# eTable 6. Quality appraisal for all other non-randomised controlled trials

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| **Study ID** | **Ganetzky & Falk 20181** | **Koga et al. 20052** | **Koga et al. 20183** | **Overall bias (between)** |
| 1. Representative sample | N | Y | Y | Low |
| 2. Inclusion/exclusion criteria clearly defined | Y | ? | ? | Unclear |
| 3. Participants at similar disease progression | N | N | N | High |
| 4. Selection of participants consecutive | ? | ? | ? | Unclear |
| 5. Data collection undertaken prospectively | N | Y | Y | Low |
| 6. Groups comparable | NA | NA  | NA | NA |
| 7. Intervention clearly defined | Y | Y | Y | Low |
| 8. Intervention delivered by experienced person | Y | Y | Y | Low |
| 9. Intervention delivered in an appropriate setting | Y | Y | Y | Low |
| 10. Important outcomes considered | ? | ? | ? | Unclear |
| 11. Objective outcome measures used | ? | ? | ? | Unclear |
| 12. Main outcome blind | N | N | N | High |
| 13. Follow-up long enough | N | NA | YP | NA | YP | High |
| 14. Information on non-respondents, dropouts | Y | NA | Y | Low |
| 15. Withdrawals unlikely to introduce bias  | N | NA | N | High |
| 16. Length of follow-up similar between groups | NA | NA  | NA | NA |
| 17. Important prognostic factors identified | N | N | Y | High |
| 18. Analyses adjusted for confounders | N | N | N | High |
| **Overall bias (within)** | High | High | High |  |
| **OCEBM Level** | 3 | 3 | 3 |  |

The 2012 risk-of-bias checklist for non-randomized studies by Brazzelli et al. 20124. Abbreviations: A, acute; NA, not applicable; N, no; OCEBM, Oxford Centre for Evidence-Based Medicine Levels of Evidence 5; P, prophylactic; Y, yes; ?, unclear

A study was judged to have an overall high risk of bias if their analyses did not adjust for (nor reporte), the influence of confounders as deemed by the investigators (i.e. use of AED/s), and if participant withdrawals were likely to introduce bias.

1. Were participants a representative sample selected from a relevant patient population (e.g. randomly selected from those seeking treatment despite age, duration of disease, primary or secondary disease and severity of disease)?a
2. Were the inclusion/exclusion criteria of participants clearly described?b
3. Were participants entering the study at a similar point in their disease progression (i.e. severity of disease)?c
4. Was selection of patients consecutive?
5. Was data collection undertaken prospectively?
6. Were the groups comparable on demographic characteristics and clinical features?
7. Was the intervention (and comparison) clearly defined?d
8. Was the intervention undertaken by someone experienced at performing the procedure?
9. Were the staff, place and facilities where the patients were treated appropriate for performing the procedure (e.g. access to back-up facilities in hospital or special clinic)?
10. Were any of the important outcomes considered (i.e. clinical effectiveness, cost-effectiveness, learning curves)?e
11. Were objective (valid and reliable) outcome measures used, including satisfaction scale?f
12. Was the assessment of main outcomes blind?
13. Was follow-up long enough (≥ 1 year) to detect important effects on outcomes of interest?
14. Was information provided on non-respondents, dropouts?
15. Were the characteristics of withdrawals/dropouts similar to those that completed the study and therefore unlikely to cause bias?
16. Was length of follow-up similar between comparison groups
17. Were the important prognostic factors identified (e.g. age, duration of disease, disease severity)?g
18. Were the analyses adjusted for confounding factors?

*Items specific to comparative groups (6, 16) were deemed ‘NA’, where studies did not have a comparison arm.*

1. ‘No, where patients had MELAS, or where clinical presentation of stroke-like episode/s treated were not conventional.
2. ‘Unclear’ if only one of either inclusion or exclusion criteria are clearly described.
3. ‘No’ where there is limited information provided on the disease burden.
4. ‘No’ where route of administration or dose of L-arginine (acute or prophylactic treatment) was inadequately reported; ‘Unclear’ where the timing of treatment in relation to the stroke-like episode/s was not reported.
5. ‘Unclear’ where other important measures such as imaging and EEG were not consistently performed.
6. ‘Unclear’ where no standardised tools or rating scale/s used for the assessment of response.
7. ‘Yes’ if two or more than two factors were identified.

#  References

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3. Koga Y, Povalko N, Inoue E, et al. Therapeutic regimen of L-arginine for MELAS: 9-year, prospective, multicenter, clinical research. Clinical Trial

Multicenter Study. *Journal of Neurology*. 2018;265(12):2861-2874.

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