PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Direct transfer to angiosuite for patients with severe acute stroke treated with thrombectomy: the multicenter randomized controlled DIRECT ANGIO trial protocol
AUTHORS	Riou-Comte, Nolwenn; Zhu, François; CHERIFI, Aboubaker; Richard, Sébastien; Nace, Lionel; Audibert, Gérard; ACHIT, Hamza; Costalat, Vincent; Arquizan, Caroline; Beaufils, Olivier; Consoli, Arturo; Lapergue, Bertrand; Loeb, Thomas; Rouchaud, Aymeric; Macian, Francisco; Cailloce, Dominique; Biondi, Alessandra; Moulin, Thierry; Desmettre, Thibaut; Marnat, Gaultier; Sibon, Igor; Combes, Xavier; Lebedinsky, Ariel; Vuillemet, Francis; Kempf, Nicolas; Pierot, Laurent; Moulin, Solene; Lemmel, Philippe; Mazighi, Mikael; Blanc, Raphael; Sabben, Candice; Schluck, Eric; Bracard, Serge; Anxionnat, René; Guillemin, Francis; HOSSU, Gabriela; Gory, Benjamin

VERSION 1 – REVIEW

REVIEWER	Anderson Chun On Tsang Division of Neurosurgery, The University of Hong Kong Hong Kong
REVIEW RETURNED	14-Jun-2020

GENERAL COMMENTS	This is the protocol of a multi-center RCT testing direct transferral to angiosuite vs standard logistics in thrombectomy outcome for LVO stroke. The topic is important and relevant and the study design is appropriate. As such this study probably deserves publication. There are however several concerns regarding the protocol that should be clarified. These are listed below. Randomization and inclusion: -It was stated that randomization occurs before hospital arrival. Can the authors clarify whether pre-hospital stroke notification is available in all the involved study sites? Also, if after hospital arrival the patient was found to be in a different clinical state (symptoms, clinical history, etc),or it was found to be a stroke mimic (eg seizure) would the patient be excluded? What about for patients who presented to the hospital directly (without being evaluated by paramedical staff?)? -Patients are included if endovascular team is immediately available? Does it mean that after office hours when interventionists are off-site, then patient recruitment will automatically be halted? Intervention:

	-"Whatever the NIHSS score at admission, patients with no ICH and with LVO were treated with MT.....A low Alberta Stroke Program Early CT Scale (ASPECTS) or low collateral score was not an exclusion criterion for MT. " This is different from current clinical practice, and there is no evidence of MT benefit for low ASPECTS (0-2). Can the authors explain this extremely liberal inclusion criteria and whether this is indeed justified / ethically sound? Imaging protocol: Please define CBCT and CBCT-A and the relevant study protocol. This is perhaps the most important detail as the accuracy of CBCT/A to rule out ICH and confirm LVO directly affects the feasibility and safety of this direct angiosuite approach. What machine and protocol is used? Is this protocol validated against conventional CT/ CTA? Study center: Please include a section on how study centers are selected, and what are the capabilities in terms of angiosuite machine, 24-hours availability of on-site interventionist etc to be eligible to participate in this study. Figure 1: The flow chart indicated that in the control arm, there will still be Neuroradiology: CBCT, CBCT-A. Please clarify Typos: (please check for accuracy) Pg 3, line 4, "transfert" should be "transfer" Pg 5, line 43 "am" should be "an"

REVIEWER	Jorge Rodríguez-Pardo La Paz University Hospital Spain
REVIEW RETURNED	23-Jun-2020

GENERAL COMMENTS	In this work, the investigators present the study protocol for the DIRECT-ANGIO clinical trial, which aims to compare direct admission to angio-suite vs conventional management in an endovascular thrombectomy-capable center. The rationale is that time reduction from symptoms onset to final treatment in thrombectomy-eligible patients would improve patients' prognosis and might reduce costs. The study is interesting and will add knowledge to a hot issue currently, which is prehospital management of thrombectomy-eligible patients. The methodology is good, although language could be much improved. The following questions need to be addressed: Major points: 1- Study setting should be better defined. Do all the participating centers provide mechanical thrombectomy (MT) in a 24h/7d basis? Please specify the functioning of the stroke network(s) participating in the study. 2- Inclusion criteria for MT should be specified. Are all the participating centers adhered to the same criteria for MT (previously or purposely for this study)? If this outcome may vary according to each center daily practice, it should be stated.

	3- LVO definition according to the authors includes basilar artery and P1 segment of the posterior cerebral artery [Page 6, line 56]. However, throughout the text the authors focus on “anterior circulation” LVO. Are all LVOs (including posterior circulation) MT-eligible? It should be noted whether anterior or posterior circulation LVO will be treated distinctly throughout the study. Minor points: 4- It is unclear how rtPA is administered in direct-to-MT patients. As it is currently written [Page 10, line 1], it suggests that it might be given after MT. 5- Points 2 and 3 of the different managements [Page 10, line 9] seem to be switched. As it is currently written, patients with no arterial occlusion would receive additional imaging to decide on further treatment (?) but not those with distal arterial occlusion.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name
Anderson Chun On Tsang

Institution and Country
Division of Neurosurgery, The University of Hong Kong
Hong Kong

Please state any competing interests or state ‘None declared’:
None declared.

Please leave your comments for the authors below
This is the protocol of a multi-center RCT testing direct transferral to angiosuite vs standard logistics in thrombectomy outcome for LVO stroke. The topic is important and relevant and the study design is appropriate. As such this study probably deserves publication.

There are however several concerns regarding the protocol that should be clarified. These are listed below.

Randomization and inclusion:
-It was stated that randomization occurs before hospital arrival. Can the authors clarify whether pre-hospital stroke notification is available in all the involved study sites? Also, if after hospital arrival the patient was found to be in a different clinical state (symptoms, clinical history, etc),or it was found to be a stroke mimic (eg seizure) would the patient be excluded? What about for patients who presented to the hospital directly (without being evaluated by paramedical staff?)?
In all centers, the neurologist will be notified of stroke alert by phone before hospital arrival. If all criteria are completed, the patient will then be randomized.
The patient will not be excluded if there is clinical status modification because randomization will be done before hospital arrival. Two statistical analyses will be done: intention to treat and per protocol. Even, if the patient presents a less severe neurological deficit, he/she will stay in the included group (for example, the severity of the patient's neurological deficit may fluctuate due to collaterals).
Patients who presented directly to the hospital could not be included in the trial because pre-hospital randomization could not be done. In France, patients are referred by the SAMU, which contacts

neurologist prior to admission.

-Patients are included if endovascular team is immediately available? Does it mean that after office hours when interventionists are off-site, then patient recruitment will automatically be halted?
In the majority of centers, the neurologist is present on site whereas the interventionist is on call. Thus, if patient arrived at the hospital before the angiosuite team, inclusion would not be possible. Thus, according to the local organization, inclusion is possible during office hours.

Intervention:
-"Whatever the NIHSS score at admission, patients with no ICH and with LVO were treated with MT.....A low Alberta Stroke Program Early CT Scale (ASPECTS) or low collateral score was not an exclusion criterion for MT. "
This is different from current clinical practice, and there is no evidence of MT benefit for low ASPECTS (0-2). Can the authors explain this extremely liberal inclusion criteria and whether this is indeed justified / ethically sound?
First, randomization will be performed before hospital arrival. The NIHSS evaluation was therefore not possible due to the paramedics management. No baseline NIHSS cut-off is defined because pre-hospital NIHSS evaluation is impossible and randomization is yet done. Second, as previously noted, patients may have a less severe neurological deficit than before randomization but with persistent proximal intracranial occlusion (fluctuation). However, patients presented a severe neurological deficit before randomization.
Pending the results of ongoing RCT such as LASTE trial, there is no evidence of thrombectomy clinical benefit for patients with ASPECTS 0-2, however, within the first 6 hours of onset, there is some data supporting benefit of early thrombectomy in these patients. In addition, the CBCT can detect ICH but is less informative for early ischemic sign. This is why, no ASPECTS cut-off was defined

Imaging protocol:
Please define CBCT and CBCT-A and the relevant study protocol. This is perhaps the most important detail as the accuracy of CBCT/A to rule out ICH and confirm LVO directly affects the feasibility and safety of this direct angiosuite approach. What machine and protocol is used? Is this protocol validated against conventional CT/ CTA?
It will use the machine and protocol of each center.
We changed the protocol concerning the direct angiosuite approach group: a CBCT is performed to rule out ICH; then an angiogram is performed to confirm LVO, and then a thrombectomy is performed in case of confirmed LVO. Thus, there is no need of validated CBCT angiogram.

Several papers reported the feasibility of CBCT to detect intracranial ICH (Effective dose to patient measurements for flat-detector computed tomography protocols in acute stroke care. Brehm A, Stamm G, Lüpke M, Riedel C, Stieltjes B, Psychogios MN. Eur Radiol. 2020 Sep;30(9):5082-5088; Diagnosing Early Ischemic Changes with the Latest-Generation Flat Detector CT: A Comparative Study with Multidetector CT. Maier IL, Leyhe JR, Tsogkas I, Behme D, Schregel K, Knauth M, Schnieder M, Liman J, Psychogios MN. AJNR Am J Neuroradiol. 2018 May;39(5):881-886; Latest generation of flat detector CT as a peri-interventional diagnostic tool: a comparative study with multidetector CT. Leyhe JR, Tsogkas I, Hesse AC, Behme D, Schregel K, Papageorgiou I, Liman J, Knauth M, Psychogios MN. J Neurointerv Surg. 2017 Dec;9(12):1253-1257.).

Study center:
Please include a section on how study centers are selected, and what are the capabilities in terms of angiosuite machine, 24-hours availability of on-site interventionist etc to be eligible to participate in this study.

10 centers participate in the trial.
There is 5 mandatory centers of the region (due to the funding of PHRC inter-regional) and 5 other centers in France. The 5 other centers were choice for the stroke management volume, and the quality of clinical research.

Figure 1:
The flow chart indicated that in the control arm, there will still be Neuroradiology: CBCT, CBCT-A. Please clarify
The modifications have been made in figure 1.
Effectively, in control arm, conventional imaging is performed (MRI/CT) and in experimental arm (CBCT and angiogram)

Typos: (please check for accuracy)
Pg 3, line 4, "transfert" should be "transfer"
Pg 5, line 43 "am" should be "an"
Corrections have been made.

Reviewer: 2
Reviewer Name
Jorge Rodríguez-Pardo

Institution and Country
La Paz University Hospital
Spain

Please state any competing interests or state ‘None declared’:
None declared

Please leave your comments for the authors below
In this work, the investigators present the study protocol for the DIRECT-ANGIO clinical trial, which aims to compare direct admission to angio-suite vs conventional management in an endovascular thrombectomy-capable center. The rationale is that time reduction from symptoms onset to final treatment in thrombectomy-eligible patients would improve patients’ prognosis and might reduce costs. The study is interesting and will add knowledge to a hot issue currently, which is prehospital management of thrombectomy-eligible patients.
The methodology is good, although language could be much improved. The following questions need to be addressed:
Major points:
1- Study setting should be better defined. Do all the participating centers provide mechanical thrombectomy (MT) in a 24h/7d basis? Please specify the functioning of the stroke network(s) participating in the study.
Yes, all centers provide mechanical thrombectomy in a 24h/7d.

2- Inclusion criteria for MT should be specified. Are all the participating centers adhered to the same criteria for MT (previously or purposely for this study)? If this outcome may vary according to each center daily practice, it should be stated.
Inclusion criteria for MT vary in the centers. However, the same inclusion criteria will be use for including patients in the DIRECT ANGIO trial.

3- LVO definition according to the authors includes basilar artery and P1 segment of the posterior cerebral artery [Page 6, line 56]. However, throughout the text the authors focus on “anterior

circulation" LVO. Are all LVOs (including posterior circulation) MT-eligible? It should be noted whether anterior or posterior circulation LVO will be treated distinctly throughout the study.
Yes, all specified LVO will be treated in intention to treat analysis.
However, according to the clinical symptoms presented at admission, the probability of posterior LVO is low.

Minor points:

4- It is unclear how rtPA is administered in direct-to-MT patients. As it is currently written [Page 10, line 1], it suggests that it might be given after MT.
rtPA will be administered according to the international guidelines after exclusion of ICH with CBCT performed in angioroom, and according to local practice of each center.

5- Points 2 and 3 of the different managements [Page 10, line 9] seem to be switched. As it is currently written, patients with no arterial occlusion would receive additional imaging to decide on further treatment (?) but not those with distal arterial occlusion.
Effectively, patients with confirmed distal arterial occlusion (on initial angiogram) will be treated with IV thrombolysis only if eligible and without additional imaging (not necessary). In contrary, patients without arterial occlusion could be treated with IV thrombolysis (if persistent neurological deficit and according to neurologist decision), but an additional imaging will be performed immediately after angioroom exit.

VERSION 2 – REVIEW

REVIEWER	Anderson Tsang The University of Hong Kong Hong Kong
REVIEW RETURNED	08-Sep-2020

GENERAL COMMENTS	The authors have addressed the concerns raised in the previous rendition.

REVIEWER	Jorge Rodríguez Pardo La Paz University Hospital and Stroke Center Spain
REVIEW RETURNED	02-Sep-2020

GENERAL COMMENTS	The authors have provided adequate responses to reviewer's comments and the text has been improved.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name
Anderson Tsang

Institution and Country
The University of Hong Kong
Hong Kong

Please state any competing interests or state 'None declared':

none

Please leave your comments for the authors below
The authors have addressed the concerns raised in the previous rendition.

Reviewer: 2
Reviewer Name
Jorge Rodríguez Pardo

Institution and Country
La Paz University Hospital and Stroke Center
Spain

Please state any competing interests or state ‘None declared’:
None declared

Please leave your comments for the authors below
The authors have provided adequate responses to reviewer's comments and the text has been improved.