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Reply to “Independent Confirmation”

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We thank Herweh and Nagel for their interest in our independent study assessing e-ASPECTS software (Brainomix Ltd, UK).

Per our recent *Annals* publication¹ and pre-specified statistical analysis plan,² RITeS had two co-primary outcomes:

1. Compare ASPECTS³ results provided by software to those of experts, and
2. Test the diagnostic accuracy of software for identifying imaging features of stroke.

ASPECTS is used to assess the middle cerebral artery territory; results range from 10 when no ischaemic lesion is identified to 0 when the entire territory is affected. We used several methods to compare ASPECTS results of software and experts but chiefly diagnostic accuracy with clinically relevant thresholds (we found software accuracy of 66–90% depending on threshold), and we pre-defined that scores would be considered equivalent if within 2 points (82% were equivalent). Non-inferiority testing was added for comparison with previous work,⁴ it was not our “primary endpoint.”

RITeS was designed to specifically avoid result inflation by favourable case selection. Our “representative” population is an attempt to emulate what might happen if all patients with stroke symptoms are processed using e-ASPECTS software. We have already seen evidence of this; early data from some hospitals in England trialling artificial intelligence (AI) software for stroke suggests more computed tomography (CT) scans are being processed per quarter than there are stroke admissions per annum. This is probably because the CT being processed by e-ASPECTS is also how we determine whether a stroke syndrome is likely to be caused by ischemia, hemorrhage, or something else. In other words, we can only decide if software processing is appropriate for a scan (in line with its intended use) after that scan has been acquired (by which time the automated processing may have occurred). It is not software replacing physicians that concerns us, rather

software replacing sufficiently experienced clinicians who know when to appropriately disregard software results.

Unlike other studies, including the analysis of ENCHANTED trial data,⁵ we did not pre-emptively exclude CTs based on quality, again to provide more realistic results. Inevitably perhaps, the 10% of cases not successfully processed by software in our study is greater than in studies which had already excluded some/many cases (and thus may have masked the true rate). We have also acknowledged that the use of archived data in RITeS (and in most other studies) may have inflated the number of scans that were not processed compared to real-time clinical practice. As stated in our methods, we processed CTs using cloud-based Brainomix servers and thus anticipate the hardware was appropriate. We understand that unsuccessful software processing due to "upload failure" and "cancellation" are more likely when processing is cloud-based rather than on a local server. However, most companies offering stroke imaging software, including Brainomix, provide cloud processing and therefore these results are clinically relevant. We were careful to avoid the word 'failure' when describing the analysis of ENCHANTED CTs. We acknowledge we could have separated true processing failure from CTs pre-emptively excluded on technical grounds, but the proportion of scans *successfully* processed would remain the same at 69%, leaving 31% not processed.⁵

Potential Conflict of Interest

No conflicts of interest declared.

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