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A Reduction in Time with Electronic Monitoring In Stroke (ARTEMIS): study protocol for a randomised multicentre trial

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ABSTRACT

Introduction Time is the most crucial factor limiting efficacy of intravenous thrombolysis (IVT) and intra-arterial thrombectomy (IAT). The delay between alarming the Emergency Medical Services (EMS) dispatch office and IVT/IAT initiation, that is, the *'total system delay'* (TSD), depends on logistics and team effort. A promising method to reduce TSD is real-time audio-visual feedback to caregivers involved. With 'A Reduction in Time with Electronic Monitoring in Stroke' (ARTEMIS), we aim to investigate the effect of real-time audio-visual feedback on actual TSD to IVT/IAT to caregivers.

Methods and analysis ARTEMIS is a multiregional, multicentre, randomised open end-point trial including patients ≥18 years considered IVT/IAT-eligible by the EMS dispatch office or on-site EMS personnel. Patients are electronically tracked and randomised for real-time audio-visual feedback on TSD to caregivers via premounted handhelds and tablets throughout the TSD trajectory. Primary outcome is TSD to IVT/IAT. Secondary outcomes comprise proportion of IVT/IAT-treated patients, symptomatic intracerebral haemorrhage, IVT/IAT-treated stroke mimics, clinical outcome after three months and cost-effectiveness. Separate analyses for IAT-patients with or without prior IVT, within or out of office hours and EMS region will be performed. With 75 IAT-patients and 225 IVT-patients in each arm, we will be able to demonstrate a 20 min difference in TSD to IAT and a 10 min difference in TSD to IVT (p=0.05 and power=0.8).

Ethics and dissemination Study findings will be disseminated through peer-reviewed journals and (inter) national conference presentations.

Trial registration number NCT02808806; Pre-results.

Strengths and limitations of this study

- A Reduction in Time with Electronic Monitoring in Stroke is a multiregional, multicentre, randomised trial providing high external validity.
- The intervention establishes a unique connection in the chain of acute stroke care bridging the gap between separate prehospital and in-hospital caregivers involved.
- The PROBE design is pragmatic and reflects standard clinical practice of acute stroke care.
- We anticipate that during the study period, treatment delays will decrease due to initiatives aimed to optimise logistics other than our intervention.
- A carryover effect of the intervention cannot be fully excluded but is estimated to be unlikely since shifts of stroke teams occur multiple times a day.

INTRODUCTION

For acute ischaemic stroke, the clinical benefit of intravenous thrombolysis (IVT) within 4.5 hours and of intra-arterial thrombectomy (IAT) within 6 hours from symptom onset is firmly established.[1–7] For both IVT and IAT, the passing of time is the most crucial factor limiting clinical effectiveness.[8–10] For example, with every 15 min delay to treatment, the chances of independent ambulation substantially decrease and 1 month of disability-free life is lost.[2–6 8 11 12] Moreover, reducing treatment delays will make IVT/IAT accessible for patients who would otherwise exceed the IVT/IAT time window. Therefore, reducing delay to IVT/IAT is of paramount importance. This has been substantiated by guidelines with the door-to-needle time (DNT) for IVT as an important practice and quality parameter,[13 14] and this will likely transpire for the door-to-groin time (DGT) for IAT as well.[15]

Since the introduction of IVT, median DNTs have been reduced, but further reduction is still possible.[13] Reducing DGT appears logistically even more challenging. More caregivers are involved and IAT frequently requires interhospital transport.

Besides in-hospital delays, prehospital delays should be considered (eg, time spent on scene by Emergency Medical Services (EMS) personnel). These delays are often

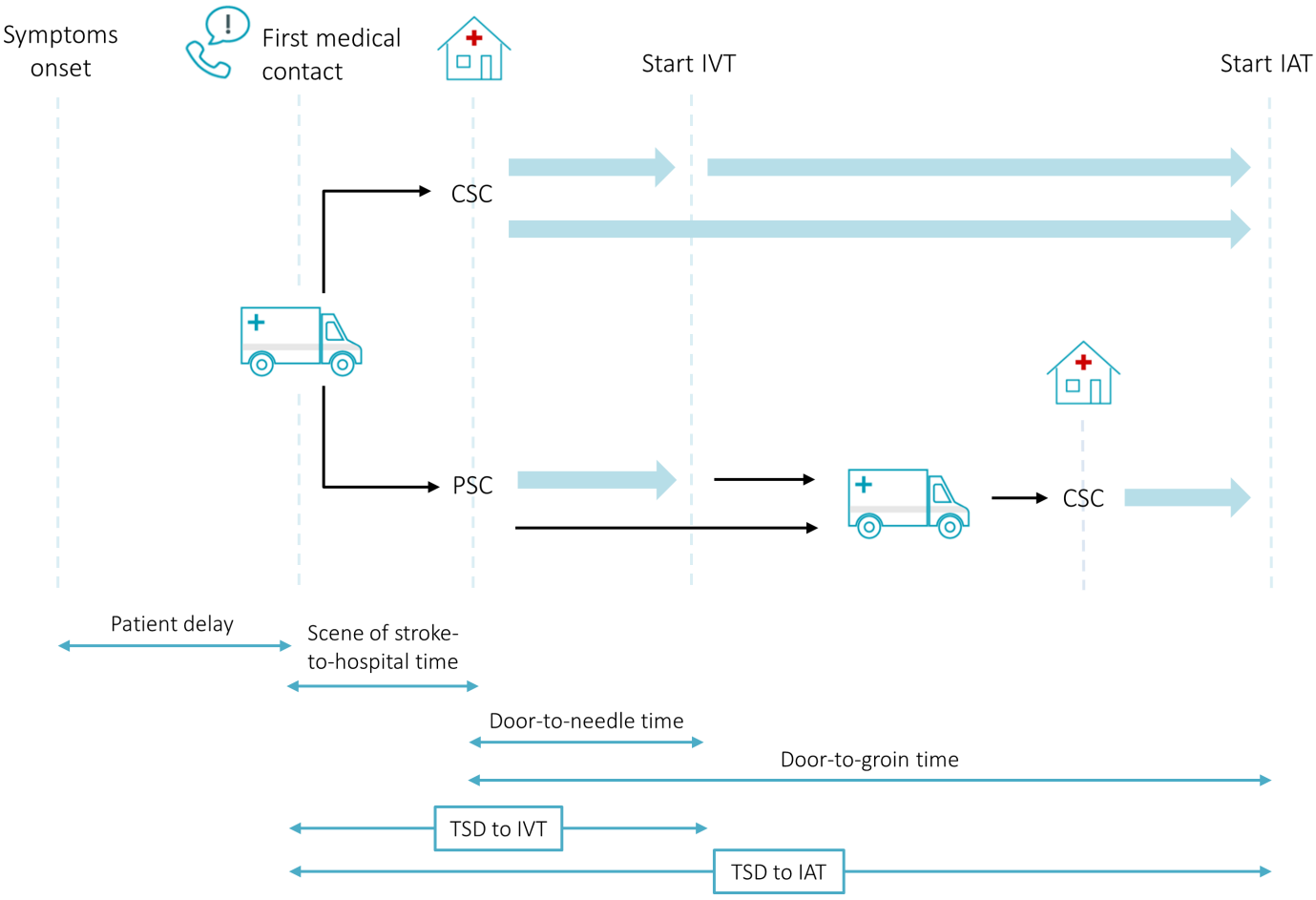

Figure 1 Treatment delays in acute ischaemic stroke care. CSC, comprehensive stroke centre; IAT, intra-arterial thrombectomy; IVT, intravenous thrombolysis; PSC, primary stroke centre; TSD, total system delay.

less recognised and have scarcely diminished over the past decades,[16–18] while relevant time reductions can be achieved.[19–22] We will further refer to the entire (prehospital and in-hospital) treatment trajectory that can be influenced by caregivers and depends on optimal logistics as the '*total system delay*' (TSD), in analogy to the literature in cardiology (see figure 1).[23]

A promising method to reduce TSD is to provide real-time audio-visual feedback to caregivers directly involved with the patient.

From the field of psychology, it is well established that awareness of being observed maximises dedication and efforts. This so-called 'Hawthorne effect' increases efficacy and leads to optimal workflow and streamlined care.[24–26]

Cohort studies have shown that feedback to caregivers reduces delays to IVT,[27–29] but feedback was not provided real-time, prehospital delays were not accounted for and IAT was not standard of care at the time. The literature on feedback as a tool to reduce TSD in patients with acute myocardial infarction is more extensive and shows promising results.[30 31] For example, in a recent Dutch study, real-time visual feedback was associated with a 18 min reduction in TSD to percutaneous coronary intervention.[32] However, this intervention was never randomised, leaving room for bias as other (logistic) factors could over time contribute to an improved process.

With our study, we aim to determine the efficacy of real-time audio-visual feedback on TSD to IVT/IAT in patients presenting with acute ischaemic stroke.

METHODS

Study design

A Reduction in Time with Electronic Monitoring In Stroke (ARTEMIS) is a multiregional, multicentre prospective randomised open-label blinded end-point (PROBE) trial, investigating if real-time audio-visual feedback to caregivers reduces TSD to IVT/IAT. The study is conducted in three both urban and peripheral EMS regions in the Netherlands, comprising over 2.5 million inhabitants. Each region contains one comprehensive stroke centre with IAT-availability and at least one local hospital treating over 30 IVT-patients per year.

We hypothesise that real-time audio-visual feedback to caregivers on actual TSD will reduce median TSD to IAT with at least 20 min and median TSD to IVT with at least 10 min compared with regular care.

Study population

All patients≥18 years considered IVT/IAT-eligible by the EMS dispatch office or on-site EMS personnel, following regional EMS' stroke algorithm.

Intervention

Real-time audio-visual feedback will be delivered through handhelds and tablets en route from ambulance to IVT/IAT initiation. Real-time visual feedback on actual treatment delays for the transferred patient will be shown to caregivers involved. Also, a colour code (green, orange or red) will provide an easy-view visualisation on whether or not preset median time delays between locations are exceeded. Additionally, on preset locations (eg, the emergency room (ER), CT room and angiography suite), auditory feedback broadcasting the elapsed time on preset moments (eg, every 3–5 min) will be installed.

In order to provide real-time audio-visual feedback, we will use an electronic patient tracking system. For every patient, a wristband with a unique ibeacon will be used that automatically activates recording once unwrapped by EMS personnel at the moment the dispatch office issues an ambulance for a potentially IVT/IAT-eligible patient. The ibeacon emits a low-voltage Bluetooth signal, which will be automatically picked up by fixed handhelds in the ambulance and premounted in-hospital tablets en route to IVT/IAT providing accurate, straightforward and automatic data on TSD and its various subtrajectories (see figure 2).

TSD ends at the moment IVT/IAT is initiated. For TSD to IVT, this is the moment the bolus of alteplase is administered, whereas the endpoint for TSD to IAT will be groin-puncture and the last angio-run. These endpoints will be registered automatically once a fixed button in the CT-room/neuro-care unit or angiography suite is pushed by the treating physician. This will be verified for every IVT/IAT-treated patient with the Electronic Patient Recording (EPR). All recordings on patient tracking are automatically stored in a protected cloud.

Other data including demographics, medical history, EMS parameters, physical and additional test results and interventional features performed as part of standard care will be documented anonymously from the EPR.

As soon as possible after hospital admission, the patient or legal representative will be informed on the study and a deferred consent will be obtained by a local investigator.

Patients are allowed to refuse the wristband application without any consequences. Subjects can leave the study at

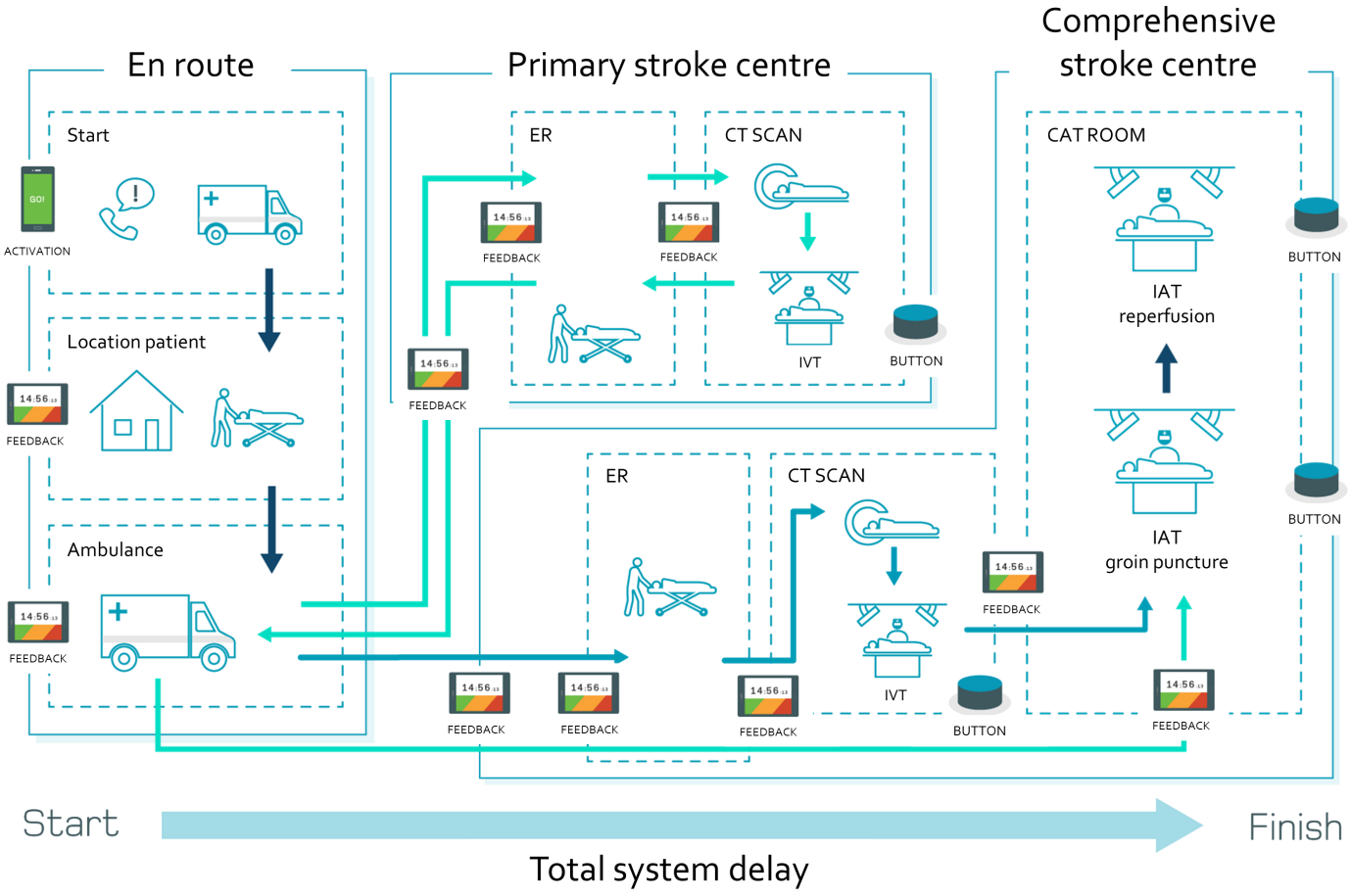

Figure 2 Real-time audio-visual feedback intervention, throughout various pathways in acute ischaemic stroke care. Endpoint registration will take place through fixed real-life push buttons. CAT room, catheterisation room; ER, emergency room; IAT, intra-arterial thrombectomy; IVT, intravenous thrombolysis.

any time for any reason if they wish to do so without any consequences.

Randomisation

Randomisation of the intervention (real-time audio-visual feedback) will be automatically generated per patient based on a computer algorithm. This will be prior to EMS distribution of (randomised) ibeacons.

Primary outcomes

TSD to IAT and TSD to IVT (minutes).

Secondary outcomes

1. TSD subtrajectories: ambulance arrival at 'scene-of-stroke', time spent on scene, 'scene-of-stroke'-to-hospital time, arrival and departure from the ER, CT room, neuro-care unit and angiography suite.
2. Proportion of patients treated with IVT/IAT, of all acute ischaemic stroke patients presented to the ER within 4.5 hours (IVT)/6 hours (IAT) after symptom onset.[13]
3. Functional outcome (modified Rankin Scale) at 3 months,[33] evaluated through a standardised and validated telephone interview by an observer blinded to treatment allocation.
4. Safety parameters:
   i. Occurrence of symptomatic intracerebral haemorrhage defined as evidence of intracranial haemorrhage on imaging associated with neurological deterioration (an increase in NIHSS of ≥4 points) or death.[34] NIHSS is routinely performed by the treating physician and will otherwise be constructed from medical records as described previously.[35]
   ii. Proportion of IVT/IAT-treated stroke mimics.

Data monitoring body

No data safety monitoring board will be installed since the trial yields no risks for participating subjects.

Patient and public involvement

For the purpose of this study, a focus group advising in design, implementation and effectuation of the study (including patients' associations, nurses, healthcare insurers, PDEng clinical informatics) was created. Next to publications in peer-reviewed journals, a public symposium is planned to disseminate study results to patients and other interested parties.

Sample size estimates

Sample size calculation is based on the hypothesis of an at least 20 min difference of TSD to IAT and an at least 10 min difference of TSD to IVT. We think these differences are feasible based on data from MR CLEAN.[2]

In the MR CLEAN trial (n=500), mean TSD to IAT (n=233) was 256 min (SD 40). To detect a 20 min difference with a p value of 0.05 and a power of 0.8, we will need 63 patients in each arm. To increase power, we aim at including 75 IAT-patients in each arm.

In the MR CLEAN trial, mean TSD for IVT was 90 min (SD 35). To detect a 10 min difference of TSD to IVT with a p value of 0.05 and a power of 0.8, we will need 193 IVT-patients in each arm. In clinical practice, approximately 9% of patients for whom the dispatch office issues an ambulance will end up being treated with IVT.[19] Of these patients, approximately 30% will be eligible for IAT.[2] Therefore, we expect that for the inclusion of 150 IAT-patients EMS personnel will have to unpack a wristband approximately 5000 times over an estimated study period of 2 years.

During a run-in phase, we will electronically collect additional data on treatment delays (without providing feedback to caregivers) to adjust sample size calculation if required.

Statistical analyses

For all analyses involving time intervals, differences in time delays between randomisation groups will be calculated with corresponding 95% CI. Analyses will be performed on an intention-to-treat basis. We will perform subgroup analysis for IAT-patients with or without prior IVT, for patients within and out of office hours and for EMS region. We will use linear regression analysis, with additional log-transformation if appropriate, to adjust for cluster effect of EMS region and for treatment location as this is expected to affect TSD to IVT/IAT. If required we will adjust for differences in EMS response and transfer times due to geographically different locations of stroke. Through additional regression analysis, we will assess a possible effect of calendar time on TSD and whether such an effect is group-dependent.

Although randomisation is computerised and by chance, baseline differences may still arise between the two groups with possible effect on outcome measures. For this reason, we will collect data on other determinants of TSD (eg, NIHSS, time from onset of symptoms, drip-and-ship vs mothership), and we will adjust for possible baseline incomparability.

The total number of times the EMS dispatch office issues an ambulance will be used to calculate the proportion of patients with a discharge diagnosis of stroke and the total number of IVT/IAT-treated patients in each group. IVT/IAT-treated patients lacking endpoint registration will be excluded from primary endpoint analysis. Exploratory analysis will be performed to relate TSD to clinical outcome in each group. Secondary outcomes will be corrected for multiple testing where appropriate.

Additionally, we will perform cost-effective analysis of the electronic tracking system including the feedback intervention.

DISCUSSION

With ARTEMIS, we aim to reduce TSD to IVT/IAT with an innovative and straightforward intervention: real-time audio-visual feedback to caregivers.

The PROBE design and the open nature of our intervention is pragmatic and reflects future clinical practice of acute stroke care. By using automatically generated primary outcomes (TSD to IVT/IAT; ie, time) study results are as valid as those derived from a double-blind placebo controlled trial.[36]

We anticipate that during the study period, treatment delays will decrease due to initiatives aimed to optimise logistics other than our intervention. Moreover, data accrual on treatment delays by itself could already be an incentive to optimise logistics. For example, DNTs reduced substantially after these became transparent.[37 38] However, we do not expect this to invalidate our results as reduction of DNT took considerably longer than the intended length of our study. Besides, such an effect would be notable in both groups. Nonetheless, we will compare available treatment delays before and after the start of ARTEMIS.

Another possible bias is that the intervention effect will carry over to controls. Since shifts of treatment teams generally occur multiple times a day, we think this is unlikely. Nevertheless, analyses to elucidate trends over time will be performed.

Also, since TSD registration depends on the unwrapping of patient wristbands and pushing a fixed button, starting times of electronic registration will be checked with automatic time logs of the ambulance, and endpoint registration will be cross-checked with the EPR. In addition, we think that small inaccuracies can occur in both arms and will therefore not lead to a systematic bias in primary outcome.

We anticipate that the intention to speed up the logistic process with real-time audio-visual feedback could theoretically lead to more stroke mimics being treated with IVT, which for this reason is one of our safety outcomes. More importantly, this could potentially lead to more haemorrhagic complications related to IVT/IAT (another safety outcome). However, we think this is an inherent risk related to treatment of patients with acute stroke, already starting before caregivers are involved by mass media campaigns to educate the public to respond rapidly to a stroke (eg, Face-Arm-Speech-Time). Moreover, with each (existent and new) intervention aimed to reduce treatment delays, the acute stroke team should work as fast as possible while remaining diagnostic accuracy. In addition, this theoretical danger is not reflected in current practice, as shortening DNTs, for example, did not to lead to an increased number of other safety parameters such as symptomatic intracerebral haemorrhages.[39] As for stroke mimics, a recent meta-analysis showed that IVT treatment in this group appears to be safe.[40] Nevertheless, since it is possible that treatment of stroke mimics may occur in our population, for a valid TSD comparison, we will perform subgroup analysis on TSD in patients in which diagnosis of ischaemic stroke and treatment have been confirmed.

Also, more patients being treated with IVT and/or IAT within the 4.5-hour (IVT) or 6-hour (IAT) time window could potentially increase mean TSD. Nonetheless, we think that in parallel to this, the proportion of treated patients within the early intervals of these time windows will also increase, minimising such an effect.

Finally, a potential limitation is that study results on TSD will particularly be applicable to areas similar to the Netherlands, with a highly concentrated network of hospitals and a relatively short 'scene of stroke'-to-hospital distance. We expect in-hospital results to be more widely generalisable.

Reducing treatment delays for acute stroke relies on team effort between various caregivers in both prehospital and in-hospital trajectories. This will always carry an inherent risk that a chain is only as strong as its weakest link. Meanwhile, the total trajectory is what matters most to the patient, as neuronal death in stroke is critically time dependent.[41] The intervention we investigate embodies the whole chain of acute stroke care, from patient's first EMS contact to start of treatment. Thus, with our intervention, we can establish a unique connection between various acute stroke team members who nowadays mainly work separately.

Because we do not exclude any (sub)groups of patients with suspected stroke and our study population encompasses both urban as peripheral areas, the ARTEMIS trial has great external validity.

Another important strength of ARTEMIS is the introduction of an innovative, accurate and straightforward technique that automatically provides healthcare professionals with data on important performance measures of acute stroke care that are currently often collected retrospectively in a time consuming effort at the expense of accuracy.

In addition, the introduced technique will likely also benefit other (neurological and non-neurological) patient groups for whom clinical benefits of treatment are time dependent.

CONCLUSION

With the introduction of real-time audio-visual feedback through an electronic patient tracking system, we expect treatment delays to become more transparent, to improve workflow, to reduce TSD to IVT/IAT, resulting in improved clinical outcomes and a larger proportion of patients with acute ischaemic stroke eligible for treatment with IVT/IAT.

STATUS OF STUDY

First recruitment was 15 February 2018. Up to this moment, 63 patients received an ARTEMIS wristband.

ETHICS AND DISSEMINATION

Participating centres will have access to their own results and collective study results will be disseminated through peer-reviewed journals and (inter)national conferences.

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Contributors GTK, NDK, MJHW, AA and JB designed the study with NDK as the principal investigator. NDK, YBR, MJHW and JB applied for, received and organised study funding. GTK and NDK drafted the study protocol and manuscript, performed literature search, reviewed and commented on tables and figures. NDK, MJHW and AA performed sample size calculations and contributed to planning of statistical analysis. All authors contributed to data collection and analysis. They have also read, reviewed and approved the study protocol and final manuscript.

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Disclaimer The ARTEMIS investigators declare that the funders have no role in study design; collection, management, analysis and interpretation of data; writing of the report and the decision to submit the report for publication.

Competing interests None declared.

Patient consent Obtained.

Ethics approval The Medical Ethics Committee of Leiden University Medical Centre (reference: NL 56747.058.016).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

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