# e1. Search strategy

We searched Medline via Ovid, Embase via Ovid, Scopus, Web of Science, and CINAHL via EBSCO from inception to January 15, 2021 with no language or other restrictions imposed. We also performed backward citation searching; the reference lists of included articles and related reviews were manually screened via hand searching to identify additional studies. and searched ClinicalTrials.gov. We did not contact authors, additional experts, manufacturers, or others for additional data.

The search was first run on 12/7/2019 and updated shortly before submission of the planned manuscript in order to include the latest references (the last date the searches were carried out on all databases was January 15, 2021).

The search was undertaken by a senior medical librarian (L.E), with the search strategies peer reviewed by the investigational team, included subject expertise (neurologists, G.S.G. and Y.S.N.) prior to execution. All records from each data source were imported using bibliographic management software (EndNote) for de-duplicating, screening and managing each stage of the inclusion/exclusion article process. Duplicates were removed using EndNote's duplicate identification functionality (LE) and then manually (R.J.S.)

The search strategy used across databases were translated as closely as possible; a variety of keyword and subject heading terms were included to cover these concepts depending upon the thesaurus terms available in each database. The only search filter used was that recommended by Cochrane to identify human not animal studies at the end of both the Ovid Medline and Embase searches.

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| --- | --- | --- | --- | --- | --- |
| **Database** | **Search** | **Search terms** | **Database** | **Search** | **Search terms** |
| MEDLINE(Ovid) | 1 | exp Arginine/  | Embase(Ovid) | 1 | Arginine/  |
| 2 | Citrulline/  | 2 | Citrulline/  |
| 3 | L-arginine.mp.  | 3 | L-arginine.mp.  |
| 4 | arginine.mp.  | 4 | arginine.mp.  |
| 5 | L-citrulline.mp.  | 5 | L-citrulline.mp.  |
| 6 | citrulline.mp.  | 6 | citrulline.mp.  |
| 7 | Nitric Oxide/  | 7 | Nitric Oxide/  |
| 8 | nitric oxide.mp.  | 8 | nitric oxide.mp.  |
| 9 | or/1-8  | 9 | or/1-8  |
| 10 | exp Mitochondrial Diseases/  | 10 | "disorders of mitochondrial functions"/  |
| 11 | MELAS.mp.  | 11 | MELAS.mp.  |
| 12 | MERRF.mp.  | 12 | MERRF.mp. |
| 13 | DNA Polymerase gamma/  | 13 | DNA directed DNA Polymerase gamma/  |
| 14 | POLG.mp.  | 14 | POLG.mp.  |
| 15 | "8344".mp.  | 15 | "8344".mp.  |
| 16 | "3243".mp.  | 16 | "3243".mp.  |
| 17 | DNA, Mitochondrial/  | 17 | DNA, Mitochondrial/  |
| 18 | mitochondria\*.mp.  | 18 |  mitochondria\*.mp.  |
| 19 | or/10-18  | 19 | or/10-18  |
| 20 | stroke-like episode\*.mp.  | 20 | stroke-like episode\*.mp.  |
| 21 | exp Epilepsy/  | 21 | exp Epilepsy/  |
| 22 | epilep\*.mp.  | 22 | epilep\*.mp.  |
| 23 | exp Seizures/  | 23 | exp Seizure/  |
| 24 | seizure\*.mp.  | 24 | seizure\*.mp.  |
| 25 | exp Brain Diseases/  | 25 | exp Brain Disease/  |
| 26 | encephalopath\*.mp.  | 26 | encephalopath\*.mp.  |
| 27 | or/20-26  | 27 | or/20-26  |
| 28 | 9 and 19 and 27 | 28 | 9 and 19 and 27  |
| 29 | exp animals/ not humans.sh.  | 29 | (animal$ not human$).sh,hw.  |
| 30 | 28 not 29  | 30 | 28 not 29  |

**Scopus** (EBSCO)

(TITLE-ABS-KEY (arginine OR citrulline OR l-arginine OR l-citrulline OR "Nitric Oxide") AND TITLE-ABS-KEY (melas OR merrf OR "DNA Polymerase gamma" OR polg OR 8344 OR 3243 OR mitochondria\*) AND TITLE-ABS-KEY ("stroke-like episode\*" OR epilep\* OR seizure\* OR "Brain Disease\*" OR encephalopath\*))

**Web of Science** (EBSCO)

TOPIC: (Arginine OR Citrulline OR L-arginine OR L-citrulline OR "Nitric Oxide") AND TOPIC: (MELAS OR MERRF OR "DNA Polymerase gamma" OR POLG OR 8344 OR 3243 OR mitochondria\*) AND TOPIC: ("stroke-like episode\*" OR epilep\* OR Seizure\* OR "Brain Disease\*" OR encephalopath\*)

**CINAHL** (EBSCO)

TX (Arginine OR Citrulline OR L-arginine OR L-citrulline OR "Nitric Oxide") AND TX (MELAS OR MERRF OR "DNA Polymerase gamma" OR POLG OR 8344 OR 3243 OR mitochondria\*) AND TX ("stroke-like episode\*" OR epilep\* OR Seizure\* OR "Brain Disease\*" OR encephalopath\*)

**Clinicaltrials.gov**

Arginine OR Citrulline OR L-arginine OR L-citrulline OR Nitric Oxide | MELAS OR MERRF OR "DNA Polymerase gamma" OR POLG OR 8344 OR 3243 OR mitochondrial disease OR "stroke-like episode