management. According to the applicant, early theoretical outcomes evaluations provide reason to be optimistic.

We noted in the proposed rule that the studies the applicant submitted to support its assertions regarding substantial clinical improvement were presented only as posters, and that information pertaining to full manuscripts with further study details were not provided. We stated that it is also unclear if the studies described in the posters have been submitted for peer-reviewed publication or whether full manuscripts with detailed methods and data tables are available.

We stated in the proposed rule that we are concerned that the studies do not appear to be designed or powered to be able to show conclusive evidence of clinical impact. In particular, the studies appear to describe analysis of clinical results for patients and state that there is potential for the results to impact clinical decisions about antimicrobial therapy. However, it appears the applicant did not submit evidence of the BioFire® FilmArray® Pneumonia Panel product in real-world, prospective use (randomized or non-randomized) with actual antimicrobial decisions or effect on patient management. This may require larger sample sizes. We stated that we are also concerned that only one study provided by the applicant (Enne, et al.) compared BioFire® FilmArray® Pneumonia Panel to Curetis Unyvero™, which is another PCR-based technology, and that a statistical difference was not reported between BioFire and Unyvero for the outcomes reported in the poster. While we understand that Curetis Unyvero™ may be somewhat slower than BioFire® FilmArray® Pneumonia Panel and does not include viruses, the clinical impact of the differences between these two products is unclear. We stated that we are also uncertain how Buchan, et al. calculated their estimate that >18,000 antibiotic hours were saved on 243 patients using the BioFire® FilmArray® Pneumonia Panel results. The applicant stated that there are currently several prospective studies underway to clarify the role that this tool may play in improving the outcomes for patients with pneumonia, reducing use of unnecessary antibiotics, improving targeted therapy and potentially reducing health care costs due to more directed and efficient patient management; however, data or results from those studies were not included with the application. We invited public comment on whether the BioFire® FilmArray® Pneumonia Panel meets the substantial clinical improvement criterion.

Comment: One commenter suggested that the BioFire® FilmArray® Pneumonia Panel, as well as other rapid infectious diseases diagnostics tests, be evaluated based on their clinical improvements over historical microbiology testing methods as opposed to other rapid tests currently in the marketplace.

Response: We appreciate the commenter's input and suggestion. We note that consistent with our current approach in evaluating the new technology add-on payment substantial clinical improvement criterion we accept a wide range of data and other evidence to support the conclusion of substantial clinical improvement, including data regarding historical technologies and currently available technologies. We refer the commenter to the FY 2020 IPPS/LTCH PPS final rule (84 FR 42289 through 42292) for further discussion of the substantial clinical improvement criterion as well as to the regulations at § 412.87(b). For the purposes of evaluating whether the BioFire® FilmArray® Pneumonia Panel meets the substantial clinical improvement criterion, data regarding both historical technologies and currently available technologies were considered.

We did not receive any public comments addressing the concerns we indicated in the proposed rule regarding whether the BioFire® FilmArray® Pneumonia Panel meets the substantial clinical improvement criterion. Accordingly, after consideration of the public comment we received, we are unable to determine that the BioFire® FilmArray® Pneumonia Panel represents a substantial clinical improvement over the currently available technologies.

After consideration of the information previously submitted in the BioFire® FilmArray® Pneumonia Panel application and previously summarized in this final rule, and the public comment we received, we are unable to determine that the BioFire® FilmArray® Pneumonia Panel meets the newness, cost and substantial clinical improvement criteria. Therefore, we are not approving new technology add-on payments for the BioFire® FilmArray® Pneumonia Panel for FY 2021.

c. ContaCT

Viz.ai Inc. submitted an application for new technology add-on payments for ContaCT for FY 2021. The individual components of ContaCT are currently marketed by Viz.ai, Inc. under the tradenames ''Viz LVO'' (for the algorithm), ''Viz Hub'' (for the text messaging and calling platform), and ''Viz View'' (for the mobile image viewer). According to the applicant, ContaCT is a radiological computer-assisted triage and notification software system intended for use by hospital networks and trained clinicians. The applicant asserted that ContaCT analyzes computed tomography angiogram (CTA) images of the brain acquired in the acute setting, sends notifications to a neurovascular specialist(s) that a suspected large vessel occlusion (LVO) has been identified, and recommends review of those images.

The applicant asserted early notification of the stroke team can reduce time to treatment and increase access to effective specialist treatments, like mechanical thrombectomy. Specifically, the applicant asserted that shortening the time to identification of LVO is critical because the efficacy of thrombectomy in patients with acute ischemic stroke decreases as the time from symptom onset to treatment increases. The applicant also asserted in a condition like stroke, where 1.9 million neurons die every minute and for which 34 percent of patients hospitalized are under the age of 65, reducing time to treatment results in reduced disability.[26] The applicant asserted ContaCT streamlines the standard workflow using artificial intelligence to substantially shorten the period of time between when a patient receives a stroke CT/CTA and when the patient is referred to a stroke neurologist and neurointerventional surgeon.

With respect to the newness criterion, according to the applicant, FDA granted marketing authorization to ContaCT on February 13, 2018 under the *de novo* pathway, which is only available to devices of a new type with low-to-moderate risk for which there are no legally marketed predicates, and classified it as a Class II medical device. We note that FDA issued a *de novo* order memorandum describing ContaCT as ''an artificial intelligence algorithm [used] to analyze images for findings suggestive of a pre-specified clinical condition and to notify an appropriate medical specialist of these findings in parallel to standard of care image interpretation.'' The order specified that ''identification of suspected findings is not for diagnostic use beyond notification.''

[26] Hall MJ, Levant S, DeFrances CJ. Hospitalization for stroke in U.S. hospitals, 1989–2009. NCHS data brief, no 95. Hyattsville, MD: National Center for Health Statistics. 2012. *https://www.cdc.gov/nchs/data/databriefs/db95.pdf.*

The applicant asserted that ContaCT was not available immediately after FDA's marketing authorization due to establishing Quality Management Systems and processes for distributing ContaCT as well as staff training and installation. Per the applicant, ContaCT was not commercially available until October 2018. The applicant submitted a request for approval for a unique ICD–10–PCS procedure code for the administration of ContaCT beginning in FY 2021 and was granted approval for the following procedure code effective October 1, 2020: 4A03X5D (Measurement of arterial flow, intracranial, external approach).

As discussed above, if a technology meets all three of the substantial similarity criteria, it would be considered substantially similar to an existing technology and would not be considered ''new'' for purposes of new technology add-on payments.

With regard to the first criterion, whether a product uses the same or a similar mechanism of action to achieve a therapeutic outcome, the applicant asserted no existing technology is comparable to ContaCT. The applicant further asserted, because of the technology's novelty, the product was reviewed under FDA's *de novo* pathway. The applicant first outlined the clinical workflow for patients presenting to a hospital with signs or symptoms of LVO prior to the availability of ContaCT:

1—Patient presents with stroke/suspected stroke to hospital emergency department (ED).

2—Patient receives stroke CT/CTA imaging after brief initial evaluation by hospital ED physician.

3—Technologist processes and reconstructs the CT/CTA imaging and manually routes to hospital picture archiving and communication system (PACS).

4—Radiologist reads CT/CTA imaging.

5—If needed, a neuroradiology consult is sought.

6—A radiological diagnosis of LVO is made.

7—The radiologist informs hospital ED physician of positive LVO either verbally or in the radiologist report.

8—ED physician performs comprehensive exam and refers the patient to a stroke neurologist.

9—The stroke neurologist reviews the CT/CTA imaging and clinical history and determines whether to prescribe or recommend prescription of thrombolysis with tissue plasminogen activator (tPA).

10—The stroke neurologist refers the patient to a neurointerventional surgeon. Together they decide whether the patient is a candidate for mechanical thrombectomy.

11—If appropriate, the patient proceeds to treatment with mechanical thrombectomy.

The applicant asserted that facilities utilizing the ContaCT system can substantially shorten the period of time between when the patient receives stroke CT/CTA imaging (step 2) and when the patient is referred to a stroke neurologist and neurointerventional surgeon (steps 9 and 10). They further asserted that ContaCT streamlines this workflow using artificial intelligence to analyze CTA images of the brain automatically and notifies the stroke neurologist and neurointerventional surgeon that a suspected LVO has been identified, and then enables them to review imaging and make a treatment decision faster. The applicant concluded that shortening the time to identification of LVO is critical because the efficacy of thrombectomy in patients with acute ischemic stroke decreases as the time from symptom onset to treatment increases.

With regard to the second criterion, whether the technology is assigned to the same or a different MS–DRG, the applicant did not specifically address whether the technology meets this criterion. However, we believe that cases involving the use of the technology would be assigned to the same MS–DRGs as cases without the technology where the patient moves through the hospital according to the traditional workflow outlined above.

With regard to the third criterion, whether the use of the new technology involves the treatment of the same or similar type of disease and the same or similar patient population, the applicant also did not specifically address whether the technology meets this criterion. However, we stated in the proposed rule that we believe cases involving the use of the technology would treat the same or similar type of disease and the same or similar patient population as the traditional workflow outlined above.

We noted that the applicant described ContaCT's mechanism of action as shortening the time to identification of LVO through artificial intelligence (AI). Specifically, the applicant asserted that facilities utilizing the ContaCT system can substantially shorten the period of time between when the patient receives stroke CT/CTA imaging and when the patient is referred to a stroke neurologist and neurointerventional surgeon. We stated in the proposed rule that we were unclear as to whether the streamlining of hospital workflow would represent a unique mechanism of action. Rather, we stated that it seems that the mechanism of action for ContaCT would be the use of AI to analyze images and notify physicians rather than streamlining hospital workflow. However, we also referred the reader to our discussion below and in the proposed rule regarding our concerns with respect to general parameters for identifying a unique mechanism of action based on the use of AI, an algorithm and/or software.

To the extent that the applicant asserted that streamlined hospital workflow through the use of ContaCT represents a unique mechanism of action, we stated in the proposed rule that it was unclear to us the degree to which ContaCT changes the traditional workflow. Per the FDA, ''ContaCT is limited to analysis of imaging data and should not be used in-lieu of full patient evaluation or relied upon to confirm diagnosis.'' [27] We stated that it was unclear to CMS how ContaCT shortens time to treatment via AI if the CT machine still performs the scanning and clinicians are still needed to view the images to diagnose an LVO and perform a full patient evaluation for the best course of treatment. The applicant also indicated to CMS that the use of ContaCT is not automatic, and the E.R. physician must submit an order to utilize it specifically when suspecting an LVO. We stated that we were unclear how ContaCT streamlines the workflow for stroke treatment via AI if it is not to be used for diagnostic purposes per the FDA and still requires personnel to order the scan and make the diagnosis.

We stated in the proposed rule that we were also generally concerned as to whether the use of AI, an algorithm or software, which are not tangible, may be considered or used to identify a unique mechanism of action. In addition, we questioned how updates to AI, an algorithm or software would affect an already approved technology or a competing technology, including whether software changes for an already approved technology could be considered a new mechanism of action. We also questioned whether, if there were competing technologies to an already approved AI new technology, an improved algorithm by a competitor would represent a unique mechanism of action if the outcome is the same as the technology first approved. We welcomed comments from the public regarding the general parameters for identifying a unique mechanism of

[27] U.S. Food and Drug Administration, DEN170073. *Evaluation of Automatic Class III Designation for ContaCT Decision Summary.*

action based on the use of AI, an algorithm and/or software.

We also invited public comments on whether the applicant meets the newness criterion, including specifically with respect to the mechanism of action.

Comment: The applicant submitted a comment to address newness concerns raised by CMS in the proposed rule. The applicant asserted that there was a brief delay in the availability of ContaCT due to establishing Quality Management Systems (QMS) and processes for distributing ContaCT. Because of this delay, the first hospital installation of ContaCT was not completed until January 2019. According to the applicant, because the commercial use of ContaCT did not begin at the start of FY 2019, the Medicare data which is used to set FY 2021 MS–DRG relative weights (data from FY 2019 October 1, 2018 through September 30, 2019), do not reflect fully the cost of the technology. Therefore, the applicant believed that the newness period should begin on the date the first installation was completed, rather than the date of commercial availability noted in the FY 2019 IPPS/LTCH PPS proposed rule (85 FR 32601), which was October 2018.

The applicant asserted that no existing technology is comparable to ContaCT. According to the applicant, with regard to the first criterion for newness, ContaCT does not use the same or a similar mechanism of action as compared to an existing technology. The applicant stated that ContaCT was reviewed through FDA's *de novo* pathway, which is only available to novel medical devices that have not previously been classified by the FDA. With regard to the second criterion for newness, the applicant stated that ContaCT is used in cases of stroke and suspected stroke. Consequently, stroke and suspected stroke cases in which ContaCT is used are expected to be assigned to the same DRGs as stroke and suspected stroke cases without the technology. With regard to the third criterion for newness, the applicant stated that cases in which ContaCT is used are expected to be the same or similar to cases without the technology.

With respect to the first substantial similarity criterion, the applicant asserted that computer-assisted triage and notification is the mechanism of action for ContaCT and that the mechanism of action for ContaCT is not AI per se. According to the applicant, AI is a necessary component of ContaCT, but is not sufficient to achieve therapeutic effect. Furthermore, the applicant stated that under 42 CFR 412.87(b)(2) and CMS criteria for evaluating a technology with respect to newness, there are no requirements that a new technology have a specific type of mechanism of action to be eligible for new technology add-on payments.

The applicant expressed concern that CMS is questioning whether AI, an algorithm or software may never be considered a unique mechanism of action, because such technology may simulate human intelligence or human processes that already exist. According to the applicant, CMS has defined an existing technology as another FDA approved or cleared technology. Human intelligence and human processes are not FDA approved or cleared technologies and, therefore, should not be used as a comparator to evaluate whether ContaCT, or any technology, meets the definition of newness. The applicant stated that, as for other new technologies, comparators for AI, algorithm or software-based devices should be other FDA approved or cleared technologies. More broadly, the applicant urged CMS not to make a broad determination that technologies that use AI, an algorithm or software to achieve a therapeutic effect are ineligible for new technology add-on payments. They stated CMS should evaluate each new technology individually with respect to whether it meets the established criteria.

In addressing CMS concerns about whether software changes for an already approved technology could be considered a new mechanism of action, the applicant stated that an update to the ContaCT algorithm that does not alter this mechanism of action would have the same or a similar mechanism of action. In addressing CMS concerns about whether an improved algorithm by a competitor would represent a unique mechanism of action if the outcome is the same as the technology first approved, the applicant likewise stated that a different technology that shortens time to notification in patients with acute ischemic stroke caused by large vessel occlusions by using an AI algorithm to identify suspected LVO, triage patients and notify the stroke team more rapidly would likely be determined to have a mechanism of action that is the same or similar to ContaCT.

In addition, the applicant stated that the newness of the overall mechanism of action or the means by which a product achieves the therapeutic outcome should be assessed, rather than the newness of the individual inputs or components. They provided an example from FY 2017 when CMS determined MIRODERM not to be ''new'' because the product achieved the intended therapeutic outcome, wound healing, in the same way as other acellular skin substitutes by providing a scaffold of collagen with a mix of matrix proteins (81 FR 56893). The applicant stated that CMS acknowledged that MIRODERM matrix proteins were different from the proteins found in other acellular skin substitutes, but the determination of newness was based on MIRODERM's overall mechanism of action—a collagen scaffold that promotes wound healing. Just as in the MIRODERM example where the matrix proteins were not sufficient to establish the technology as new, changes to the AI, algorithm and/or software would not be sufficient to establish future computer-aided triage and notification systems for large vessel occlusion ischemic stroke as new if these involve essentially the same mechanism of action as ContaCT. The applicant thus argued that technologies that utilize AI, an algorithm and/or software should be evaluated for newness in the same way as CMS evaluates any other medical device applying for new technology add-on payments.

Other commenters responded to CMS' concerns about whether the applicant meets the newness criterion. In response to our stated uncertainty regarding how ContaCT streamlines the workflow for stroke treatment via AI if it is not to be used for diagnostic purposes per the FDA and still requires personnel to order the scan and make the diagnosis, a commenter responded that ContaCT will enhance, not replace, human action as it relates to patient outcomes, and asserted that all innovation will be based upon AI in some fashion moving forward. Another commenter responded to our concerns as to whether the use of AI, an algorithm or software may be considered or used to identify a unique mechanism of action and also how updates to AI, an algorithm or software would affect an already approved technology or a competing technology for purposes of new technology add-on payments. The commenter stated that technologies that utilize AI, an algorithm and/or software may be evaluated for newness in the same way CMS evaluates any other medical device applying for new technology add-on payments. Such a technology would not be new if there is an existing FDA-approved technology that has been on the market for more than 2 to 3 years and that has the same mechanism of action, is assigned to the same DRGs, or is used in the same or similar type of disease and patient population. The commenter further suggested that this apply to both incremental changes to

the same device as well as to competing devices. The commenter urged CMS to consider that evaluating technologies that use AI, an algorithm and/or software is no different than evaluating other technologies for purposes of new technology add-on payments. They stated that technologies are not required to have a specific type of mechanism of action to be eligible for add-on payment, and as such, each submission must be evaluated independently.

Response: After considering the comments received regarding the new technology add-on payment application for ContaCT, we agree that ContaCT does not use the same or a similar mechanism of action to achieve a therapeutic outcome when compared to existing treatments because there are currently no FDA approved or cleared technologies that use computer-assisted triage and notification to rapidly detect an LVO and shorten time to notification. Therefore, we believe that ContaCT is not substantially similar to an existing technology and meets the newness criterion. We consider the beginning of the newness period to commence on October 1, 2018. We have previously stated in the FY 2013 IPPS/LTCH PPS final rule (77 FR 53348) and FY 2019 IPPS/LTCH PPS final rule (83 FR 41313), generally, our policy is to begin the newness period on the date of FDA approval or clearance or, if later, the date of availability of the product on the U.S. market. Without additional information, we continue to believe that the newness period for ContaCT begins on October 1, 2018. We may consider any further information that may be provided regarding the date of availability in future rulemaking.

We will continue to consider the issues related to determining newness for technologies that use AI, an algorithm or software, including devices classified as radiological computer aided triage and notification software, as discussed in the proposed rule, including how these technologies may be considered or used to identify a unique mechanism of action, how updates to AI, an algorithm or software would affect an already approved technology or a competing technology, whether software changes for an already approved technology could be considered a new mechanism of action, and whether an improved algorithm by competing technologies would represent a unique mechanism of action if the outcome is the same as an already approved AI new technology, as we gain more experience in this area.

With respect to the cost criterion, the applicant provided the following analysis. First, the applicant extracted claims from the FY 2018 MedPAR dataset. The applicant explained that many patients present to the emergency department with signs or symptoms suggesting an LVO. That presentation would be the basis for ordering a CTA with ContaCT added. Of these patients, some will be identified as stroke and LVO, some as stroke but not from an LVO, and others will have diagnoses completely unrelated to stroke. As a result, according to the applicant, there may be a very broad range of principal diagnoses and MS–DRGs representing patients who would be eligible for and receive a CTA with ContaCT. The applicant noted that it used admitting diagnoses codes rather than principal or secondary diagnosis codes to identify cases of stroke due to LVO, stroke not due to LVO, and no stroke. The applicant utilized a multi-step approach:

- *Step 1:* The applicant first extracted claims from the stroke-related MS–DRGs (023, 024, 061, 062, 063, 064, 065, 066, 067, 068, and 069).
- *Step 2:* The applicant analyzed the admitting diagnosis on claims extracted in Step 1 to identify the reason for admission. The applicant found that the top five admitting diagnoses for patients in the stroke-related MS–DRGs included: Cerebral infarction, unspecified (I63.9), transient cerebral ischemic attack, unspecified (G45.9), slurred speech (R4781), aphasia (R4701), and facial weakness (R29.810).
- *Step 3:* The applicant identified all MS–DRGs assigned to the admitting diagnosis codes identified in Step 2 to identify ContaCT cases that did not map to one of the stroke MS–DRGs.
- *Step 4:* The applicant identified a list of unique MS–DRGs and admitting diagnosis code combinations to which cases involving ContaCT would map. The applicant stated that it reviewed with clinical experts the MS–DRG and admitting diagnosis combinations and eliminated any that were unlikely to include the use of ContaCT.

The applicant identified a total of 375,925 cases across 143 MS–DRGs, with approximately 66 percent of cases mapping to MS–DRGs 039, 057, 064, 065, 066, 069 and 312. The average unstandardized case-weighted charge per case was $52,001. The applicant noted it did not remove any charges for a prior technology, as it asserted that no other technology is comparable to ContaCT. Based on the results of a research study,[28] the applicant assumed ContaCT cases resulting in mechanical thrombectomy would have charges reduced by 38% as a result of reduced specialty care days and therefore removed the related charges, which only affected cases mapping to MS–DRGs 023, 024, 025, and 026. The applicant standardized the charges and applied an inflation factor of 11.1 percent, which is the same inflation factor used by CMS to update the outlier threshold in the FY 2020 IPPS/LTCH PPS final rule (84 FR 42629), to update the charges from FY 2018 to FY 2020.

The applicant then added the charges for the new technology. The applicant explained it calculated the cost per patient by dividing the total overall cost of ContaCT per year per hospital by the number of total estimated cases for which ContaCT was used at each hospital that currently subscribes to ContaCT (based on the estimated number of cases receiving CTA), and averaging across all such hospitals. The following is the methodology the applicant used to determine the cost per case:

- *Step 1:* The applicant first determined the estimated total cases (both Medicare and non-Medicare) for each current subscriber hospital. The applicant explained it used total cases for both Medicare and non-Medicare cases since the cost per case is not specific to Medicare cases. In order to determine total cases, which include both Medicare and non-Medicare cases, the applicant divided the total Medicare cases per subscriber hospital from the FY 2018 MedPAR data by the percentage of Medicare beneficiaries (71 percent) in the CONTACT FDA research study (for example, 1,136 Medicare cases divided by 0.71 equals 1,600 total Medicare and non-Medicare cases).
- *Step 2:* To analyze actual rates (percentages) of CTA across subscriber hospital cases, the applicant first used the beneficiary ID in the FY 2018 SAF data set to find matching physician claims in the carrier file for CT and CTA services with a site of service of 21 (Inpatient hospital) or 23 (emergency department) and a date of service consistent with the inpatient stay. The applicant then calculated provider-specific CTA rates (percentages) for each subscriber hospital. The applicant dropped five hospitals with a low volume of Medicare inpatient stays that had no matching services in the carrier file. The applicant calculated an average CTA rate of 21.6 percent across all hospitals that subscribe to ContaCT.

[28] Goldstein ED, Schnusenberg L, Mooney L, et al. Reducing Door-to- Reperfusion Time for Mechanical Thrombectomy With a Multitiered Notification System for Acute Ischemic Stroke. Mayo Clin Proc Innov Qual Outcomes. 2018;2(2): 119–128.

• *Step 3:* The applicant determined the estimated total number of cases that received CTA for each current subscriber hospital by multiplying the total cases (Medicare and non-Medicare) for each subscriber hospital in step 1 by the provider-specific CTA rate calculated in Step 2. In cases where a provider had fewer than 11 cases in the carrier file or where a provider had a CTA rate that was an outlier, the applicant multiplied the total cases for the provider by the average CTA rate of 21.6 percent.

• *Step 4:* The applicant then calculated the cost per year per hospital. If a hospital had multiple sites under the same CCN, the applicant multiplied the total overall cost of ContaCT per hospital by the number of sites. For example, if the cost for ContaCT was $25,000 per year and Hospital A had only one site under its CCN, then the total cost for ContaCT for Hospital A would be $25,000. However, if Hospital B had three sites under its CCN, then the total cost for ContaCT for Hospital B would be $75,000 per year ($25,000 × 3).

• *Step 5:* The applicant then divided the cost per year per hospital by the total cases that received CTA for each customer hospital in Step 3 to determine the estimated cost per case for each customer hospital. If Hospital A from the example in Step 4 had 50 patients, then the total hospital cost per case would be $500 per patient ($25,000/50). If Hospital B (with three sites under its CCN) also had 50 patients, then the total hospital cost per case would be $1,500 per patient ($75,000/50).

• *Step 6:* The applicant averaged the cost per case across all hospitals to determine the average cost per patient. The average cost per case across Hospital A and Hospital B in the previous example would be $1,000.

• *Step 7:* To convert the cost of the technology in Step 6 to charges, the applicant divided the average cost per patient by the national average cost-to-charge (CCR) of 0.14 for the Radiology cost center from the FY 2020 IPPS/LTCH PPS final rule (84 FR 42179). Although the applicant submitted data related to the cost of the technology, the applicant noted that the cost of the technology was proprietary information.

The applicant calculated a case-weighted threshold amount of $51,358 and a final inflated average case-weighted standardized charge per case of $62,006. Based on this analysis, the applicant asserted that ContaCT meets the cost criterion because the final inflated average case-weighted standardized charge per case exceeds the case-weighted threshold amount.

The applicant submitted three additional cost analyses to demonstrate that it meets the cost criterion using the same methodology above but with limits on the cases. The first alternative limited the analysis to only those cases in the primary stroke-related MS–DRGs 023, 024, 061, 062, 063, 064, 065, 066, 067, 068, and 069. This first alternative method resulted in a case-weighted threshold of $53,885 and a final inflated average case weighted standardized charge per case of $62,175. The second alternative limited the analysis to cases in MDC 01 (Diseases and Disorders of the Nervous System) with the following MS–DRGs:

MS-DRG	MS-DRG Description
023	Craniotomy with Major Device Implant or Acute Complex CNS PDX with MCC or Chemotherapy Implant or Epilepsy with Neurostimulator
024	Craniotomy with Major Device Implant or Acute Complex CNS PDX without MCC
025-027	Craniotomy and Endovascular Intracranial Procedures with MCC, with CC, and without CC/MCC, respectively
037-039	Extracranial Procedures with MCC, with CC, and without CC/MCC, respectively
061-063	Ischemic Stroke, Precerebral Occlusion or Transient Ischemia with Thrombolytic Agent with MCC, with CC, and without CC/MCC, respectively
064-066	Intracranial Hemorrhage or Cerebral Infarction with MCC, with CC or TPA in 24 hours, and without CC/MCC, respectively
067-068	Nonspecific CVA and Precerebral Occlusion without Infarction with and without MCC, respectively
069	Transient Ischemia without Thrombolytic
091-093	Other Disorders of Nervous System with MCC, with CC, and without CC/MCC, respectively

This second alternative method resulted in a case-weighted threshold of $55,053 and a final inflated average case weighted standardized charge per case of $63,741. The third alternative limited cases to MS–DRGs where the total volume of cases was greater than 100. This third alternative method resulted in a case-weighted threshold of $49,652 and a final inflated average case-weighted standardized charge per case of $59,365. Across all cost-analysis methods, the applicant maintained that the technology meets the cost criterion because the final inflated average case-weighted standardized charge per case exceeds the average case-weighted threshold amount.

We noted in the proposed rule that we believe a case weight would provide more accuracy in determining the average cost per case as compared to the average of costs per case across all hospitals that was used by the applicant in Step 6 as summarized previously. We therefore computed a case-weighted cost per case across all current subscriber hospitals. We then inflated the case-weighted cost per case to a charge based on Step 7 above and used this amount in the comparison of the case-weighted threshold amount to the final inflated average case-weighted standardized charge per case (rather than the applicant's average cost per case). In all the scenarios above, the final inflated average case-weighted standardized charge per case exceeded the case-weighted threshold amount by an average of $2,961.

We stated in the proposed rule that we had the following concerns regarding whether the technology meets the cost criterion. The applicant used a single list price of ContaCT per hospital

with a cost per patient that can vary based on the volume of cases. We stated that we were concerned that the cost per patient varies based on the utilization of the technology by the hospitals. The cost per patient could be skewed by the small number of hospitals utilizing the technology and their low case volumes. It is possible, if hospitals with large patient populations adopt ContaCT, the cost per patient would be significantly lower.

We stated in the proposed rule that an alternative to the applicant's calculation may be a methodology that expands the applicant's sample from total cases (which include both Medicare and non-Medicare cases) receiving CTA at subscriber hospitals in Step 1 to all inpatient hospitals for the use of ContaCT (and then using the same steps after Step 1 for the rest of the analysis). In this alternative, the applicant would continue to extract cases representing patients that are eligible for the use of ContaCT from MedPAR, but the cost per patient would be determined by dividing the overall cost per year per hospital by the average number of patients eligible for the use of ContaCT across all such hospitals. For example, if the cost for ContaCT is $25,000 per year and the average hospital has 500 patients who are eligible to receive ContaCT per year, then under this alternative methodology, the total cost per patient would be $50 ($25,000/500).

We noted in the proposed rule that if ContaCT were to be approved for new technology add-on payments for FY 2021, we believed the cost per case from the cost analysis above may also be used to determine the maximum new technology add-on payment (that is, 65 percent of the cost determined above). We stated that we understood there are unique circumstances to determining a cost per case for a technology that utilizes a subscription for its cost. We welcomed comments from the public as to the appropriate method to determine a cost per case for such technologies, including comments on whether the cost per case should be estimated based on subscriber hospital data as described previously, and if so, whether the cost analysis should be updated based on the most recent subscriber data for each year for which the technology may be eligible for the new technology add-on payment.

We also invited public comments on whether the applicant meets the cost criterion.

Comment: One commenter, who was also the applicant, maintained that ContaCT met the cost criterion and submitted two additional analyses following CMS' suggestions in the FY 2021 IPPS/LTCH PPS Proposed Rule.

First, the applicant updated its cost analyses to include all IPPS hospitals, utilizing the same methodology described in detail in the proposed rule. Under this methodology, the cost per patient is calculated by dividing the total overall cost of ContaCT per year per hospital by the number of total estimated cases for which ContaCT would be used at each hospital (based on the estimated number of cases receiving CTA), and then averaging across all such hospitals. The applicant's updated cost analysis included 3,035 Medicare provider numbers representing 3,062 general acute care hospitals. The updated analysis yielded a final inflated average case-weighted standardized charge per case of $71,568, which exceeded the threshold amount of $51,358.

The applicant also updated the three alternative analyses (which used the same methodology as above but limited the cases included) to include all IPPS hospitals. The parameters of these analyses were discussed in detail in the proposed rule (85 FR 32602 through 32603). Per the applicant, the first alternative analysis resulted in a case-weighted threshold of $53,885 and a final inflated average case-weighted standardized charge per case of $71,736; the second alternative analysis resulted in a case-weighted threshold of $55,053 and a final inflated average case weighted standardized charge per case of $73,302; and the third resulted in a case-weighted threshold of $49,652 and a final inflated average case-weighted standardized charge per case of $68,925. In all three alternative analyses, the final average case-weighted standardized charge per case exceeded the average case-weighted threshold amount, meeting the cost criterion.

The applicant also calculated a case-weighted average cost per case for each of the analyses above in response to CMS' suggestion that a case-weighted average cost per case would be more accurate compared to the average of costs per case across all hospitals, as the applicant had done initially. The applicant analyzed the average number of patients eligible to receive ContaCT per hospital among subscribers and compared it to the average number of patients eligible to receive ContaCT among all IPPS hospitals. The applicant found that, among ContaCT subscribers, the average number of patients eligible to receive ContaCT per Medicare provider number and per hospital are 141 and 121, respectively. In contrast, among all IPPS hospitals, the applicant found that the average number of patients eligible to receive ContaCT per Medicare provider number and per hospital are 99 and 82, respectively. The applicant concluded that ContaCT subscribers have a higher average number of patients eligible to receive ContaCT compared to all IPPS hospitals, and that the cost per patient for ContaCT is skewed to yield a higher cost per patient across all IPPS hospitals than among ContaCT subscribers alone. The applicant noted that the cost per patient among ContaCT subscribers is lower than if all IPPS hospitals adopted ContaCT, and that expanding the analyses above to include all IPPS hospitals increased the cost per patient.

Per the applicant, ContaCT would meet the cost criterion in each of these average number of patients eligible to receive ContaCT across all cost-analysis methods. Using a case-weighted cost per case, the applicant also met the cost criterion across all cost-analysis methods, as the final inflated average case-weighted standardized charge per case exceeded the average case-weighted threshold amount.

The applicant also noted that technologies sold on a subscription basis are provided to the customer at a recurring price at regular intervals. As a result, the cost per unit for a subscription technology is directly impacted not only by the price, but how frequently the customer utilizes the technology, in that customers with low utilization of a subscription-based technology have a higher cost per unit than customers with high utilization. The commenter stated that, because the overall cost per unit of subscription technologies is determined by each customer's ratio of price to utilization, an analysis that requires an estimate of cost per unit should be limited to subscribers. The commenter believed that including estimates of cost per unit for potential customers that do not currently subscribe to the technology may result in a cost-per-case that does not reflect the actual costs of current users. The commenter recommended that the cost per unit of technologies sold on a subscription basis, like ContaCT, should be based on data from current subscribers only. However, the applicant agreed with CMS that yearly updates to the cost per unit analysis are reasonable to reflect changes in subscribers and thus the overall cost per unit.

The commenter offered several examples of how its recommendation is consistent with CMS' methodology in calculating costs across a variety of payment systems and programs. The commenter noted that CMS considers only costs from hospitals for cases billed

to Medicare when setting MS–DRG relative weights. In addition, if a hospital does not provide the type of care described by a specific MS–DRG, CMS does not attempt to estimate what the cost and MS–DRG relative weights might be if a broader range of hospitals delivered that type of care. The commenter stated that another example is the average sales price methodology used by CMS to determine payment for certain separately payable products, which includes only data from actual customer sales. The commenter noted that although the unit price for these products often varies based on utilization, with customers with low utilization paying more per unit than customers with higher utilization, CMS does not attempt to calculate average sales price by forecasting how future customers may alter the current average sales price. The applicant concluded that, consistent with these examples, the cost per unit for subscription technologies should be based on data from current subscribers only and yearly updates are reasonable.

Response: After consideration of the applicant's updated cost analyses for ContaCT, we agree that the average case-weighted standardized charge per case exceeded the average case-weighted threshold amount in all scenarios. Therefore, ContaCT meets the cost criterion for FY 2021. CMS will continue to consider the issues relating to calculation of the cost per unit of technologies sold on a subscription basis as we gain more experience in this area.

With respect to the substantial clinical improvement criterion, according to the applicant, ContaCT represents an advance that substantially improves the ability to diagnose a large vessel occlusion stroke earlier by automatically identifying suspected disease in CTA images and notifying the neurovascular specialist directly in parallel to the standard of care. The applicant further asserted a major limitation in the traditional acute stroke workflow is the time delay from initial image acquisition of a suspected LVO patient (CT, CT angiography, and CT perfusion), notification of the interventional team, and execution of an endovascular thrombectomy. The time from stroke onset to reperfusion (when blood supply returns to tissue after a period of ischemia or lack of oxygen) is negatively correlated with the probability of an independent functional status.[29] The applicant stated the time from initial presentation to eventual reperfusion can be long, resulting in poor outcomes, using the existing standard of care. The median onset-to-revascularization time has been reported as 202.0 minutes for patients presenting directly to interventional centers (or comprehensive stroke centers), and 311.5 minutes for patients that initially presented to a non-interventional center.[30] The applicant further stated that part of that time is the time from initial CTA to the time that the neurovascular specialist is notified of a possible LVO (the CTA to notification time). A retrospective study examined work-flow for stroke patients and demonstrated an initial CT to CSC (Comprehensive Stroke Center) notification time per standard of care >60 minutes in patients transferred for endovascular reperfusion in acute ischemic stroke.[31]

The applicant asserted that ContaCT facilitates a workflow parallel to the standard of care workflow and results in a notified specialist entering the workflow earlier. In the applicant's study to support the De Novo request, ContaCT's performance was compared with standard of care workflow, demonstrating that ContaCT resulted in faster specialist notification. According to the applicant, the average time to specialist notification for ContaCT was 7.32 minutes [95% CI: 5.51, 9.13] whereas time to notification for standard of care workflow was 58.72 minutes [95% CI: 46.21, 71.23]. The applicant also asserted that ContaCT saved an average of 51.4 minutes, an improvement that could markedly improve time to intervention for LVO patients. In addition, the applicant noted that the standard deviation was reduced from 41.14 minutes in the standard of care workflow to 5.95 minutes with ContaCT, demonstrating ContaCT's potential to reduce variation in care and patient outcome across geographies and time of day.[32]

To support the applicant's assertion that ContaCT substantially improves the ability to diagnose a large vessel occlusion stroke earlier, the applicant presented a multicenter prospective observational trial, DISTINCTION, which is ongoing and compares a prospective cohort of patients in which ContaCT is used (intervention arm) to a retrospective cohort in which ContaCT was not used (control arm). Patients are also segmented based on whether they initially present to a non-interventional center or an interventional center. Per the applicant, early data from one non-interventional hospital in the Erlanger Health System indicates that for the control arm the median time from CTA to clinician notification was 59.0 minutes. For the intervention arm, early data indicates that the median time from CTA to clinician notification was 5.3 minutes. The applicant stated that these early data indicate time savings of approximately 53 minutes, which is consistent with the 51.4 minute time savings demonstrated in the studies sponsored/conducted by the De Novo requester.[33]

Next, the applicant presented the Automated Large Artery Occlusion Detection In Stroke Imaging Study (ALADIN), a multicenter retrospective analysis of CTAs randomly picked from a retrospective cohort of acute ischemic stroke patients, with and without anterior circulation LVOs, admitted at three tertiary stroke centers, from 2014–2017. Per the applicant, ALADIN evaluated ContaCT's performance characteristics including area under the curve, sensitivity, specificity, positive predictive value, negative predictive value, and processing or running time. The applicant asserted that, through this study, researchers concluded that the ContaCT algorithm may permit early and accurate identification of LVO stroke patients and timely notification to emergency teams, enabling quick decision-making for reperfusion therapies or transfer to specialized centers if needed.[34] [35] [36]

[29] Khatri P, Abruzzo T, Yeatts SD, et al. Good clinical outcome after ischemic stroke with successful revascularization is time-dependent. *Neurology.* 2009; 73(13):1066–1072.

[30] Froehler MT, Saver JL, Zaidat 00, et al. Interhospital transfer before thrombectomy is associated with delayed treatment and worse outcome in the STRATIS registry. *Circulation.* 2017; 136(24):2311–2321.

[31] Sun CH, Nogueira J, Glenn RG, et al. Picture-to-puncture: A novel time metric to enhance outcomes in patients transferred for endovascular reperfusion in acute ischemic stroke. *Circulation.* 2013; 127:1139–1148.

[32] U.S. Food and Drug Administration (FDA). Center for Devices and Radiological Health. Evaluation of Automatic Class III Designation for ContaCT. Decision Memorandum No. 170073 (DEN170073). 2018. Retrieved from: *https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN170073.pdf.*

[33] U.S. Food and Drug Administration (FDA). Center for Devices and Radiological Health. Evaluation of Automatic Class III Designation for ContaCT. Decision Memorandum No. 170073 (DEN170073). 2018. Retrieved from: *https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN170073.pdf.*

[34] Barreira C, Bouslama M, Lim J, et al. E–108 ALADIN study: Automated large artery occlusion detection in stroke iaging study—a multicenter analysis. *J Neurointerv Surg.* 2018;10(Suppl 2):A101–A102.

[35] Barreira C, Bouslama M, Haussen D, et al. Abstract WP61: Automated large artery occlusion detection in stroke imaging—ALADIN study. *Stroke.* 2018;49:AWP61.

Continued

According to the applicant, the use of ContaCT to facilitate a faster diagnosis and treatment decision directly affects management of the patient by enabling early notification of the neurovascular specialist and faster time to treatment utilizing mechanical thrombectomy to remove the large vessel occlusion. The applicant stated that mechanical thrombectomy with stent retrievers is one of the standards of care for treatment of acute ischemic stroke patients caused by LVO and that mechanical thrombectomy therapy is highly time-critical with each minute saved in onset-to-treatment time resulting in a reported average of 4.2 days of extra healthy life.[37] According to the applicant, the use of ContaCT affects the management of the patient by facilitating early identification of patients with suspected LVO and early notification of the neurovascular specialist. The applicant asserted that this may affect the management of the patient in two ways. First, it may offer improved access to mechanical thrombectomy for patients who would otherwise not have access because of factors such as time of day and the specialty capabilities of the hospital they are in, and second, it may involve the neurovascular team earlier, decreasing the time to thrombectomy. The applicant stated that ContaCT saved an average of 51.4 minutes in time to notification relative to standard of care workflow and reduced standard deviation in time to notification from 41.14 minutes (standard of care workflow) to 5.95 minutes (ContaCT).[38] Furthermore, the applicant stated that ContaCT could markedly improve time to intervention for LVO patients and has the potential to reduce variation in care and patient outcome across geographies and time of day.

The applicant stated that according to five clinical trials, the clinical efficacy of endovascular mechanical thrombectomy has been demonstrated for patients with LVO strokes up to 6 hours after onset of stroke.[39] The applicant also stated that two meta-analyses of these randomized trials have been completed.[40] Campbell et al. performed a patient-level pre-specified pooled meta-analysis of four randomized clinical trials which concluded that thrombectomy for large vessel ischemic stroke is safe and highly effective at reducing disability. Goyal et al. pooled and analyzed patient-level data from all five trials. Per the applicant, the results indicated that mechanical thrombectomy leads to significantly reduced disability. According to the applicant, together, these five randomized trials and two meta-analyses, have demonstrated that treatment for intracranial large vessel occlusion with mechanical thrombectomy with stent retrievers is the standard of care.

The applicant also asserted that real world evidence further supports the efficacy of mechanical thrombectomy. Data from the STRATIS registry (Systematic Evaluation of Patients Treated With Neurothrombectomy Devices for Acute Ischemic Stroke), which prospectively enrolled patients treated in the United States with a Solitaire Revascularization Device and Mindframe Capture Low Profile Revascularization Device within 8 hours from symptom onset, was compared with the interventional cohort from the patient-level meta-analysis from Campbell et al. to assess whether similar process timelines and technical and functional outcomes could be achieved in a large real-world cohort as in the randomized trials. The article concluded that the results indicate randomized trials can be reproduced in the real world (Mueller-Kronast et al., 2017).[41]

The applicant stated that based on these data, U.S. clinical guidelines now recommend mechanical thrombectomy for the treatment of large vessel occlusion strokes when performed ≤6 hours from symptom onset. The American Stroke Association/American Heart Association (ASA/AHA) ''2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke'' recommended mechanical thrombectomy with a stent retriever in patients that meet the following criteria: (1) Prestroke modified Rankin Scale (mRS) 0–1; (2) causative occlusion of the internal carotid artery (ICA) or middle cerebral artery (MCA) segment 1 (M1); (3) age ≥18; (4) National Institute of Health Stroke Scale (NIHSS) ≥6; (5) Alberta Stroke Program Early CT Score (ASPECTS) ≥6; and (6) treatment can be initiated within 6 hours of symptom onset (Powers et al., 2018). The ASA/AHA notes the need for expeditious treatment with both intravenous thrombolysis and mechanical thrombectomy.[42]

The applicant also stated that recently, randomized trials have demonstrated the clinical efficacy of mechanical thrombectomy for large vessel occlusion strokes for select patients from 6 to 24 hours after symptom onset.[43] Among patients with acute stroke who were last known well 6 to 24 hours earlier and who had a mismatch between clinical deficit and infarct, outcomes for disability at 90 days were better with thrombectomy plus standard care compared with standard care alone.

The applicant asserted that the use of ContaCT reduces time to treatment by notifying the stroke team faster than the standard of care and enabling the team to diagnose and treat the patient earlier, which is known to improve clinical outcomes in stroke, and that mechanical thrombectomy has been shown to reduce disability, reduce length of stay and recovery time (Campbell et al., 2017).[44]

[36] Rodrigues GM, Barreira CM, Bouslama M, et al. Automated large artery occlusion detection in stroke imaging study (ALADIN). Abstract WP71: Multicenter ALADIN: Automated large artery occlusion detection in stroke imaging using artificial intelligence. *Stroke.* 30 Jan 2019;50:AWP71.

[37] Fransen PS, Berkhemer OA, Lingsma HF, et al. Time to reperfusion and treatment effect for acute ischemic stroke: A randomized clinical trial. *JAMA Neurol.* 2016;73:190–196 ; Meretoja A, Keshtkaran M, Tatlisumak T, Donnan GA and Churilov L. Endovascular therapy for ischemic stroke: save a minute-save a week. *Neurology.* 2017;88(22):2123–2127.

[38] U.S. Food and Drug Administration (FDA). Center for Devices and Radiological Health. Evaluation of Automatic Class III Designation for ContaCT. Decision Memorandum No. 170073 (DEN170073). 2018. Retrieved from: *https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN170073.pdf.*

[39] Berkhemer OA, Fransen PS, Beumer D, et al. MR CLEAN Investigators. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med.* 2015;372:11–20.doi: 10.1056/NEJMoa1411587; Campbell BCV, Mitchell PJ, Kleinig TJ, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med.* 2015;372(11):1009–1018; Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, et al.; REVASCAT Trial Investigators. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N Engl J Med.* 2015;372(24):2296–2306.

[40] Campbell BC, Hill MD, Rubiera M et al. Safety and efficacy of solitaire stent thrombectomy: Individual patient data meta-analysis of randomized trials. *Stroke.* 2016;47(3):798–806; Goyal M, Menon BK, van Zwam WH, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: A meta-analysis of individual patient data from five randomised trials. *Lancet N Am Ed.* 2016;387(10029):1723–1731.

[41] Mueller-Kronast NH, Zaidat OO, Froehler MT, et al. Systematic evaluation of patients treated with neurothrombectomy devices for acute ischemic stroke: primary results of the STRATIS registry. *Stroke.* 2017;48(10):2760–2768.

[42] Powers WJ, Rabinstein AA, Ackerson T et al. On behalf of the American Heart Association Stroke Council. 2018 Guidelines for the early management of patients with acute ischemic stroke: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2018;49:e46–e110.

[43] Albers GW, Marks MP, Kemp S, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med.* 2018;378(8):708–718; Nogueira RG, Jadhav AP, Haussen DC, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med.* 2018;378(1):11–21.

[44] Campbell BCV, Mitchell PJ, Churilov L, et al. Endovascular Thrombectomy for Ischemic Stroke

According to the applicant, other studies have also demonstrated that time to reperfusion is a predictor of patient outcomes. The applicant asserted that several major randomized controlled trials for mechanical thrombectomy have demonstrated improvements in functionality with faster time to reperfusion. The primary outcome of some of these trials was the modified Rankin scale (mRs) score, a categorical scale measure of functional outcome, with scores ranging from 0 (no symptoms) to 6 (death) at 90 days.[45] Pooled patient-level data from these five trials demonstrated that in the mechanical thrombectomy group the odds of better disability outcomes at 90 days (mRS scale distribution) declined with longer time from symptom onset to expected arterial puncture. Among the mechanical thrombectomy plus medical therapy group patients in whom substantial reperfusion was achieved, delays in reperfusion times were associated with increased levels of 3-month disability.[46]

The applicant referred to the American Stroke Association/American Heart Association (ASA/AHA) ''2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke,'' which recognized that the benefit of mechanical thrombectomy is time dependent, with earlier treatment within the therapeutic window leading to bigger proportional benefits. The guidelines also state that any cause for delay to mechanical thrombectomy, including observing for a clinical response after intravenous alteplase, should be avoided.[47]

The applicant asserted that the phrase ''time is brain'' emphasizes that human nervous tissue is rapidly lost as stroke progresses. Per the applicant, recent advances in quantitative neurostereology and stroke neuroimaging permit calculation of just how much brain is lost per unit time in acute ischemic stroke. To illustrate this point, the applicant stated that in the event of a large vessel acute ischemic stroke, the typical patient loses 1.9 million neurons, 13.8 billion synapses, and 12 km (7 miles) of axonal fibers each minute in which stroke is untreated. Furthermore, for each hour in which treatment fails to occur, the brain loses as many neurons as it does in almost 3.6 years of normal aging.[48] The applicant asserted that given the time-dependent nature of treatment in acute ischemic stroke patients, ContaCT could play a critical role in preserving human nervous tissue, as the application results in faster detection in more than 95 percent of cases and saves an average of 51.4 minutes in time to notification.[49]

We stated in the proposed rule that we had the following concerns regarding whether the technology meets the substantial clinical improvement criterion. The applicant provided a total of 19 articles specifically for the purposes of addressing the substantial clinical improvement criterion: four retrospective studies/analyses, nine randomized clinical trials (RCTs), three meta-analyses, one registry, one guideline, and one systematic review.

The four retrospective studies/analyses included the FDA decision memorandum, a single site of a RCT, and two abstracts related to the Automated Large Artery Occlusion Detection in Stroke Imaging (ALADIN) study. The applicant stated that the studies sponsored/conducted by the De Novo requester indicated that ContaCT substantially shortens the time to notifying the specialist for LVO cases as compared with the standard of care. However, the sample size was limited to only 85 out of 300 patients having sufficient data of CTA to notification time available. To calculate the sensitivity and specificity of ContaCT, neuro-radiologists reviewed images and established the empirical evidence. Specifically, the sensitivity and specificity was 87.8 percent (95% CI: 81.2–92.5%) and 89.6 percent (83.7–93.9%), respectively. In the proposed rule, we stated that we had concerns regarding whether this represents a substantial clinical improvement, as ContaCT missed approximately 12 percent of images with a true LVO and incorrectly identified approximately 10 percent as having an LVO. Additionally, the small sample size of less than 100 raises concerns for generalizability. Additionally, we agree with the FDA that ContaCT is limited to analysis of imaging data and should not be used in lieu of full patient evaluation or relied upon to make or confirm diagnosis.[50]

With respect to the study that was a single site of an RCT[51] presented by the applicant, the study conducted a retrospective review of the time between an initial CT at an outside hospital and the notification to the comprehensive stroke center. This retrospective analysis was conducted for one site enrolled in one of the RCTs (unspecified). The authors noted there was substantial difference in the time between initial CT at the outside hospital to comprehensive stroke center notification, due to multiple factors, including delays in neurological assessments, interpretation of imaging, utilization of advance modality imaging, and determination of tPA effectiveness. Specifically, the authors noted in their study that obtainment of advanced imaging contributed to a 57-minute delay in decision making without substantial benefits in patient outcome. We stated in the proposed rule that it was unclear whether and how this time delay and the utilization of faster notification would affect the clinical outcome of patients.

The applicant also submitted two separate abstracts for a retrospective analysis of the ALADIN study, which only provide interim results. The applicant noted for the primary analysis, the algorithm obtained sensitivity of 0.97 and specificity of 0.52, with a positive predictive value (PPV) of 0.74 and negative predictive (NPV) of 0.91, and overall accuracy of

Increases Disability-Free Survival, Quality of Life, and Life Expectancy and Reduces Cost. *Front Neurol.* 2017;8:657.

[45] Berkhemer OA, Fransen PS, Beumer D, et al. MR CLEAN Investigators. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med.* 2015;372:11–20.doi: 10.1056/NEJMoa1411587; Campbell BCV, Mitchell PJ, Kleinig TJ, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med.* 2015;372(11):1009–1018; Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, et al.; ESCAPE Trial Investigators. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J* Med. 2015;372(11):1019–1030; Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, et al.; REVASCAT Trial Investigators. Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med. 2015;372(24):2296–2306; Saver JL, Goyal M, Bonafe A, Diener HC, Levy EI, Pereira VM, et al.; SWIFT PRIME Investigators. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med. 2015 Jun 11;372(24):2285–95.

[46] Saver JL, Goyal M, van der Lugt A, et al.; HERMES Collaborators. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: a meta-analysis. *JAMA.* 2016;316:1279–1288.

[47] Powers WJ, Rabinstein AA, Ackerson T et al. On behalf of the American Heart Association Stroke Council. 2018 Guidelines for the early management of patients with acute ischemic stroke: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2018;49:e46–e110.

[48] Saver JL. Time is brain—quantified. *Stroke.* 2006 Jan;37(1):263–6.

[49] U.S. Food and Drug Administration (FDA). Center for Devices and Radiological Health. Evaluation of Automatic Class III Designation for Contact. Decision Memorandum No. 170073 (DEN170073). 2018. Retrieved from: *https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN170073.pdf.*

[50] U.S. Food and Drug Administration (FDA). Center for Devices and Radiological Health. Evaluation of Automatic Class III Designation for ContaCT. Decision Memorandum No. 170073 (DEN170073). 2018. Retrieved from: *https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN170073.pdf.*

[51] Sun CH, Nogueira J, Glenn RG, et al. Picture-to-puncture: A novel time metric to enhance outcomes in patients transferred for endovascular reperfusion in acute ischemic stroke. *Circulation.* 2013;127:1139–1148.

0.78. For the secondary analysis, which included analysis of additional (secondary) vessels, the algorithm obtained sensitivity of 0.92 and specificity of 0.75, with a PPV of 0.92 and NPV of 0.75, and overall accuracy of 0.88. In the proposed rule, we stated that we were concerned both that these are only partial results as it is not clear what the full outcome of the ALADIN study will indicate, and also that the initial overall accuracy of ContaCT varied by 10 percent between the types of strokes.

The RCTs included the following: (1) Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands (MR CLEAN);(2) Thrombolysis in Emergency Neurological Deficits—Intra-Arterial (EXTEND–IA) Trial; (3) The Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (ESCAPE) trial; (4) Randomized Trial of Revascularization with Solitaire FR Device versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting within Eight Hours of Symptom Onset (REVASCAT); (5) Solitaire with the Intention for Thrombectomy as Primary Endocascular Treatment (SWIFT PRIME) trial; (6) Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke; (7) DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo (DAWN) trial; and (8) Interventional Manage of Stroke (IMS) Phase I and II trials. The MR CLEAN trial, EXTEND–IA trial, ESCAPE trial, REVASCAT trial, SWIFT PRIME trial, Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke trial, and DAWN were all multicenter prospective RCTs evaluating a treatment group of either a microcatheter with a thrombolytic agent or mechanical thrombectomy versus a control group of the standard of care. These RCTs were evaluating the outcomes from specific treatment for patients who suffered from various strokes and not the time of imaging to treatment. While each study may have included a time-element as an experimental analysis or additional end-point, we stated that we are unsure how they support the use of ContaCT as a substantial clinical improvement over existing technologies. Also, while the IMS trials provided evidence to support a positive clinical outcome following technically successful angiographic reperfusion using time from stroke onset to procedure termination, they did not specify which part of the overall standard of care treatment affected an increase or decrease of time. The three meta-analyses utilized data from the RCTs. The Safety and Efficacy of Solitaire Stent Thrombectomy examined four trials, ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND–IA. The Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials (HERMES) collaboration authored two of the three meta-analyses. The HERMES collaboration examined data and results from five RCTs, MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND–IA. These meta-analyses confirmed the results of each of the individual RCTs of the benefits of thrombectomy versus the standard of care. However, we stated that we have concerns as to whether these meta-analyses, along with the RCTs, indicate a substantial clinical improvement with shorter notification times of an LVO.

Two articles submitted by the applicant evaluated data using the STRATIS registry. One article [52] evaluated the use of mechanical thrombectomy in consecutive patients with acute ischemic stroke because of LVO in the anterior circulation. The two groups consisted of (1) patients who presented directly to a comprehensive stroke center; and (2) patients who were transferred to a comprehensive stroke center. This study identified a difference of 124 minutes between groups, which was primarily related to longer door-to-tPA times at nonenrolling hospitals, delay between IV-tPA and departure from the initial hospital, and length of transport time. The author's primary outcome was functional status at 90 days, which found those with shorter time to treatment achieved better functional independence at 90 days. There was no difference in mortality in the two groups. While this article supports that shorter time to treatment may increase positive clinical outcomes for functional status, the study indicated time to departure from the non-enrolling hospital and transfer time as primary reasons in delayed thrombectomy treatment. These two time lapses include multiple covariates; for example, the distance between the facilities and the response of available transport (for example, ambulance). We stated in the proposed rule that these potential confounders raise questions as to the use of ContaCT shortening time to treatment.

Lastly, the applicant submitted the AHA/ASA guidelines and a systematic literature review as support for clinical improvement. We stated that we are concerned the guidelines do not support a finding of substantial clinical improvement for ContaCT because the guidelines are for the current standard of care. The systematic literature review identified the quantitative estimates of the pace of neural circuity loss in human ischemic stroke. While this supports the urgency of stroke care, we stated that we were unsure how it demonstrates a substantial clinical improvement in how ContaCT supports the urgency of stroke care.

We invited public comment as to whether ContaCT meets the substantial clinical improvement criterion.

Comment: In addressing substantial clinical improvement concerns raised by CMS in the proposed rule, the applicant summarized additional clinical evidence demonstrating ContaCT reduces time to notification, and that the device also reduces time to treatment and improves clinical outcomes.

With respect to improved clinical outcomes, the applicant described a study submitted for publication that used a prospectively-maintained database of patients undergoing thrombectomy for LVO and assessed the impact of ContaCT implementation on door-to-treatment time and patient outcomes for all patients who presented to a Primary Stroke Center currently utilizing ContaCT in the Mount Sinai Health System in New York and who subsequently underwent mechanical thrombectomy. To evaluate impact in a controlled fashion, data from pre-ContaCT implementation (October 1, 2018 to March 15, 2019) and post-ContaCT implementation (October 1, 2019 to March 15, 2020) were compared from a total of 42 patients who met the inclusion criteria. According to the applicant, the study investigators found that the post-ContaCT cohort had significantly better clinical outcomes and level of disability, as measured by a lower 5-day NIH Stroke Scores (NIHSS) and lower discharge modified Rankin Score (mRS) scores compared to the pre-ContaCT cohort, 10.78 vs. 21.93 (p=0.02) and 2.92 vs. 4.62 (p=0.03), respectively. The post-ContaCT cohort also demonstrated significantly lower median 90-day mRS scores compared to the pre-ContaCT cohort (3 vs. 5; p=0.02). In addition to these outcome measures, the post-ContaCT cohort also had significantly shorter median door-to-interventional radiologist (INR)

[52] Froehler MT, Saver JL, Zaidat 00, et al. Interhospital transfer before thrombectomy is associated with delayed treatment and worse outcome in the STRATIS registry. *Circulation.* 2017; 136(24):2311–2321.

notification time (21.5 vs. 36 minutes, p=0.02) and shorter median door-to-puncture time (165 vs. 185 minutes, p=0.20).

With respect to shorter time to treatment, the applicant summarized unpublished data from three distinct single center, retrospective investigator-initiated reviews from hospital systems that have implemented ContaCT in Colorado, Georgia, and Tennessee. The three reviews evaluated ContaCT's impact on the time from hospital arrival (Door) to skin puncture (Puncture), or DTSP, for LVO patients initially presenting to the clinical site.

At the first site, 32 patients initially presented to the emergency department at SkyRidge Medical Center in Colorado. Patients included in the analysis were divided into two cohorts. The pre-ContaCT cohort included the 16 thrombectomy patients immediately preceding ContaCT implementation and the post-ContaCT cohort included the 16 thrombectomy patients immediately after ContaCT implementation. Overall, ContaCT implementation resulted in an average reduction in door-to-puncture time of 24 minutes. Additionally, ContaCT implementation resulted in statistically significant improvements in the percentage of patients with door to puncture times of less than 90 minutes (p=0.013) and less than 60 minutes (p=.005). After installing ContaCT, 94 percent of thrombectomy cases had DTSP <90 minutes (p=0.013).

At the second site, 120 patients initially presented to the emergency department at Wellstar Hospital in Georgia. Patients included in the analysis were divided into two cohorts. Patients from pre-ContaCT implementation (July 2018 through June 2019) and patients from post-ContaCT implementation (July 2019 to June 2020) were compared. Overall, ContaCT implementation resulted in an average reduction in door to puncture time of 30 minutes (p=0.01).

At the third site, 46 patients initially presented to a Primary Stroke Center currently utilizing ContaCT in the Methodist LeBonheur Healthcare System in Tennessee. Patients included in the analysis were divided into two cohorts: Patients with LVOs identified by ContaCT and patients with LVOs not identified by ContaCT. Overall, ContaCT implementation resulted in an average reduction in door-to-puncture time of 44 minutes (p=0.03).

With respect to shorter time to notification, the applicant described data maintained by Viz.ai indicating that real-world performance of ContaCT is consistent with the results achieved in the FDA clinical study. Across 4,763 patients analyzed by ContaCT in the past six months, the median time from CT angiogram to notification of the specialist was 4.31 minutes. This compares with 5.6 minutes in the ContaCT cohort (compared with 58.7 minutes in the standard of care cohort) in the FDA clinical trial. The percentage of notifications viewed by the specialist within five minutes was 90 percent in the same cohort of patients.

In addressing concerns raised by CMS in the proposed rule regarding whether the clinical study supporting the applicant's De Novo request for ContaCT represents a substantial clinical improvement, the applicant stated that the sensitivity and specificity (87% and 90%, respectively) of ContaCT are consistent with the performance characteristic for other diagnostic services that inform clinical care and that no tests have perfect performance. Moreover, the applicant stated that because ContaCT is a triage and notification system, no harm is expected to result from false positives or false negatives. ContaCT will triage and alert on false positives resulting in an earlier read of the CT angiogram image than what otherwise would be and are quickly reviewed and appropriately triaged to non-treatment. False negatives, when no alert is sent, are managed exactly the same as today's standard of care without ContaCT, as no alert is sent in the standard of care. The applicant noted the benefit for patients with LVO that are correctly identified by ContaCT (true positives).

In addressing concerns raised by CMS in the proposed rule regarding whether the results of the clinical study supporting the applicant's De Novo request for ContaCT are generalizable, the applicant stated that data maintained by Viz.ai (and referenced above) suggest that real-world performance of ContaCT is even faster than what was found in the FDA clinical trial. According to the applicant, these internal data are supported by the additional clinical evidence provided to CMS that demonstrate not only does ContaCT reduce time to notification of the neurointerventionalist, it reduces time to treatment and improves clinical outcomes as demonstrated by lower 5-day NIHSS and lower discharge mRS.

The applicant also addressed concerns noted by CMS that results provided in the new technology application from the ALADIN study were partial results and showed somewhat more variable accuracy estimates than the FDA study. The applicant stated that complete results from the ALADIN study were unnecessary to support the performance of the ContaCT system as the primary objective of the ALADIN study was to fine-tune and optimize the ContaCT algorithm prior to the FDA study. According to the applicant, the best and most reliable data on the performance of the ContaCT device is the data from the pivotal study conducted for and submitted to the FDA as part of the *de novo* classification request.

In the proposed rule, CMS pointed to the multiple steps and variables that impact time to treatment and clinical outcomes in LVO, questioning the ability of ContaCT to shorten time to treatment. In their comment, the applicant stated that the existence of other variables that impact time to treatment and clinical outcomes does not preclude clinical benefits from one variable, such as time to notification. The applicant stated that alerting the stroke specialist earlier than the standard of care enables them to make treatment decisions earlier, shortening the amount of time to treatment and improving clinical outcomes.

The applicant also addressed CMS' concern about whether and how utilization of faster analysis and notification of suspected LVOs derived from CTA images would affect the clinical outcome of patients, considering evidence demonstrating that obtainment of advanced imaging like CTA contributed to a 57-minute delay in decision making.[53] The applicant stated that AHA's ''2019 Update to the 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke'' recommend vessel imaging, such as CTA, for patients with suspected LVOs.[54] Furthermore, according to the applicant, the AHA's broad recommendations supporting vessel imaging are consistent with requirements of pivotal trials for mechanical thrombectomy, all of which required noninvasive CTA or MR angiography (MRA) diagnosis of LVO as an inclusion criterion. Additionally, secondary analyses from the Interventional Management of Stroke (IMS) III Trial, which helped established vessel imaging as standard of care in

[53] Sun CH, Nogueira J, Glenn RG, et al. Picture-to-puncture: A novel time metric to enhance outcomes in patients transferred for endovascular reperfusion in acute ischemic stroke. *Circulation.* 2013;127:1139–1148.

[54] Powers WJ, Rabinstein AA, Ackerson T, et al; on behalf of the American Heart Association Stroke Council. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2019;50:e344–e418.

stroke imaging,[55] found that use of CTA with or without CT perfusion did not delay IV-tPA or endovascular therapy as compared to non-contrast CT in the IMS III trial.[56]

Finally, with regards to CMS' concerns about whether ContaCT provides substantial clinical improvement, the applicant stated that all available clinical guidelines support faster time to treatment. They reiterated that the importance of time in stroke care is well established, and that reducing time to treatment improves clinical outcomes. They asserted that the new clinical evidence provided in their comment demonstrated the direct effect that ContaCT has on both time to treatment and patient outcomes and they maintained that these data are consistent with a well-established body of evidence that reduced time to notification and treatment of LVO improves outcomes in patients with ischemic stroke.

We also received comments from many other commenters expressing their support for new technologies that reduce time to treatment for stroke patients, noting that rapid identification and treatment of these patients at comprehensive stroke centers offers the possibility to minimize the stroke burden and deficit and maximize the potential of a good outcome and return to function. Several commenters also recognized that rapid triaging of stroke patients has been endorsed as a best practice in published clinical guidelines. Some commenters supported the use of AI in the care of stroke patients and neuroscience patients generally, but did not endorse a particular technology, device, product, or manufacturer.

Several commenters noted their direct experience with ContaCT upon implementation of the new technology at their hospitals, asserting that communication between all providers involved in the acute care of patients with stroke has significantly improved. A commenter stated that the ContaCT triage and notification system directly saved the lives of many patients at their hospital. The commenter referenced that their hospital team performed analyses which demonstrated that the use of the ContaCT system resulted in a statistically significant improvement on transfer patient outcomes. Another commenter experienced with the ContaCT system stated it led to a dramatic improvement in patient workflow for acute stroke patients and has significantly decreased door-in door-out times for patients needing emergent treatment who present to spoke hospitals, improved decision times for ''go'' or ''no go'' for endovascular therapy at patients presenting to both spoke and hub hospitals, and has led to improved overall outcomes of patients.

Some commenters stated that rapid identification of stroke patients is especially pressing at smaller hospitals that are trying their best to transfer stroke patients to the nearest stroke center. A commenter noted that the reduction of time to treatment by ContaCT is leading to better outcomes clinically, less societal drain of resources, and fewer financial burdens to families requiring the incomes of the patients suffering from stroke disability. Another commenter asserted that if ContaCT receives approval for add-on payments, more hospitals would be able to implement this technology and, as a result, more patients would have access to life saving treatment, leading to a significant reduction of disability from stroke. According to the commenter, allowing hospitals to receive reimbursement for ContaCT would not only benefit communities in large metro areas but, more importantly, in rural areas where access to stroke care and technology is limited due to limited resources.

Response: We appreciate the commenters' input, including the additional information and analysis provided by the applicant in response to our concerns regarding substantial clinical improvement. After reviewing the additional clinical information and other analysis submitted by the applicant in response to our concerns raised in the proposed rule, we have determined that ContaCT represents a substantial clinical improvement over existing technologies because, based on the information provided by the applicant, the technology shortens time to notification, which has been shown in some instances to be critical in improving long-term outcomes in the treatment of stroke.

After consideration of the public comments we received, we have determined that ContaCT meets all of the criteria for approval for new technology add-on payments. Therefore, we are approving new technology add-on payments for ContaCT for FY 2021. Cases involving the use of ContaCT that are eligible for new technology add-on payments will be identified by ICD–10–PCS procedure code 4A03X5D.

In its application, the applicant stated that the cost per patient of ContaCT will vary based on the number of cases. As discussed previously, per the applicant, the cost per patient is calculated based on the annual list price of ContaCT multiplied by the number of subscribers, and divided by the number of ContaCT cases across such subscribers. We noted that, if ContaCT were to be approved for new technology add-on payments for FY 2021, we believed the cost per case from the applicant's original cost analysis above may also be used to determine the maximum new technology add-on payment (that is, 65 percent of the cost determined above). The applicant estimated that the average cost of ContaCT to the hospital is $1,600 based on customer data. Under § 412.88(a)(2), we limit new technology add-on payments to the lesser of 65 percent of the costs of the new medical service or technology, or 65 percent of the amount by which the costs of the case exceed the MS–DRG payment. As a result, the maximum new technology add-on payment for a case involving the use of ContaCT is $1,040 for FY 2021.

d. Supersaturated Oxygen (SSO_2) Therapy (DownStream® System)

TherOx, Inc. submitted an application for new technology add-on payments for Supersaturated Oxygen (SSO_2) Therapy (the TherOx DownStream® System) for FY 2021. We note that the applicant previously submitted an application for new technology add-on payments for FY 2019, which was withdrawn prior to the issuance of the FY 2019 IPPS/LTCH PPS final rule. We also note that the applicant again submitted an application for new technology add-on payments for FY 2020, but CMS was unable to determine that SSO_2 Therapy represents a substantial clinical improvement over the currently available therapies used to treat STEMI patients.

Per the applicant, The DownStream® System is an adjunctive therapy that creates and superoxygenated arterial blood and delivers it directly to reperfused areas of myocardial tissue which may be at risk after an acute myocardial infarction (AMI), or heart attack. Per FDA, SSO_2 Therapy is indicated for the preparation and delivery of SuperSaturated Oxygen Therapy (SSO_2 Therapy) to targeted ischemic regions perfused by the patient's left anterior descending coronary artery immediately following revascularization by means of

[55] Menon BK, Qazi E, Nambiar V, et al.; for the Interventional Management of Stroke III Investigators. Differential effect of baseline computed tomographic angiography collaterals on clinical outcome in patients enrolled in the Interventional Management of Stroke III Trial. *Stroke.* 2015; 46:1239–1244.

[56] Vagal A, Foster LD, Menon B, et al. Multimodal CT Imaging: Time to Treatment and Outcomes in the IMS III Trial. *AJNR Am J Neuroradiol.* 2016;37(8):1393–1398.