the workshop to develop an overall strategy to promote advances in this technology while maintaining appropriate patient protections. This workshop will inform the development of FDA guidance on clinical trial design and premarket submissions for evaluating acute ischemic stroke devices, and help to facilitate the development and approval or clearance of future submissions.

Acute ischemic stroke medical devices are intended to retrieve or remove blood clots from the cerebral neurovasculature. This could potentially be achieved through a variety of mechanisms, such as via mechanical, laser, ultrasound, or a combination of technologies. Investigational studies of acute ischemic stroke medical devices have revealed challenges with assessing the safety and effectiveness of these devices as well as challenges in study design and data analysis when reviewing clinical studies.

This discussion paper provides background information and questions for workshop attendees to consider in advance and will help facilitate discussion. While the scientific and clinical considerations for acute ischemic stroke devices provided represent FDA's focus, we look forward to hearing other considerations and questions at the workshop.

The information and questions contained in this document are not binding and do not create new requirements or expectations for affected parties, nor is this document meant to convey FDA's recommended approaches or guidance. Rather the information contained in this document offers background and the basis for discussions at the Public Workshop.

II. Scientific and Clinical Considerations for Acute Ischemic Stroke Devices

The field of acute ischemic stroke medical devices is progressing rapidly from proof-of-concept to clinical applications. The FDA recognizes the value of supporting medical device innovation to address clinical needs that improve patient care, particularly when alternative treatments are unavailable, ineffective, or associated with substantial risks to patient safety.

The information contained in this background document presents scientific, clinical, and regulatory issues associated with acute ischemic stroke medical devices, including the following topic areas:

A. Clinical Study Design and Patient Populations

B. Clinical Outcomes, Imaging Assessments, and Safety Endpoints

C. Statistical Considerations

D. Registries

A. Clinical Study Design and Patient Populations

Clinical Study Design

FDA generally recommends well controlled studies, such as randomized controlled trials (RCTs), for device approval or clearance. Well controlled studies typically involve the investigational device and a control comparator randomly assigned to patients to provide a head-to-head comparison. For acute ischemic stroke, control treatments include best medical management (standard of care) and acute ischemic stroke medical devices legally marketed in the United States (US).

A strong advantage of an RCT is that the device is concurrently compared to a control, using the same pool of patients. Randomization and a concurrent control allow individual characteristics of patients to be probabilistically balanced across groups, and thus, the only systematic difference

between groups is the treatment received. Because of this, RCTs can provide an unbiased assessment of benefits and risks associated with both the device and the proposed indication for use.

While an RCT is the gold standard of trial design for supporting a marketing submission, other trials designs may be considered. For example, a single-arm study may be an option if a control group cannot be identified or is considered unethical. With this type of study, the performance of the device is compared to a prospectively specified numerical target value (i.e., objective performance criterion (OPC) or performance goal (PG)). An OPC is a numerical target value typically derived from historical data from prior clinical studies, including a meta-analysis of several studies. If a meta-analysis is used, it should include all relevant studies and sources. The meta-analysis can provide a point estimate of the clinical outcome that summarizes the outcomes of the prior studies and/or registries. A PG refers to a numerical value (point estimate) that is considered sufficient by FDA for use as a comparison for a safety and/or effectiveness endpoint. In some instances, a PG may be based on the upper (or lower) confidence limit of a prior effectiveness and/or safety estimate from prior clinical studies. In a single-arm study, a confidence interval limit from the proposed clinical study is compared to the OPC or PG to decide if the study result meets the OPC or PG to demonstrate success.

Single-arm clinical studies are by definition smaller than two-arm studies. In addition, the characteristics of patients in the prospective studies can be very different from those of the patients in the prior studies on which an OPC or PG is based. Single-arm clinical studies do not directly control for such potential confounding covariates. Furthermore, OPCs and PGs can become obsolete over time as the device technology improves and/or matures and as surgical techniques improve.

Questions for Consideration:

1. For acute ischemic stroke medical devices, what are appropriate control therapies? If a control arm is “standard of care,” should it be limited to relatively few treatments? A potential concern with unlimited choice in standard of care is that the observed control

group performance may be difficult to characterize and interpret due to heterogeneity of treatment strategies.

2. In some cases, patients may require concurrent therapies (such as an acute ischemic stroke medical device in addition to carotid stenting). How should these multiple-therapy patients be analyzed if the active treatment group is the acute ischemic stroke device?
3. Are there situations where an OPC or PG is appropriate (e.g., based on intended use, etc.)? What are acceptable sources of information for developing an OPC or PG in addition to prior clinical studies and/or registries? How should we account for uncertainty in the estimation of an OPC or PG from a meta-analysis of prior studies?
4. In what situations in the development of an acute ischemic stroke medical device could a clinical trial not be necessary or should it be required for all acute ischemic stroke technologies given that this is a high risk patient population?

Patient Populations

Patients with acute ischemic stroke have varying background or baseline characteristics which may predict their potential benefit and/or risks from treatment interventions and long-term outcomes. Different patient characteristics, such as gender, age, ethnicity, and varying co-morbidities may affect the evaluation and/or treatment options. In addition, patient outcomes may be impacted by the acute ischemic stroke presentation (e.g., differences in time of symptom onset, baseline severity, location, etc.). At the current time, neurothrombectomy devices (i.e., mechanical clot retrieval devices) are cleared for revascularization in patients who present with large vessel stroke and a persistent arterial occlusion with treatment to be initiated within 8 hours of symptom onset. FDA has not limited therapy to specific vascular distributions or further specified populations intended for therapy. Patients often present with stroke outside the FDA cleared 8-hour time window or present with uncertain time of onset (e.g., wake-up stroke). Therefore, the data supporting currently cleared devices may not cover the breadth of patient experiences and characteristics commonly seen in clinical practice.

In order to identify patients who may have increased benefit and/or reduced risk from neurothrombectomy, developers and innovators have explored a variety of selection criteria based on baseline characteristics of the patient and/or the stroke presentation. While such

selection criteria may be helpful in patients who present within 8 hours from stroke onset, they may be most critical for patients who present outside the time frame for which there is clinical data. As we move toward a more selective approach to patient eligibility for different treatments, the role of neuroimaging is becoming more important in identifying suitable candidates for therapy. Neuroimaging examples include the use of diffusion and perfusion mismatch on magnetic resonance imaging (MRI), ischemic penumbra on computed tomography (CT) perfusion scans, and use of rating systems such as the Alberta Stroke Program Early CT Score (ASPECTS) to potentially select patients who are more likely to benefit from revascularization via neurothrombectomy. However, many questions have yet to be answered with regard to identifying patients who are most likely to benefit from acute ischemic stroke medical device therapies and how to most effectively mitigate risk.

Certain enrichment strategies can focus a clinical trial on an appropriate patient population based on the prospectively specified characteristics of patients who respond best to a therapy. An enrichment segment might be included within an initial feasibility phase prior to a pivotal trial, or could be included within a pivotal trial where the patient population is altered midway based on accruing results. There may be statistical consequences depending on the strategy chosen. We discuss these strategies in more detail in a later section.

Questions for Consideration:

1. Mechanical neurothrombectomy devices have been cleared with clinical studies evaluating patients within 8 hours of symptom onset. However, there may be subgroups of patients that warrant examination in future mechanical neurothrombectomy studies to expand the safe and effective clinical use of these devices to a wider patient population. Some populations to consider may be patients with varying presentations based on time from symptom onset, vascular distribution of stroke, infarct location, and/or infarct size. What are some unique risks and/or benefits that may be present in these or alternative subgroups? How should these issues be addressed in clinical trials?
2. How can we design studies to select patients most suitable for particular acute ischemic stroke medical devices? It is possible that common stroke patient characteristics exist that can be applied to all acute ischemic stroke medical device trials when determining

inclusion and exclusion criteria for patient enrollment. How would such characteristics be identified prospectively and validated? This may include selecting certain types of patients (e.g., specific anatomical location) or including assessments such as validated instruments or imaging tools. Are there certain types of patients that can be identified for enrollment in a clinical trial (e.g., stroke presenting in a specific anatomical location) in which the safety and effectiveness of the acute ischemic stroke medical device can be generalized to all acute ischemic stroke patients (e.g., stroke presenting anywhere in the neurovasculature)? What specific patient characteristics can and cannot be generalized?

3. To date, no single imaging assessment or combination of assessments has been universally identified as the best predictor of which patient populations may benefit most from revascularization or treatment with acute ischemic stroke medical devices. How would such an assessment be identified? How would differences in the type of imaging assessments used to select patients for acute ischemic stroke clinical trials affect treatment and outcomes of patients with these devices? If you believe that the decision to identify appropriate treatment patient populations with an acute ischemic stroke device should be based on clinical judgment and standard of care, how would this be correlated with published data?
4. The patient population in which the cleared mechanical neurothrombectomy devices were studied for revascularization included those who failed or were ineligible for intravenous thrombolytics, which is the most widely accepted standard of care for acute ischemic stroke patients. Recent publications have shown that clinical evaluations of these mechanical neurothrombectomy devices exhibit successes in treating this patient population combined with the use of intravenous thrombolytics. For novel acute ischemic stroke treatment (aside from mechanical neurothrombectomy devices), is there a patient population that can be defined in which clinical equipoise still exists? If so, how can we define these patients?
5. How can we use enrichment strategies so that devices benefit the most appropriate patients?

B. Clinical Outcomes, Imaging Assessments, and Safety Endpoints

Several tools have been used to evaluate the clinical status of patients before enrollment and during a clinical trial. However, no single outcome measure can predict all of the aspects of stroke recovery.

Clinical Outcomes

Stroke outcome can be dependent on a number of factors including recanalization, neurological deficit, ability to perform tasks and/or engage in activities of daily living, and quality of life. Tools that are frequently used to measure stroke outcome include the National Institutes of Health Stroke Scale (NIHSS) score, modified Rankin Scale (mRS), Barthel Index (BI), and Stroke Impact Scale (SIS). The NIHSS is an impairment scale and a systematic assessment tool that provides a quantitative measurement of stroke-related neurologic deficit. It is often used to obtain baseline data to determine patient eligibility for treatment, establish stroke severity and predict patient outcome. It does not provide an assessment of disability or function. The mRS, BI, and SIS are measures reflecting disability (activities dimension) or handicap (participation dimension), and are often used as primary or secondary outcome measures in acute stroke trials.

Each metric has its own strengths and weaknesses. As one example, the mRS is frequently used as a measure of disability; however, its inter-observer variability is a potential weakness. The mRS incorporates components of body function, activity, and participation. However, the mRS does not directly measure other sources of disability, such as those directly related to the neurological deficit (e.g., vision loss, language impairment, cognitive dysfunction, pain, etc.) nor does it account for other non-stroke causes of disability (e.g., concomitant leg fracture). There are also multiple versions of the mRS available and clinical trials may include different ranges of scores which are clinically meaningful. This variability can make comparison or data pooling between studies challenging.

The clinical metric scales mentioned above use ordinal rankings. However, typical use of the scales categorizes several rankings into a “success” or “responder” category, and the remaining rankings into a “failure” category. Dichotomization of ordinal scales may provide an easier

interpretation of results, but it can also reduce the amount of information available from a study because it does not account for any incremental improvements between the ranks within a category. A common criticism of ordinal scales such as those above is that the rankings may not represent meaningful categories of the benefit and/or risk to a patient. In particular, the rank numbers themselves do not have numerical meaning or utility.

Surrogate measures, such as the use of a radiographic marker for recanalization, are also often used in acute ischemic stroke trials. Surrogate measures should be reproducible, not interfere with other interventions, be easy to perform, and sensitive to changes produced by the intervention. The mechanical neurothrombectomy devices that are currently on the market are cleared for revascularization claims based on radiographic recanalization measures. However, the correlation between revascularization and functional outcomes has been unclear. Future studies may help shed light on the complex relationship between vessel occlusion, recanalization, and functional outcomes.

Questions for Consideration:

1. A variety of clinical metrics have been developed and utilized to provide measurements of stroke related disability and/or functional outcome in acute ischemic stroke clinical trials. What are key primary and secondary outcome measures that should be used routinely in clinical trials for acute ischemic stroke medical devices? What is the range of scores on these scales that is most indicative of a clinically meaningful improvement?
2. Are incremental improvements in ordinal rankings such as the mRS clinically meaningful to patients and physicians, or must a device increase the likelihood of being a "responder" (e.g., mRS ≤ 2) compared to a control in order to be considered effective? Can a treatment that shifts the assessment toward the more favorable end of the scale be meaningful even if the treatment does not significantly increase the proportion of "responders?"
3. What is the relationship between revascularization and functional outcomes?
4. What is the role of patient reported outcomes (PROs) and are there methods to obtain PROs that are most meaningful to patients? To what extent do meaningful PROs

contribute to the ability to clear or approve a device with respect to other clinical and/or imaging assessments?

Imaging Assessments

Imaging has been used within acute ischemic stroke clinical trials at various time points for a variety of reasons, including determining eligibility, assessing severity of the stroke, monitoring patients during a study, or as an outcome measure. Revascularization, as measured by imaging, has varied widely across clinical trials from imaging modality used to acquire the data (MRI versus CT versus digital subtraction angiography) to post-processing software algorithms and quantitative measurements to qualitative image assessment scales (e.g., Thrombolysis in Cerebral Infarction [TICI], modified TICI, or Thrombolysis in Myocardial Infarction [TIMI] to measure the degree of recanalization).

Consistent use of imaging within the patient population and within and across clinical trials may reduce the variability introduced during image acquisition, post processing, and interpretation. In addition, using the same imaging technique within the patient population over the duration of the clinical trial may provide additional insight into disease progression and treatment effectiveness. Furthermore, using a uniform grading scheme across clinical studies is preferable to facilitate comparison or data pooling between studies.

Questions for Consideration:

1. What imaging modalities, tools, and/or assessments should be used routinely in acute ischemic stroke medical device clinical studies? What qualitative assessment scales are preferred? For example, what angiographic grading scheme (such as TICI or modified TICI) is preferred in acute ischemic stroke medical device clinical studies and why?
2. What are the benefits and challenges of using consistent imaging assessments before and after treatment within the patient population in the same clinical trial and across all acute ischemic stroke clinical trials? How can the challenges be minimized?

Safety Endpoints

In general, devices indicated for the treatment of acute ischemic stroke have been categorized as significant risk devices and therefore warrant study under an IDE application. Assessing safety is an important measure for all medical device studies, including neurothrombectomy studies. The clinical studies of neurothrombectomy devices to date have identified a number of safety endpoints, including risks of symptomatic intracerebral hemorrhage (sICH), new ischemic stroke in different vascular territory, and death. Measuring and evaluating the rate of adverse events in neurothrombectomy medical device studies is important to FDA.

Questions for Consideration:

1. What risks (besides intracerebral hemorrhage, new stroke, or death) are unique to patients eligible for mechanical neurothrombectomy and warrant further investigation? Have any signals emerged from the recent published literature that suggests there are unique risks or adverse events associated with current or novel acute ischemic stroke medical devices? What common risks can be applied to all acute ischemic stroke patients when designing safety endpoints for clinical studies of acute ischemic stroke medical devices?
2. We have previously required intracranial hemorrhage with a change in the National Institutes of Health Stroke Scale (NIHSS) of $\geq$ 4 points as evidence of neurologic deterioration in acute ischemic stroke device trials. What alternative or more meaningful methods of assessing neurologic deterioration could be included in clinical studies to assess the safety of novel acute ischemic stroke medical devices?
3. What stopping rules should be utilized to best protect patients from unknown or known risks associated with acute ischemic stroke medical devices?
4. Given our concerns for the translation of patient safety in the clinical trial setting to the "real world" following premarket approval or clearance of acute ischemic stroke medical devices, would the establishment of a Registry be beneficial and should it be a requirement and condition of approval/clearance for all acute ischemic stroke medical devices? If so, what information should be collected in the Registry? (Please refer to discussion of Registries below in "Leveraging Data Across Studies.")

5. With the development of novel acute ischemic stroke medical devices, in order to specify an appropriate patient population, the patients selected may have been treated with previous medical therapies. What are the increased risks to patients if multiple acute ischemic stroke medical therapies are used on the same patient and how should these risks be captured/mitigated in the clinical trial design?

C. Statistical Considerations

Heterogeneity across Studies and Within Studies

Several studies have been published in recent months that suggest a benefit of mechanical neurothrombectomy devices for the treatment of acute ischemic stroke with persistent large vessel occlusion. However, these studies have used different enrollment and selection criteria, employed various medical devices, and allowed a number of different therapies to be instituted at the same time as the mechanical neurothrombectomy devices (including intravenous thrombolytics, other mechanical treatments, and concomitant procedures such as stenting). Such heterogeneity across studies can make it challenging to form overall interpretations of treatment benefits and risks, especially when using meta-analyses to determine OPC or PG.

In addition, within a single study, acute ischemic stroke patients can have varying infarct or clot sizes, varying infarct locations, different prior uses of intravenous tissue plasminogen activator (IV t-PA) therapy, different imaging assessments, and different windows of time since last seen well. Devices for treating acute ischemic stroke may be capable of treating heterogeneous instances of stroke occurrence, with potentially varying treatment effect sizes. However, the sample sizes needed to demonstrate an individual device's effectiveness or safety for each type of acute ischemic stroke may be burdensome for a single trial, especially for infarcts in rarely occurring regions such as the posterior circulation.

At the time of designing a study, there are several methods for reducing heterogeneity within a study. First, one might define entry criteria such that enrolled patients are likely to be somewhat homogeneous. For example, enrolling high risk patients who are more likely to benefit from treatment, or enrolling non-responders to a standard of care who may be less likely to exhibit a

placebo response might ensure a homogeneous patient population. Stratification by a baseline covariate (including stratified randomization) is another method for reducing heterogeneity in the assessment of a treatment effect.

The enrollment criteria may be adapted in a prospectively specified manner as the trial proceeds. As mentioned in a previous section, adaptive enrichment strategies alter the patient population midway through a trial based on trial results. The eligibility criteria for the trial are modified so that characteristics from patients who have received the most benefit from the active treatment are considered when enrolling new patients into the trial. As such, not only will the effect size likely be larger, but the number of patients needed to achieve statistical significance may be reduced. Adaptive design modifications are recommended to be planned in advance, while also considering the effect on decision error rates and statistical inference so that the trial's integrity and validity are maintained.

A potential risk in using adaptive enrichment strategies is narrowing to a suboptimal population by chance. Simulations can be useful evaluate the adaptive enrichment strategies during the study design stage to mitigate that risk. It is also important to note that the less responsive population may indeed benefit from the device, just not as much. Therefore, depending on the intended indication, it might be beneficial to design the statistical analysis so that the overall population can be tested as well, or at least evaluated for safety considerations.

Combining Subgroups within the Study

A trial's patient population may contain heterogeneous subgroups such as strokes in different locations, sizes, or etiologies. There are multiple potential options for analyzing the safety and effectiveness of a device across subgroups.

One option pools all patients together regardless of known heterogeneity among their stroke characteristics. This option is advantageous in situations where the heterogeneity is independent of the performance of the device. A disadvantage to this option is that it will be difficult to determine in which patient population the device might work best or not at all. Stratified randomization may help so that roughly equal numbers of treatment and control patients fall

within each stroke stratum. The subsequent analysis then averages over strata to obtain an averaged effect of the device.

A second option is similar to the stratified analysis, but the treatment effect estimate within each stratum borrows or leverages information from the other strata. With this option, it may be possible to gain enough power through borrowing so that stratum-specific treatment effect estimates can be declared statistically significant more easily than if they were each studied in a stand-alone trial. A disadvantage of this option is that in order for each subgroup or stratum to borrow information from other subgroups, it is expected that their treatment effects are roughly similar to each other. Otherwise, borrowing may allow a subgroup or stratum to show a significant treatment effect when the observed effect alone is weaker.

A third option is to study each subgroup or stratum separately so that it is clear where the device works or not. This option requires sufficient number of patients for each subgroup to provide appropriate statistical power. However, powering each subgroup separately may result in a large sample size such that the study may become infeasible.

Leveraging Data across Studies

A number of recently published studies (including randomized controlled trials) have compared neurothrombectomy devices plus medical therapy to medical therapy alone. The information available from these studies may be useful for future studies of neurothrombectomy devices. As with the previous section on combining information across subgroups, a Sponsor with a new device could leverage information about similar neurothrombectomy devices that were studied in other trials. For example, suppose a company proposes an indication for a device to treat acute ischemic stroke in both the anterior and posterior circulation areas. The device may be expected to perform similarly as other devices in the anterior region, but the posterior region may not be well-studied. The company may be able to use statistical modeling to incorporate the wealth of information about the anterior circulation from the prior studies, while collecting prospective data about the device's performance mainly in the posterior circulation. If the prior studies also have information about the posterior circulation, then that information could be combined with the prospective data from the new device, as well. Doing so may lessen the burden of collecting

new, prospective data on a device that may be expected to perform similarly as the approved devices.

In addition to borrowing strength from prior studies, a proposed medical device trial may be able to use a historical control constructed from patient-level data available from the prior studies or construct a PG or an OPC from a meta-analysis of the prior studies. For the former, the distribution of patient characteristics from the pool of potential historical control patients should have sufficient overlap with the distribution of patient characteristics from the proposed trial. Otherwise, different distributions of patient characteristics across treatment groups may be responsible for clinical outcomes, rather than the treatment applied. Therefore, if a proposed trial intends to use a historical control, selection criteria should ensure sufficient overlap with a subset of the pool of potential historical controls. Note that randomization to treatment groups essentially eliminates this concern (see section on Clinical Study Design and Patient Populations). The same concern applies to creating an OPC from historical data.

Questions for Consideration:

1. What key criteria should be considered to allow combining patients across heterogeneous subgroups (e.g., with different locations, size and etiology of stroke) in order to make a broader device indication?
2. What approaches in clinical trial design are preferred to adequately capture and appropriately interpret information regarding acute ischemic strokes in vascular territories that may present less frequently than others?
3. What criteria or mechanism(s) can be used to allow data borrowing among multiple studies or subgroups? How can a prospective study be designed to leverage such data borrowing? Under what circumstances can borrowing be useful (e.g., if a pivotal study has a sparse number of patients for a certain patient/stroke subgroup, can an applicant still make labeling claims regarding the subgroup by borrowing information from other subgroups that are deemed to be sufficiently "similar")? To what extent should data be borrowed across studies?

D. Registries

Development of registries for clinical data collection is consistent with FDA's plans to create a national post-market medical device evaluation and surveillance system that can serve multiple functions throughout the total product life cycle (TPLC). In September 2012, the FDA released a report, entitled "Strengthening Our National System for Medical Device Postmarket Surveillance," which provides an overview of FDA's medical device postmarket authorities, the current U.S. medical device postmarket surveillance system, and which proposes four specific initiatives using existing resources and under current authorities to strengthen the medical device postmarket surveillance system in the United States including promoting the development of National and International device Registries for selected products.

http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/UCM301924.pdf

The update to the report, issued in 2013, details the concrete steps that FDA will complete to develop an integrated system that achieves its four basic functions (from timely identification of postmarket signals to facilitating premarket device clearance and approval) efficiently and effectively.

http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/ucm301912.htm

In both reports, FDA described its vision for an integrated medical device surveillance system that is embedded in the national health care delivery system and could serve all stakeholders throughout the entire product life cycle

FDA vision led to the establishment of the National Medical Device Registry Task Force, a multi-stakeholder group of experts convened via Medical Device Epidemiology Network (MDEpiNet) Public Private Partnership. In August of 2015 the Registry Task Force released its comprehensive report announcing recommendations for the development of the strategically Coordinated Registry Networks (CRNs) to build the foundation of the national medical device evaluation system.

http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/UCM459368.pdf

Within the context of acute ischemic stroke and acknowledging that the registries linked to other electronic data sources could serve as a strong foundation for advancing opportunities for data collection, harmonizing definitions around medical devices, and doing the ground work for the future nesting of clinical trials in existing registries, the use of registries may accelerate the safe and effective development of neurothrombectomy devices. Registries often contain longer term data on patients or can be linked to other electronic data sources (e.g., electronic health records (EHR), claims data) allowing the creation of the longitudinal file. Registry information can help design new studies with longer term endpoints, or could be used to develop the PG. Moreover, if an intervention becomes common for a certain indication, the proportion of patients treated by the intervention may reflect that in a registry. In addition, a sizeable registry can provide a good pool of potential historical controls that sufficiently overlap with the prospective study in distribution of patient characteristics. However, the lack of accessible registries can be a limiting factor. Also, registries may focus on collecting safety outcomes (e.g., mortality), rather than functional or neurological outcomes. In addition to a proper design, a high quality registry also requires ongoing resource for maintenance, such as data quality monitoring and a sustained effort to recruit patients.

Questions for Consideration:

1. How can registries be leveraged in the design of new acute ischemic stroke studies? What procedures should be used to construct new registries, if existing ones are not accessible or lack important information?
2. How can we support the development of common definitions and develop common data elements that are entered into Registries? What is the role of professional medical societies and FDA in this effort? How can Registry data best be utilized to create sufficient value to all potential stakeholders so as to enable sustainability of the Registry?

III. Submitting Public Comments

Regardless of attendance at the public workshop, if you have information related to this workshop that you wish the FDA to consider, please post your material to Docket Number FDA-2014-N-1130 at http://www.regulations.gov. Instructions for posting material can be found at: http://www.fda.gov/RegulatoryInformation/Dockets/Comments/ucm089193.htm or in writing to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852 (Docket ID: FDA-2014-N-1130). Both individuals and groups may submit materials.

Please note that the docket will be public, and not appropriate for addressing individual confidential medical device concerns

IV. Appendix A: A Backgrounder on Medical Device Regulation

For general information on how to market a medical device please refer to the following FDA website: http://www.fda.gov/training/cdrhlearn/default.htm. This is a link to the CDRH web page for multimedia industry education that includes learning modules describing many aspects of medical device and radiation emitting product regulations, covering both premarket and postmarket topics.

Additional resources are provided as follows:

A. Medical Device Classification

There are three classes of devices: Class I (general controls), Class II (special controls), and Class III (premarket approval), with the level of regulatory control increasing from Class I to Class III based on the types of regulatory controls considered necessary to provide reasonable assurance of safety and effectiveness. For more information on device classification please refer to the following FDA website:

http://www.fda.gov/medicaldevices/deviceregulationandguidance/overview/classifyyourdevice/default.htm

B. Marketing Applications

Information on the various types of marketing applications can be found on the following

FDA websites:

i. Premarket Notification (510(k)): http://www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/premarketsubmissions/premarketnotification510k/default.htm
ii. Premarket Approval (PMA): http://www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/premarketsubmissions/premarketapprovalpma/default.htm

iii. Humanitarian Device Exemption (HDE): http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/HumanitarianDeviceExemption/default.htm

iv. Evaluation of Automatic Class III Designation (De Novo Classification Process): http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM273903.pdf

C. Investigational Device Exemptions (IDEs)

Section 520(g) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) establishes a framework for FDA to study medical devices for investigational use. This provides an exemption from certain requirements so that experts qualified by scientific training and experience can investigate their devices' safety and effectiveness. This exemption is known as an Investigational Device Exemption (IDE). The FDA considers acute ischemic stroke medical devices to be "significant risk devices" because they are "for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject." In order to study a significant risk device in human subjects, a sponsor (defined here as the person responsible for initiating the investigation) must receive approval of an investigational device exemption (IDE) application prior to beginning the investigation. Investigational acute ischemic stroke medical devices (as defined above for purposes of this workshop) are generally evaluated by the Division of Neurological and Physical Medicine Devices (DNPMD), one of seven divisions in CDRH's Office of Device Evaluation (ODE).

A number of pathways exist to study acute ischemic stroke medical devices including:

- Early Feasibility Study (EFS): A limited clinical investigation of a device early in development, typically before the device design has been finalized, for a specific indication (e.g., innovative device for a new or established intended use, marketed device for a novel clinical application).
- First in Human (FIH) Study: A type of study in which a device for a specific indication is evaluated for the first time in human subjects.

- Traditional Feasibility Study: A clinical investigation that is commonly used to capture preliminary safety and effectiveness information on a near-final or final device design to adequately plan an appropriate pivotal study.
- Pivotal Study: A clinical investigation designed to collect definitive evidence of the safety and effectiveness of a device for a specified intended use, typically in a statistically justified number of subjects. It may or may not be preceded by an early and/or a traditional feasibility study.

D. Medical Device Master Files (MAFs)

Often a sponsor submitting a premarket submission (i.e., an applicant) needs to use another party's product (e.g., ingredient, subassembly, or accessory) or facility in the manufacture of the device. In order that a sound scientific evaluation may be made of the premarket medical device submission, the review of data and other information related to the other party's product, facility, or manufacturing procedures is required. The other party, while willing to allow FDA's confidential review of this information, may not want the applicant to have direct access to the information. To help preserve the trade secrets of the ancillary medical device industry and at the same time facilitate the sound scientific evaluation of medical devices, FDA established the device master file system. Please refer to the following FDA webpage for additional information on device master files:

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/ucm142714.htm

Table 1 – Factors to Consider when Evaluating Benefits and Risks

Considerations for Assessing Benefits	**Considerations for Assessing Risks**
• Type • Magnitude • Probability of patient experiencing one or more benefit • Duration of effect(s)	• Severity, type, number and rates of harmful events associated with the device • Probability of harmful event • Duration of harmful event
Additional Benefit-Risk Considerations	
• Type of submission • Stage of Device Development • Uncertainty • Characterization of Disease • Patient tolerance for risk and perspective on benefit • Availability of alternative treatments • Risk Mitigation	

V. Appendix B: FDA Guidance Documents

The following is a list of current FDA guidance documents that may of interest when developing premarket submissions:

Benefit-Risk

- "Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications" http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM296379.pdf

IDE

- "Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies" http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm279103.pdf
- "FDA Decisions for Investigational Device Exemption Clinical Investigations" http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm279107.pdf
- "Design Considerations for Pivotal Clinical Investigations for Medical Devices" http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM373766.pdf

510(k)

- "The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]" http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM284443.pdf

Pre-Submission

- "Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff" http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf

PMA

- "Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products" http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm332181.pdf
- "Adaptive Designs for Medical Device Clinical Studies" http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm446729.pdf

Technical

- "Recognition and Use of Consensus Standards" http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm077295.pdf
- "Establishing Safety and Compatibility of Passive Implants in the Magnetic Resonance (MR) Environment" http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm107708.pdf
- "Pre-Clinical and Clinical Studies for Neurothrombectomy Devices" http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071405.pdf

Report on Good Guidance Practices

- "Food and Drug Administration Report on Good Guidance Practices" http://www.fda.gov/downloads/AboutFDA/Transparency/TransparencyInitiative/UCM285124.pdf

VI. Appendix C: Glossary of Acronyms and Abbreviations

510(k) - Premarket Notification Submission

ASPECTS - Alberta Stroke Program Early CT Score

BI - Barthel Index

CT - Computer Tomography

FDA - United States Food and Drug Administration

HDE - Humanitarian Device Exemption

IDE - Investigational Device Exemption

IV t-PA - Intravenous Tissue Plasminogen Activator

MAF - Medical Device Master Files

MRI - Magnetic Resonance Imaging

mRS - modified Rankin Scale

NIH - National Institutes of Health

NIHSS - National Institutes of Health Stroke Scale

OPC - Objective Performance Criteria

PG - Performance Goal

PMA - Premarket Approval

RCT - Randomized Controlled Trial

sICH - Symptomatic Intracebral Hemorrhage

SIS - Stroke Impact Scale

TICI - Thrombolysis in Cerebral Infarction

TIMI - Thrombolysis in Myocardial Infarction

TOSO - Time of Symptom Onset