Web-supplement:

Title:

Colchicine for prevention of Vascular Inflammation in Non-CardioEmbolic stroke (CONVINCE) – study protocol for a randomised controlled trial

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Detailed description of Inclusion Criteria:

1. Written informed consent consistent with ICH-GCP guidelines and local laws signed prior to all trial-related procedures.

2. Age 40 years or greater

3. Patient has had either;-

- An ischaemic stroke without major disability (defined as modified Rankin score *3 or less.* Retinal infarction due to retinal artery occlusion is allowed)

or

a high-risk TIA*

AND
A brain CT or MRI has excluded primary intracranial haemorrhage

AND
The stroke/TIA has occurred more than 72 hours before randomisation AND no more than 28 days prior to randomisation

- **High-risk TIA is defined as transient focal neurological symptoms of presumed vascular cause with, in addition, one or more of the following criteria:*
  - *(a) ABCD2 score 4 or more, with motor or speech symptoms (dysarthria or dysphasia)*
  - *(b) DWI hyperintensity on acute MRI*
  - *(c) Stenosis (lumen narrowing of 50% or greater on ultrasound, MRA, CTA, or invasive angiography) of the internal carotid, vertebral, middle cerebral, anterior cerebral, or basilar artery in the arterial territory consistent with symptoms*

4. Qualifying stroke/TIA probably caused by large artery stenosis, small artery occlusion (lacunar stroke), or cryptogenic embolism, with cardiac embolism or other defined stroke mechanism deemed unlikely in the opinion of the treating physician.

5. eGFR greater than or equal to 50 ml/min.

6. In the opinion of the treating physician, patient is medically-stable, capable of participating in a randomised trial, and willing to attend follow-up.

Detailed description of Exclusion Criteria:

Subjects are excluded from the study if any of the following criteria are met:

1. Stroke/TIA, probably caused by identified atrial fibrillation (permanent or paroxysmal), in the opinion of the treating physician.

2. Stroke/TIA probably caused by other identified cardiac source (intra-cardiac thrombus, endocarditis, metallic heart valve, low ejection fraction <30%),

3. Stroke/TIA caused by dissection, endocarditis, paradoxical embolism, drug use, venous thrombosis, carotid or cardiac surgery, hypercoagulability states, migraine, or inherited cerebrovascular disorders.

4. History of myopathy or myalgias with raised creatine kinase (CK) on statin therapy.

5. Blood dyscrasia (haemoglobin<10g/dL,platelet count <150 $x10^9$/L, white cell count <4 $x10^9$/L)

6. Impaired hepatic function (bilirubin or transaminases [ALT and/or AST] greater than twice upper limit of normal (ULN)

7. Concurrent treatment with colchicine contraindicated drugs:- CYP3A4 inhibitors (clarithromycin, erythromycin, telithromycin, other macrolide antibiotics, ketoconazole, itraconazole, voriconazole, tolbutamide, ritonavir, atazanavir, indinavir, other HIVprotease inhibitors, verapamil, diltiazem, quinidine, digoxin, disulfiram) or P-gp inhibitors (cyclosporine) at randomisation.

8. Symptomatic peripheral neuropathy and pre-existing progressive neuromuscular disease

9. Inflammatory bowel disease (Crohn's or ulcerative colitis) or chronic diarrhoea.

10. Dementia, sufficient to impair independence in basic activities of daily living.

11. Active malignancy, known hepatitis B or C, or HIV infection.

12. Impaired swallow preventing oral administration of Colchicine

13. History of poor medication compliance.

14. Unlikely to comply with study procedures due to severe or fatal comorbid illness or other factor (eg. inability to travel for follow up visits), in opinion of randomising physician.

15. Women of childbearing potential (WCBP), or pregnant or are breastfeeding, are not eligible to participate in this study. A woman of childbearing potential is a woman who:

- has not had surgery to remove the uterus and ovaries

- has had menstrual periods at any time in the preceding 24 consecutive months
- Menstrual periods interrupted due to cancer chemotherapy treatment are considered WCBP as this may still allow conception.

Pregnancy is considered highly unlikely during the trial because women of childbearing potential are excluded. However, in the unlikely event that a woman in the trial becomes pregnant, pregnancy information will be collected.

16. Patient concurrently participating in another clinical trial with an investigational drug or device, or use of investigational drug within 30 or 5 half-lives before the Screening visit (whichever is longer).

17. Known allergy or sensitivity to colchicine.

18. Requirement for colchicine therapy for treatment of acute gout, gout prevention, or other rheumatological disorder

19. Requirement for chronic daily immunosuppressants oral steroids, or non-steroidal anti-inflammatory drugs (NSAIDs)