Author’s response to reviews

Title: Asymmetrical Bioimpedance in the Anterior Circulation for Urgent Stratification of suspected Stroke (ABACUS Stroke): study protocol for a diagnostic accuracy study

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Reviewer reports:

Reviewer #1: I read with interest the protocol "Asymmetrical Bioimpedance in the Anterior Circulation for Urgent Stratification of Stroke (ABACUS Stroke): study protocol for a diagnostic accuracy study". The authors plan on a diagnostic accuracy study of a novel device using volumetric impedance phase shift spectroscopy (VIPS). There long-term aim is to reliably detect and triage "complex strokes" and large vessel occlusion to comprehensive stroke centers in a prehospital setting. But this study will be conducted in a ED setting.

The tool seemed promising in preliminary studies and the publication of protocols are necessary to ensure well-conducted research. The protocol is overall suitable and may be of interest to (vascular) neurologists, prehospital care teams, and ED physicians. However, the technical details of VIPS can hardly be understood by physicians. The topic does carry clinical relevance.
The discussion is reasonable and proves knowledge in the area. Overall, the protocol is clearly written. However, the terms used are somewhat unusual and the compound endpoint, details of the statistics as well as methodology somewhat questionable.

Below is a list of major and minor concerns:

Major:

1) Page 25: is this a derivation cohort study or are you going to used a prespecified cutoff of the VIPS-output?

RESPONSE: Thank you, we agree that this is not clear. Based on previous work (Kellner 2018), we intend to validate a pre-specified cut off (a CBA value ≥ 10 would indicate a positive state) to determine test accuracy. This threshold will be considered acceptable if it results in specificity of at least 80% and sensitivity of at least 70%. These values have been chosen as clinically important.

However, the population to be recruited to this study is likely to differ from this earlier work in that it will be more representative of the suspected stroke population where the test would be most usefully deployed. Therefore, the threshold of 10 may not meet the criteria described above. If this is the case, a new threshold will be estimated.

Based on this comment and comments from reviewer #2, we have considerably updated the statistical analysis section. As this is a large block of text, for ease we have not copied it here but it can be seen as ‘tracked changes’ in the revised manuscript.

2) in the decision tree a small cortical (non-lacunar) infarct can "overrule" a ICH of 29ml in the basal ganglia. I think this should be changed, that any ICH overrules "territorial infarctions", which will almost never cause the symptoms leading to ED admission.

RESPONSE: Thank you for this point but we think that the reviewer has misinterpreted the diagram. The diagram describes the systematic process for allocation of the combined radiological and clinical outcome state (reference standard) per patient. It is not a clinical diagnostic tool. Box 4 in the decision tree describes previous territorial infarction i.e. previous large stroke. If this is present on imaging (provided the earlier states of LVO, SSAVS and large ICH do not exist), this will be the outcome state assigned. This is because, as explained in the background, previous territorial infarction in some healthcare systems are preferentially directed towards specialist stroke centres and therefore it is considered to be a state which is desirable to detect with the visor. Because of this, prior territorial stroke ‘overrules’ a small ICH in care priorities and therefore amongst the diagnostic outcome states. Specialist views may vary about this latter hierarchy and data will be reported transparently so that individuals can consider what the results mean for their own practice.

Minor:
1) Title: AC only? What about PC Strokes?

RESPONSE: The device has been engineered to detect changes within the cerebral hemispheres rather than posterior fossa. This is because a main proposed use is early identification of people suitable for thrombectomy. However, the visor readings will be taken from people with suspected stroke, some of whom may turn out to have posterior circulation stroke. As the study definition of LVO covers only anterior vessel occlusion, the decision tree will render such patients as ischaemic stroke without LVO. An exploratory analysis is planned to examine the impact of posterior stroke. The title concurs with the intended device use which relates to problems with the anterior circulation.

2) Abstract: "… stroke aetiologies including LVO" and "can identify key stroke aetiologies". Etiologies are usually referred to for TOAST classification (Large artery, small vessel, cardioembolic … ). Doubt that the machine can do this. Would rewrite "System device may be able to identify presence of LVO in AIS".

RESPONSE: Thank you, we have amended the sentence to:

Cerebral Bioimpedance Asymmetry (CBA) measurement obtained with the portable and rapid Cerebrotech VisorTM System device may be able to identify certain types of stroke including LVO.

3) Abstract: "intracerebral haemorrhage &gt;59 or &lt;60mls» What about 59.5??

RESPONSE: Thank you, we have amended the sentence to clarify:

….ischaemic stroke +/- large vessel occlusion; symptomatic severe anterior vessel stenosis; large (≥60ml) and small (&lt;60mls) vessel intracerebral haemorrhage; transient ischaemic attack; stroke mimic conditions; prior territorial stroke.

4) Page 5 line 104 "may not be offered thrombectomy treatment": if angiography is not available, all patients should be transferred to a center where CT/MR-angiography is available. Would remove this statement.

RESPONSE: Thank you, however, as stated within this sentence, in many healthcare settings (including the UK) the situation is that CTA/MRA is not always available. One future use of CBA measurement may be in such centres to detect the need for urgent transfer out for further assessment.

5) Page 5 line 127 "severe anterior vessel stenosis (SSAVS)»: the usual term is intracranial artery stenose (ICAS), would rephrase to (anterior circulation) ICAS.

RESPONSE: Thank you for raising this point. We acknowledge that there are variations in terminology for this state, and both terms are used somewhat interchangeably. The choice of SSAVS is to emphasize that the device is seeking anterior cerebral circulation stenosis which is
responsible for the current symptoms. ICAS would include other vessels and possibly incidental
discovery e.g. in a stroke mimic presentation.

6) Page 6 line 132: "whether urgent stenting should be offered on a case by case basis":
Despite recent WEAVE positive results, the primary treatment for ICAS is dual
antiplatelet, statin therapy and aggressive risk factor management. Stenting is ultima ratio
and should therefore not be mentioned here until all conservative treatment options fail.

RESPONSE: Although we agree with the reviewer on this management approach for intracranial
stenosis, we also have to acknowledge that there are international variations based upon
individual patient assessment. It is not the purpose of the device to decide upon management,
and the background of the protocol cannot cover all possible treatment preferences. The main
purpose of detection of this state would be to transport the patient to a location where stenting
was available, if that was the local clinical practice.

7) Page 17: Stenosis grade SSAVS: In MRA, especially TOF, this is going to be very
unreliable. Even in CTA, this is difficult. Are you doing perfusion imaging in all
patients? Are you going to double-check with intracranial ultrasound?

RESPONSE: The study is evaluating whether the visor can identify states compared against
reference standards which reflect the standard clinical assessment used in the study setting. In the
UK it is not standard practice to initially identify high grade stenosis using CTP or doppler, and
as the purpose of the visor is initial screening it is being compared against CTA/MRA, which is
the standard clinical approach for initial assessment. Clinical assessment of symptoms by NIHSS
is used to determine whether a stenosis is symptomatic. The visor is not intended to replace
advanced imaging which is not performed routinely.

8) Page 17 "the severity of the focal symptoms is &gt;= 6 on the NIHSS scale.": in iCAS
NIHSS is often fluctuating, which one will you count? Highest/lowest/admission?

RESPONSE: Thank you. We agree that this was not clear. We intend to use the admission
NIHSS and have modified the sentence to:

.....c) the severity of the focal symptoms is ≥ 6 on the NIHSS scale (measured on admission).

9) Page 19: What to do with posterior circulation stroke?

RESPONSE: Please see the response above.

Reviewer #2: Nice to see a protocol for a dedicated diagnostic accuracy study. Below are my
comments focusing of completeness & clarity of the protocol and the rationale behind
choices in the design and analyses.

1. Title
I would add "…urgent stratification of patients suspected of stroke" to highlight the correct population.

RESPONSE: Thank you. We have altered the title to:

Asymmetrical Bioimpedance in the Anterior Circulation for Urgent Stratification of suspected Stroke (ABACUS Stroke): study protocol for a diagnostic accuracy study

2. Abstract: use of "double bind"

Double blind is a confusing term even in the context of RCTs, but even less useful in a diagnostic accuracy study. I would rather describe what information was available to the readers of the Cerebral Bioimpedance Asymmetry (CBA) measurement and whether the result of the CBA measurement was used in the further work-up.

RESPONSE: Thank you. We agree that the term ‘double blind’ is potentially confusing. We have removed this terminology from the abstract. However, word count limitations in the abstract prevent longer explanation. Instead, we have altered the ‘study design’, ‘index test’ and ‘blinding’ sections in the main text to be clearer about this issue. As this is several blocks of text, we have not copied it here but it can be seen as ‘tracked changes’ in the revised manuscript.

3. Abstract: index test results

Please add what type of result the CBA measurement produces (binary, ordered categories, continuous) and whether any predefined threshold exist.

RESPONSE: Thank you, we have added this information and the sentence now reads as:

Index Test: Cerebral Bioimpedance Asymmetry measurement performed using the Cerebrotech Visor™ System. Measurement values produce continuous data (range 0 – 100); pre-defined threshold for positive state ≥ 10.

4. Background, page 4, line 79 following

The current information about the treatments is rather uninformative. Please provide the absolute risks for the outcome for these interventions in relation to the absolute risk in the control groups.

Furthermore, is the outcome long-term disability only or a composite including death as well?

RESPONSE: Thank you for raising this. There is already extensive literature about the risks and benefits of different interventions to treat acute stroke which is summarised in the referenced systematic reviews. These relationships are complicated due to strong interactions with time after stroke, the technologies used and outcome definitions. For the purpose of this diagnostic protocol we do not think it would be helpful to give additional detail as it is the principle of early stratification which is important, and average NNT from the systematic reviews is the simplest
justification. Regarding the specific treatments mentioned (thrombolysis and thrombectomy), evidence shows that these reduce disability but do not reduce mortality, and the text is correct to refer to long term disability.

5. Background, page 8, second bullet

I would rephrase as: To explore whether key clinical characteristics and radiological features are associated with the diagnostic accuracy of CBA

RESPONSE: Thank you for this suggestion which we considered. However, we intend that this objective covers different analyses and believe that our original wording is preferable. Based on comments below, we have revised the statistical analysis section considerably and hope this is now clearer.


See previous remark about double blinding.

RESPONSE: As above, we have amended this.

7. Methods page 9, line 217 and following about inclusion criteria and study flow

The intended use in practice will be that CBA measurement is performed first followed by further investigations and management. The protocol now allows for imaging to be performed first. The danger becomes that performing the imaging or any findings on imaging will influence the decision to do the CBA measurement. The study population will then not be the correct reflection of the suspected population. Ideally perform the CBA before the imaging, or ensure that such drop-out will not occur (minimalized) and clearly report the numbers, reasons and characteristics of suspected patients not undergoing CBA.

RESPONSE: We agree that ideally all readings should be taken before brain imaging but emergency imaging is generally performed rapidly because of the time-critical nature of stroke treatments, and research procedures must not delay patient care. If CBA readings were only permitted before brain imaging then many arriving suspected stroke patients would not be able to be included in the study as time would not permit. This would result in an unrepresentative population.

The CBA readings are being conducted by trained staff, predominantly research nurses. We believe that it is very unlikely that these staff will not perform a CBA reading because of a particular imaging result. All have received training about the study and understand that the purpose of the study is evaluation of the device accuracy when used on the broad suspected stroke population. Nevertheless, staff have been encouraged to take a CBA reading before imaging if this is possible.

Unfortunately, it is not logistically possible to collect data about all arriving suspected stroke patients. Whilst we agree with the reviewer that these data would likely be very valuable, the
clinical and research systems in which we operate make this impossible. Suspected stroke patients turn out to have many different diagnoses and from the emergency department are onward diverted to many different places in hospitals. Clinical systems have no robust way of logging these patients as suspected stroke which would be necessary in order to allow their later location for data collection. In addition, if a robust logging system could be put into operation, to collect data about these patients as suggested by the reviewer (characteristics) would require their consent. Consent plus the additional data collection (≥1000 patients per year attend with suspected stroke) would add considerably to the workload of staff involved in the project. However, there is published literature describing the suspected stroke population and their final diagnoses. We will be able to use this literature to review whether our study population appears to be representative of the suspected stroke population.

8. Methods page 10, about study flow, line 254

This study will not be based on a consecutive series, as inclusion may depend on availability of personal trained in CBA measurement. Careful document and describe all patients fulfilling the in- and exclusion criteria, but in whom no CBA measurement was performed and state reasons. This information will be crucial to judge the risk of bias and concerns about applicability.

RESPONSE: Please see response to point 7 above. Whilst we agree with the reviewer that such data would be very valuable, it will not be possible to do this. However, as noted above, we can review whether our population appears to be representative using published series about suspected stroke. As both stroke and stroke mimic presentations occur at random, we do not think that the availability of trained staff will create a bias within the case-mix.

9. Methods page 14, Index test section, type of measurement

Please describe what the (final) result of CBA measurement looks like with respect to its measurement scale like ordinal categories, percentage, continuous measurement.

RESPONSE: We have added the following to the last paragraph in this section:

In order to create the numerical value for CBA (continuous data values 0 – 100), raw data from the CVS must be further analysed by software held by the device manufacturer (Cerebrotech Medical Systems Inc).

10. Methods page 14, Index test section, use thresholds

Add information whether thresholds in case of a continuous measurement will be used and whether these thresholds are pre-defined (report thresholds) or will be determined.

RESPONSE: Thank you, we agree that this was not clear. However, in keeping with a comment from reviewer #1, we have included this information in the statistical analysis section.

11. Methods page 14, Index test reading
Explicitly state which patient characteristics and other test results will be available to the person(s) reading the index test.

RESPONSE: The index test result (CBA reading) will be prepared by the manufacturer following receipt of anonymised raw data from the device. No clinical data will be available to the person(s) providing the CBA reading. We have added the following sentence to the last paragraph in this section:

No clinical data will be available to the manufacturer prior to provision of a CBA reading.

12. Methods page 15, Reference standard test section

Remove the word comparator. In diagnostic accuracy research we aim to reserve the word comparator and comparative for studies comparing two or more index tests. Your study is a single test diagnostic accuracy study.

RESPONSE: This has been removed.

13. Methods page 15, Reference standard test section

This section might be more informatively labelled as "Target conditions" as the techniques how to establish these target conditions are described in the next section correctly labelled as "Reference standards"

RESPONSE: We have simplified this section by removing the second ‘Reference standards’ subheading and used ‘Reference standards’ for the main section heading. The first paragraph then serves as a necessary introduction about the complexity of the clinical states involved in this study.

14. Methods page 23, Blinding

Also clearly state which information was available to those performing and reading the CBA measurement

RESPONSE: The following has been added to this section:

In addition, staff from Cerebrotech Medical Systems Inc who will provide CBA readings from raw measurement data, will not have access to any clinical data prior to provision of a CBA reading.

15. Methods page 25, Statistical analysis section

This section is now too generic and not directly linked to the different objectives of the study. So please describe the statistical analysis for each of the objectives. First: To determine the diagnostic accuracy of CBA measurement to identify complex stroke. If sens, spec and predictive values will be calculated, clearly state which threshold will be used or selected. Explain
how the ROC curve will be constructed and if the ROC is constructed from a logistic regression indicate whether other factors than CBA will be added to the model. Second, To determine the diagnostic accuracy of CBA measurement to identify LVO. See remarks above.

Third, To explore key clinical and radiological influences upon the diagnostic accuracy of CBA measurement for complex stroke and LVO. Clearly indicate which variables will be examined and in which way.

RESPONSE: Thank you for this point and point 16. We accept that this section was too generic and we have revised it considerably. As this is a large block of text, for ease we have not copied it here but it can be seen as ‘tracked changes’ in the revised manuscript.

A fully detailed statistical analysis plan will also be prepared prior to data analysis.

16. Methods page 25, Statistical analysis section

Please pre-specify in the protocol which subgroups will be analyzed and which factors will used in the multivariable modelling.

RESPONSE: As above

17. Methods page 25, Statistical analysis section

Good to see the clear description which patients will be excluded from the analysis. Can you provide the values for the pre-defined physiological range? Please add specifically that patients in whom the GBA reading failed will be reported but excluded from the analysis.

RESPONSE: Thank you for raising these points. In hindsight, we have used the phrase ‘pre-defined physiological range’ incorrectly. All readings will be checked for a plausible bioimpedance pattern. If a plausible pattern is present, a CBA reading will be provided. However, if an implausible pattern is noted, a CBA reading will not be provided and it will be recorded that the reading resulted in implausible data. The number of implausible readings will be reported. We have revised the sentence as follows:

All CBA readings obtained will be checked for a plausible bioimpedance pattern. Participants with CBA readings which are perceived to be implausible will not be included in the analyses e.g. readings obtained from patients with previously unknown cranial metallic implants.

In relation to the reviewer’s point about exclusion of patients with failed readings, the following has been added to the exclusion section:

d. Participants where a CBA reading is attempted but this is unsuccessful (the CVS alerts the operator to failure to capture data).

18. Methods page 26, Sample size consideration
I miss the rationale for focusing on specificity in the sample size section. Please provide this rationale. Also provide an indication what kind of precision can be expected around estimates of sensitivity.

RESPONSE: We have added the following rationale to the start of the sample size section:

The future intended purpose of CBA measurement is to ‘rule in’ patients with complex stroke and/or LVO from the suspected stroke population. The sample size calculation is therefore based on detection of test specificity. ‘Rule in’ is chosen as the test results would be used to re-direct individuals to a neuroscience centre for highly specialist care. Suspected stroke patients without a diagnosis of complex stroke or LVO do not need transportation to a neuroscience centre and should be admitted to the nearest local hospital.

In terms of sensitivity, with the given sample size (which would give 30 participants with LVO, and 38 with complex stroke), and an expected sensitivity of 85%, the expected 95% confidence intervals for sensitivity would be:

- Complex stroke = (63%, 100%).
- LVO = (61%, 100%).

We have added the following to the sample size section:

In terms of sensitivity, the 112 participants would detect a sensitivity of 85% (95%CI: 63%-100%) for complex stroke and 85% (95%CI: 61%-100%) for LVO.

19. Methods page 25, Statistical analysis section

STARD is general guideline to improve the reporting (complete and accurate) for diagnostic accuracy studies. It is useful reminder what type of information needs to be present however, it provides no guidance how to set-up the statistical analysis or how to design the study. Therefore, remove it from the statistical analysis section. Only have a general statement in the Methods that STARD will be used in the reporting of the study.

RESPONSE: As advised, we have moved this statement to the start of the methods section.

20. General remark

Check whether all the abbreviations are necessary as reading becomes more difficult especially for more general readers.

RESPONSE: We have removed several abbreviations to aid reading.