Selection criteria for large core trials: rationale for the ANGEL-ASPECT study design

Zenguang Ren,1 Xiaochuan Huo,2 Gaoting Ma,2, Xu Tong,2, Jay Kumar,3 Elliot Pressman,4 Wenhui Chen,5 Guangxiong Yuan,6 Alvin Yi-Chou Wang,7 Ming Wei,8 Jianguang Zhang,9 Guangxian Nan,10 Qiyi Zhu,11 Yajie Liu,12 Liyong Zhang,13 Weigen Song,14 Zhiming Zhou,15 Guoqing Wang,16 Tianxiao Li,17 Jun Luo,18 En Wang,19 Wentong Ling,20 Dongsheng Ju,21 Cunfeng Song,22 Shu-Dong Liu,23 Lqiagang Gu1, Tong Li,25 Yan Liu,26 Junfeng Zhao,27 Zaiyu Guo,28 Hongbo Zheng,29 Yaxuan Sun,30 Na Xu,31 Yong Jun Wang,32 Zhongrong Miao,2 on behalf of ANGEL-ASPECT Investigators and ANGEL-ASPECT Steering Committee

Two recently published JNIS commentaries1,2 on eligibility criteria for the clinical trials on patients with large core, acute ischemic stroke (AIS) with large vessel occlusion have caused some debate. Five trials were included.3 Our ongoing trial, ANGEL-ASPECT (NCT 04551664), which represents the only large core trial currently ongoing in the Chinese population, was not included in the discussion. One issue of the debate is the addition of CT perfusion (CTP)/diffusion-weighted imaging of magnetic resonance imaging (DWI-MRI) to the inclusion criteria, which only the SELECT-2 trial chose to adopt. This raised concern about whether patients already known to benefit from endovascular thrombectomy (EVT) are being randomized to EVT treatment or no treatment. Like the SELECT-2 trial, our ANGEL-ASPECT trial also added CTP/DWI-MRI to our inclusion criteria, but in a manner different from SELECT-2. Here we review the merits of ANGEL-ASPECT’s design and suggest that it be included in the discussion of patient selection criteria in large core trials.

**THE ANGEL-ASPECT TRIAL**
The ANGEL-ASPECT trial is an ongoing, multicenter, randomized controlled trial (RCT) currently being conducted in China and sponsored by Beijing Tiantan Hospital. Patients are enrolled according to a prespecified protocol. Each randomized patient is qualified by two core laboratory members who are available at all hours to calculate Alberta Stroke Program Early CT Score (ASPECTS) and infarct core volume using the specialized RAPID software.

As for the other five trials discussed in the commentary by Jadhav et al.,1 the primary goal of our trial is to determine whether EVT will benefit or harm patients with AIS and large vessel occlusion and a ‘large core’ infarct. While the ANGEL-ASPECT and SELECT-2 trials both include core volume as defined by CTP in the inclusion criteria in addition to ASPECTS, the other four trials define large core using only ASPECTS. The inclusion and exclusion criteria of the six trials are summarized in table 1. Briefly, the inclusion criteria for ANGEL-ASPECT are: 1. If ASPECTS is 3–5 and presentation is within 24 hours of onset, patients are enrolled without obtaining CTP. If ASPECTS is >5 and presentation is beyond 6 hours of onset, only patients with expected (rCBF) of <30% by CTP or apparent diffusion coefficient (ADC) of <620 on MRI and estimated core volume of 70–100 cc are enrolled. 3. If ASPECTS is <3, only patients with rCBF <30% or ADC on MRI <620 and estimated core volume of 70–100 cc are enrolled. The goal of the ANGEL-ASPECT trial is to include the maximum number of patients with a true large core for whom EVT is not recommended under current guidelines with level 1 evidence. Infarct core volume between 50 and 70 cc is not universally accepted as a ‘large core,’ so this population is excluded. By enrolling patients with ASPECTS <6, expanding the window to 24 hours from stroke onset (beyond the windows in DAWN and DEFUSE 3), and defining large core volume as >70 cc, ANGEL-ASPECT maximizes the inclusion of patients with true large cores. ANGEL-ASPECT is also important because it represents the Asian population where intracranial atherosclerotic disease...
is more common than in the Western world where most of the previous trials have been performed. This study will shed more light on how intracranial atherosclerotic disease might influence EVT results in this subgroup.

**CONCERNING INCONSISTENCY OF ASPECTS GRADING AND ABILITY OF ASPECTS TO DEFINE THE ‘LARGE CORE’**

Multiple studies\(^1\,^4\) have shown that estimated ischemic core volume is independently associated with functional independence and functional improvement. Outcomes may vary significantly in the same ASPECTS category depending on infarct volume.\(^6\) Moreover, ischemic changes in some areas of the brain are difficult to grade for ischemia on non-contrast CT (NCCT) using the ASPECTS criteria, leading to interoperator variability in ASPECTS, as was seen in the TENSION trial.\(^5\) An inaccurate ASPECTS can mis-assign the subgroup of patients eligible for ‘class I treatment guideline of ASPECTS >5’ into the untreated group, or the subgroup patients not eligible for the ‘class I treatment guideline’ into the treatment group, weakening the conclusions from the trial. If we use rCBF determined by CTR or the ADC sequence on MRI, to help to define large core, we may have a better chance of catching patients with true large cores but questionable ASPECTS.

**UNRELIABILITY OF CTP PREDICTION OF ACCURATE CORE VOLUME AND WHY INCLUDE THE CTP IN INCLUSION CRITERIA**

As indicated by JadHAV in the commentary, many studies\(^7\,^8\) have overestimated real infarct core volume from the prediction by CTP. It is known that in the early window, CTP is more likely to overestimate core volume,\(^9\) especially in the patients with very low ASPECTS, such as 0–2.\(^10\) To avoid this pitfall, in ANGEL-ASPECT, CTP is used in the inclusion criteria in only two situations: one is in the later window (>6 hours after stroke onset) in patients with ASPECTS >5 where the accuracy of CTP is maintained; the second is for patients with ASPECTS 0–2 at any time, to include patients with true large but not ‘pseudo too-large’ core. Unlike SELECT-2 whose inclusion criteria use CTP-estimated core volume in both early and later windows, and the lower inclusion threshold of 50 cc, ANGEL-ASPECT minimizes the risk of enrolling patients with favorable ASPECTS and low core volume of 50–70 cc—the two groups that may be denied proven treatment by randomization to the non-intervention group.

Many studies\(^3\,^11\,^12\) have demonstrated that patients without a mismatch do not have a favorable clinical response to reperfusion. It has been suggested that that the size of the penumbra might affect the outcome of reperfusion, and 80% of patients with AIS have penumbra regardless of the volume of the infarct core.\(^11\) Randomized trials are needed to determine the role of penumbra in clinical outcomes in patients with a large core.

**BENEFIT OF EVT IN FAVORABLE ASPECTS, LARGE CTP CORE IN THE EARLY WINDOW**

Use of EVT for patients with NCCT ASPECTS 6–10 within early window (onset within 6 hours) is supported by level 1 evidence, and CTP is generally not recommended for these patients. However, among these patients, there are some with CTP-defined ischemic core volumes ≥50 cc. Very few of these patients were included in the published RCTs and there is debate about whether these patients will benefit from EVT.\(^2\) Inclusion of patients with CTP-defined ischemic core volumes ≥50 cc may help to clarify this question.

The benefit of EVT in patients with favorable ASPECTS regardless of large’ CTP-defined core in the early window has been confirmed in multiple RCTs, and EVT for these patients is recommended by guidelines endorsed by many stroke societies.\(^15\,^15\) Choosing to randomize these patients is difficult to defend in applications to institutional review boards regulating the clinical trials in China. Furthermore, lumping patients of this group with others into a single large core’ population would hinder the ability to draw meaningful conclusions. Considering these factors, a decision was made

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**Table 1** Comparison of all six ‘large core’ trials

| Trial | TENSION | LASTE | TESLA | RESCUE-Japan LIMIT | SELECT-2 | ANGEL-ASPECT |
|-------|---------|-------|-------|-------------------|----------|-------------|
| Official title | Efficacy and Safety of Thrombectomy in Stroke With Extended Lesion and Extended Time Window | Large Stroke Therapy Evaluation - ASPECTS 0–5 | Thrombectomy for Emergent Salvage of Large Anterior Circulation Ischemic Stroke | Randomized Controlled Trial of Endovascular Therapy for Acute Large Vessel Occlusion With Large Ischemic Core | A Randomized Controlled Trial to Optimize Patient’s Selection for Endovascular Treatment in Acute Ischemic Stroke | Study of EVT in Acute Anterior Circulation Large Core Patients with a Large Infarct Core |
| NCT number | NCT03904715 | IN EXTREMIS | NCT03805308 | NCT03702413 | NCT03876457 | NCT04551664 |
| Country | Austria, Canada, Czechia, Denmark, France, Germany, Norway, Slovenia, Spain | USA, Europe | United States | Japan | United States (Canada , Europe , ) | China |
| Imaging inclusion criteria | NCCT or DWI ASPECTS 3–5 | NCCT or DWI ASPECTS 0–5 | NCCT ASPECTS 2–5 | CT-ASPECTS 3–5 or DWI-ASPECTS 3–5; 1. ASPECTS 0-6andcore<50cc 2. ASPECTS 3–5sandcore<50cc 3. ASPECTS 3–5sandcore<50cc | 1. ASPECTS 3–5 2. ASPECTS >5 (6-hour) and core 70–100 cc 3. ASPECTS <3 and core 70–100 cc |
| NIHSS score | <26 | >5 | >6 | >6 | >6 | 6–30 |
| Age (years) | >18 | 18–80 | 18–45 | >18 | 18–45 | 18–80 |
| Time | <12 hour LSW | <6.5-hour LK(U) | Random <24 hour | Random <6 hour LK(U), 6–24 FLAIR ( ) | Treat <24 hour (0–12v6–24 ) | Random <24 hour |
| Primary outcome | mRS score shift analysis | mRS score at 90A and 180 days | Utility-weighted 90-day mRS score | mRS score 0–3 at 90 days | Shift on 90-day mRS score | mRS score at 90 days |
| Actual start study date | July 20, 2018 | – | July 16, 2019 | November 2018 | October 11, 2019 | September 28, 2020 |
| Estimated primary completion date | August 31, 2020 | – | July 16, 2022 | November 2020 | May 1, 2021 | November 2022 |

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Core: CTR=90% on CT perfusion or ADC=62%; Information source: - https://clinicaltrials.gov and Website; ADC, apparent diffusion coefficient; ASPECTS, Alberta Stroke Program Early CT Score; DWI, diffusion-weighted imaging; FLAIR, fluid attenuated inversion recovery; LK(U), last known well; LSW, last seen well; LVO, large vessel occlusion; mRS, modified Rankin Scale; NCCT, non-contrast CT; rCBF, relative cerebral blood flow.
not to use CTP-defined core volume in the inclusion criteria for this population with early onset (within 6 hours) in the ANGEL-ASPECT trial.

**CTP DEFINITION OF LARGE CORE: 50 CC VERSUS 70 CC IN THE EARLY OR LATE TIME WINDOW**

As shown by several studies, overestimation of infarct core in the early window, especially within 3 hours, affects the accuracy of using CTP to evaluate the infarct core. Almost all the studies and trials use 70 cc as the criterion for large core. We believe that lowering the threshold of CTP in the early windows may exaggerate this issue considerably, resulting in enrolling more patients with pseudo-large core infarcts. Given this concern, we used the 70 cc criteria only for patients in the early window (onset <6 hours) with ASPECTS 0–2. It is also noted that the investigators of SELECT-2 have planned to make a similar change, decreasing the threshold of infarct core of rCBF on CTP from <30% to <20%, but only in patients presenting 0–2 hours after the time last known well.²

Although there is some evidence in different studies showing the benefit of EVT for patients with 50–70 cc core volume, we agree that the evidence is not that substantial, and no RCTs have confirmed this finding. Core lesions between 50 and 70 cc are not considered by all to be large core. Adding patients with 50–70 cc core lesions into the large core trial, may compromise trial conclusions. Given this concern, we set 70 cc as our lower limit. So far, CTP-based enrollment accounts for only about 10% of all enrolled patients in ANGEL-ASPECT based on the initial core-laboratory adjudication. Given the small percentage, we do not expect the power of our trial to be significantly affected in comparison with the four trials that do not use CTP-defined inclusion criteria.

**ADVANTAGES OF USING CTP-DEFINED ISCHEMIC CORE VOLUME**

Some patients have poor ASPECTS but moderate core volumes and significant penumbra. Due to the inter-rater variability of the ASPECT score, using CTP-defined ischemic core volume may be advantageous.

First, we know that patients with low ASPECTS and favorable CTP core volume may benefit from EVT. This has been confirmed by high-quality studies, although few patients with ASPECTS <6 have been previously included. CTP offers a more objective measure than ASPECTS, but this has not yet been confirmed in a high-quality RCT. Including patients with low ASPECTS and favorable CTP-defined core volume allows for comparison of these two criteria. We believe that if a patient has values of ASPECTS and CTP-defined core volume available, subgroup analysis might help to clarify the mechanism of any benefit found from EVT.

Second, debate exists about the ideal ASPECTS cut-off point. Patients with ASPECTS 0–2 are not included in our study, as in other large core trials, given the poor outcome expected in these patients. But the significant inter-rater variability of reading NCCT ASPECTS can easily lead to inclusion or exclusion of borderline patients. In a study of 337 patients with onset >6 hours, CT ASPECTS 0–2 comprised 11.6% of all ASPECTS patients, and 30.2% of all patients with ASPECTS <6. The study showed that patients with ASPECTS 2 had an average core volume of 70 cc in overall population versus 100 cc in the later window (onset time >6 hours).⁵ We believe that adding CTP inclusion criteria to this population with CTP-defined rCBF <30% 70–100 cc, given the guidelines that recommend using >70 cc to define large core volume, could avoid including patients who truly have ASPECTS 0–2 and are EVT-futile while catching more patients with a large core.

**RISK OF EARLY STOPPING FOR EFFICACY OR FUTILITY**

In contrast to the other four trials, the SELECT-2 and our ANGEL-ASPECT trials incorporated CTP-defined ischemic core volume to select patients. We believe that should either of these trials be stopped early for efficacy or futility, the other trials should continue. The different results from other trials may demonstrate the different effects of different selection strategies.

Since onset to reperfusion time is the most important modifiable factor contributing to good outcome, shortening this time should be prioritized. Under the current guideline, use of multiple imaging modalities to select patients for EVT caused an approximate 20 min EVT treatment delay, this is especially a problem in China, given that informed consent is required for contrast application and additional nursing staff are needed for contrast injection. If the trials with and without CTP inclusion criteria demonstrated non-inferiority and no increased safety concern with EVT regardless of whether penumbra was present, this would be as good as the positive result of the benefit of EVT on patients with a large core. This result would provide strong support for direct transfer to the angiography suite.

**CONCLUSION**

We believe that defining core volume using CTP can compensate for the inconsistencies of ASPECTS if we exclude patients with onset within 6 hours and core volume of 50–70 cc since these patients have already been shown to benefit from EVT in multiple RCTs. We believe that this decision captures more patients with true large core volumes for the trial. The sample size of our ANGEL-ASPECT trial is calculated based on studies excluding these populations. The power of the trial was maintained for the relatively consistent patient population with large core volume.

Twitter Alvin Yi-Chou Wang @freenalvin

Collaborators ANGEL-ASPECT Investigators: Miao Zhongrong (Beijing Tiantan Hospital, Capital Medical University; Department of Interventional Neuroradiology); Ren Zeguang (University of South Florida, Tampa General Hospital, United States of America; Department of Neurosurgery); Vitor Mendes Pereira (St. Michael’s Hospital, Toronto, Canada; Division of Neurosurgery, Department of Surgery); Hui Xiaoqian (Beijing Tiantan Hospital, Capital Medical University; Department of Interventional Neuroradiology); Ma Gaoting (Beijing Tiantan Hospital, Capital Medical University; Department of Interventional Neuroradiology); Tong Xue (Beijing Tiantan Hospital, Capital Medical University; Department of Interventional Neuroradiology); Zhang Ming (Beijing Tiantan Hospital, Capital Medical University; Department of Interventional Neuroradiology); Zhang Yuting (Beijing Tiantan Hospital, Capital Medical University; Department of Interventional Neuroradiology); Nie Ximing (Beijing Tiantan Hospital, Capital Medical University; Department of Interventional Neuroradiology); Wei Na (Beijing Tiantan Hospital, Capital Medical University; Department of Interventional Neuroradiology); Meng Bo (Beijing Tiantan Hospital, Capital Medical University; Department of Interventional Neuroradiology); Pan Yuesong (Beijing Tiantan Hospital, Capital Medical University, China National Clinical Research Center for Neurological Diseases; Center of Neurology); Zhang Xiaochuan (Beijing Tiantan Hospital, Capital Medical University; Department of Interventional Neuroradiology); Shi Xiaowei (Beijing Tiantan Hospital, Capital Medical University; Department of Interventional Neuroradiology); Liu Zhenqiang (Beijing Tiantan Hospital, Capital Medical University; Department of Interventional Neuroradiology); Pan Yuesong (Beijing Tiantan Hospital, Capital Medical University, China National Clinical Research Center for Neurological Diseases; China National Clinical Research Center for Neurological Diseases; China National Clinical Research Center for Neurological Diseases; Wang Anxin (Beijing Tiantan Hospital, Capital Medical University, China National
Clinical Research Center for Neurological Diseases; China National Clinical Research Center for Neurological Diseases; Liu Liping (Beijing Tiantan Hospital, Capital Medical University; Department of Neurology); Wang Yulong (Beijing Tiantan Hospital, Capital Medical University; Department of Neurology); Wang Yongjun (Beijing Tiantan Hospital, Capital Medical University; Department of Neurology); Ji Xunming (Capital Medical University, Xuanwu Hospital; Department of Neurosurgery); Liu Xinfeng (University of Science and Technology of China; Department of Neurology); Dong Qiang (Huashan Hospital Affiliated to Fudan University; Department of Neurology); Xu Anding (Guangzhou Overseas Chinese Hospital, the First Affiliated Hospital of Jinan University; Department of Neurology); Yang Qingwu (Xinquiao Hospital Army Medical University; Department of Neurology); Geng Xiaokun (Beijing Luhe Hospital, Capital Medical University; Department of Neurology); Zhang Shiyong (Beijing Fentai You'an Hospital; Department of Neurology); Zhou Zhiming (Yijishan Hospital of Wannan Medical College; Department of Neurology); Chen Wenhao (Zhangzhou Municipal Hospital of Fujian Province; Department of Neurology); Wang Yizhou (Guangdong General Hospital of TCM; Department of Neurosurgery); Liao Geng (Maoming People's Hospital; Department of Neurology); Liu Yuejie (Southern Medical University Shenzhen Hospital; Department of Neurosurgery); Ling Wentong (Changshun People's Hospital; Department of Neurology); Li Tong (The Second Naming People's Hospital; Department of Neurology); Xu Guodong (Hebei General Hospital; Department of Interventional Neuroradiology); Gui Liqiang (Langfang Changzheng Hospital; Emergency and Critical Stroke Ambulance Center); Li Tianxiao (Henan Province Hospital; Department of Neurology); Zhang Jiangan (The People's Hospital Of Anyang City; Department of Neurology); Ju Dongsheng (Songyuan Jilin Oilfield Hospital; Department of Neurosurgery); Zhao Junfeng (Siping Central People's Hospital; Department of Neurology); Shi Haibin (Jiangsu Province Hospital; Department of Interventional radiology); Ren Ya (The First People's Hospital of Changzhou; Department of Neurosurgery); Liu Yan (Qingjiang People's Hospital; Department of Neurology); Shi Hongchao (Nanjing First Hospital; Department of Neurology); Wu Jinhui (The Second Affiliated Hospital of Nanjing Medical University; Department of Neurology); Ding Yasuo (Jiangsu Taizhou People's Hospital; Department of Neurology); Song Weigen (Yancheng Third People's Hospital; Department of Neurology); Li Di (Dalian Municipal Central Hospital Affiliated to Dalian Medical University; Department of Interventional therapy); Jiang Changshun (Baotou Central Hospital; Department of Neurology); Zhu Qiyi (Linyi People's Hospital; Department of Neurology); Han Hongxing (Linyi People's Hospital; Department of Neurology); Wang Guoqing (Binzhou People's Hospital; Department of Neurology); Song Chunfeng (Liaocheng Third People's Hospital; Department of Neurology); Li Weirong (Taiyuan Central Hospital of Shanxi Medical University; Department of Neurology); Zhao Jing (Minhang Hospital Affiliated to Fudan University; Department of Neurology); Bi Yong (Shanghai Fourth People’s Hospital; Department of Neurology); Zheng Hongbo (West China Hospital, Sichuan University; Department of Neurology); Luo Jun (Sichuan Mianyang 404 Hospital; Department of Neurology); Li Jinglin (The Affiliated Hospital Of Southwest Medical University; Department of Neurology); Wei Ming (Tianjin Huahnu Hospital; Department of Neuroradiology); Guo Zaiyu (Teda Hospital; Department of Neuroradiology); Yin Congguo (Affiliated Hangzhou First People’s Hospital, Zhejiang University School of Medicine; Department of Neurology); Wang En (Taizhou Hospital Of Zhijiang Province; Department of Neurology); Liu Shudong (Yongchuan Hospital Of Chongqing Medical University; Department of Neurology); Cai Chuwei (Shantou Central Hospital; Department of Neurosurgery); Zhang Meng (Daping Hospital; Department of Neurology); Cai Xueli (Lishui City Center Hospital; Department of Neurosurgery); Nan Guangxian (China-Japan Union Hospital Of Jilin University; Department of Neurology); Zhang Liqiong (Liao city brain hospital in Shandong Province; Department of Neurosurgery); Yang Hua (The Affiliated Hospital Of Guizhou Medical University; Department of Neurosurgery); Sun Yaxuan (Shanxi Province Hospital; Department of Neurology); Xu Na (The Second Affiliated Hospital Of Xiamen Medical College; Department of Neurology); Yang Xingguang (The Second Affiliated Hospital Of Guangzhou Medical University; Department of Neurology); Yuan Guangxiang (Xiangtan Central Hospital; Department of Critical Care Medicine); Dai Linzhi (First Affiliated Hospital, School of Medicine, Shhezi University; Department of Neurosurgery); Huang Wengu (Maoming Hospital of Traditional Chinese Medicine; Department of Neurology); Gao Zongen (Shengli Oilfield Central Hospital; Department of Neurology); Shi Qing (Wayi Hospital of traditional Chinese medicine, Jiangmen city; Department of Encephalopathy); Tang Yufeng (Mianyang Central Hospital; Department of Neurology); Yue Wencan (Zhoukou Central Hospital; The centre of stroke); Wen Changming (Nanyang Central Hospital; Department of Neurology); Yue Wencan (Zhoukou Central Hospital; The centre of stroke); Wen Changming (Nanyang Central Hospital; Department of Neurology); ANGEL-ASPECT Steering Committee: Miao Zhongrong (Beijing Tiantan Hospital, Capital Medical University; Tiantan Interventional Neuroradiology); Ren Zeguang (University of south Florida, Tampa General Hospital, United States of America; Tiantan Interventional Neuroradiology); Vitor Mendes Pereira (St. Michael’s Hospital, Toronto, Canada; Division of Neuroradiology, Department of Surgery); Wang Yongjun (Beijing Tiantan Hospital, Capital Medical University; Department of Neurology); Wang Yulong (Beijing Tiantan Hospital, Capital Medical University; Department of Neurology); Liu Liping (Beijing Tiantan Hospital, Capital Medical University; Department of Neurology); Li Xin (Beijing Tiantan Hospital, Capital Medical University; Department of Neurology); Liu Xin (Beijing Tiantan Hospital, Capital Medical University; Department of Neurology); David Liebeskind (UCLA Comprehensive Stroke Center; Department of Neurology).

Contributors ZR drafted and revised the paper. KH, GM, XT, JK, and EP revised the paper. ZM monitored data collection for the whole trial. All members of ANGEL-ASPECT designed and implemented the trial.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. Data are available upon reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information.

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ZR and XH contributed equally.

ZR and XH are joint first authors.

To cite Ren Z, Hua X, Ma G, et al. J Neurointervent Surg Epub ahead of print: [release include Day Month Year]. doi:10.1136/neurintsurg-2021-017798

Accepted 4 July 2021

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