Genetically determined brain abnormalities in Down Syndrome –towards a treatment : A randomised, single-blind, placebo controlled trial of lithium carbonate in Down Syndrome
Down Syndrome Lithium Trial (DownsLit)

END OF STUDY REPORT TO MHRA

1. Details of Chief Investigator

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2. Details of study

Full title of study:	Genetically determined brain abnormalities in Down Syndrome –towards a treatment : A randomised, single-blind, placebo controlled trial of lithium carbonate in Down Syndrome
REC reference number:	09/H1102/3
Sponsor:	King's College London
EudraCT Number:	2008-008342-20
Number of Centres	1 main study centre plus several PICs
Number of Patients	Ethics approved N=34 Recruited & screened N=24 (5 screen fails) Completed study N=19

3. Commencement and completion dates in the UK

First Patient First Visit	13-Jan-2010
Last Patient Last Visit	19-Dec-2011

4. Study Design

This was a randomised, single blind, placebo controlled trial. Recruited participants who met inclusion/exclusion criteria, who were consented and underwent the screening and baseline assessments, were randomised to receive the trial intervention. Participants were registered with the South London and Maudsley NHS Foundation Trust and the study was coordinated by the Institute of Psychiatry.

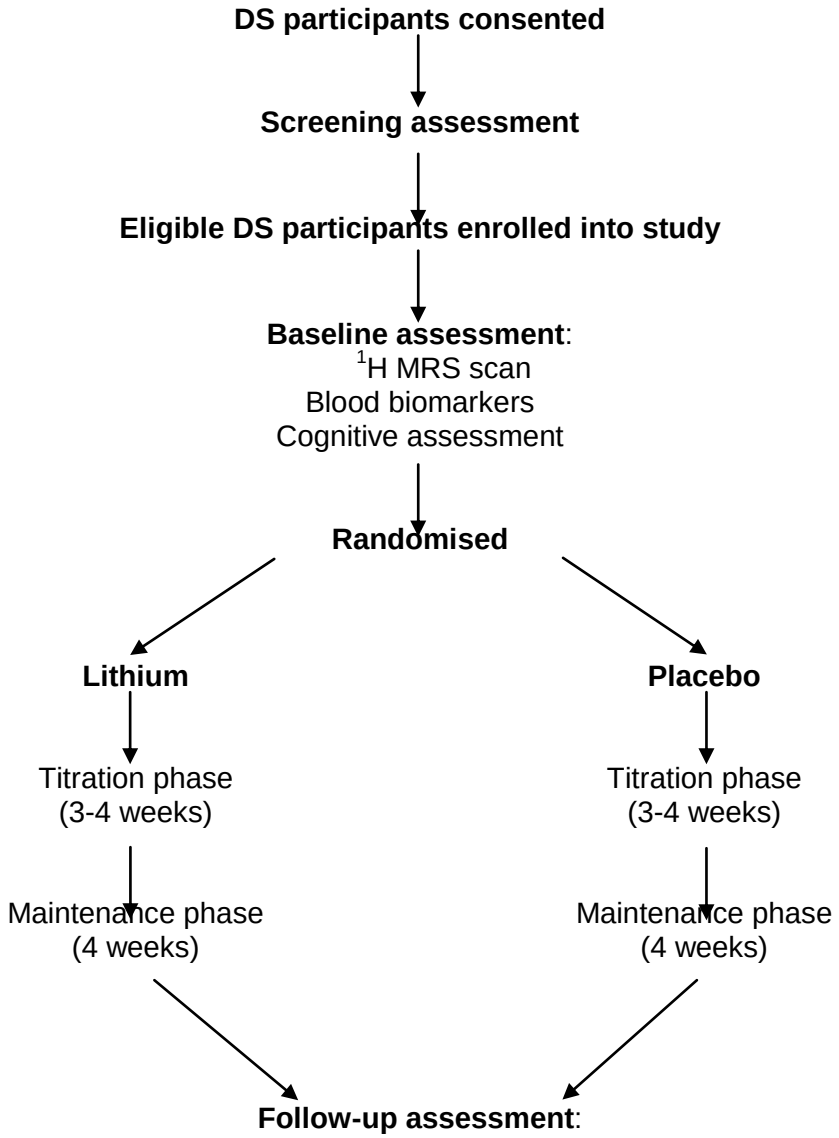
It was planned that up to 34 non-demented adults with DS, with equal numbers in each arm, were entered into a randomised single blind trial of placebo versus lithium carbonate treatment at a dose adjusted to obtain a plasma level of 0.4 – 1.0mmol/L (based on British National Formulary (BNF) recommendations) for 4 weeks once doses have been titrated up to therapeutic plasma levels.

Lithium carbonate was started at 250mg once daily initially and plasma lithium levels will guide dose increases to attain a therapeutic dose. Any potential side effects in this therapeutic dose range were closely monitored by regular phone contacts with participants and their carers and lithium side-effects rating scales were also used to monitor the dose range. Participants took the lithium carbonate for 4 weeks once therapeutic plasma level has been achieved. There was a similar titration schedule for dose escalation of placebo but plasma lithium levels were not required. Participants and their carers knew that they were on placebo. It was felt that it would be ethically difficult to justify taking blood from participants on the placebo group. However, the researchers doing the outcome assessments were blind to the treatment of the participants.

Cognitive and blood biomarker measurements as well as ^{1}H MRS scan were carried out at baseline and after the treatment intervention. Researchers doing the pre and post treatment cognitive measures were blind to the treatment intervention.

This trial was not powered to determine if changes in brain *myo*-inositol are paralleled by those in cognition. However, the experience of treating DS people with lithium and with extensive clinical and biomarker evaluation was sufficient to inform future clinical trials and may provide preliminary data indicative of an effect of lithium.

5. Clinical assessment flow chart



^{1}H MRS scan
Blood biomarkers
Cognitive assessment

End of study

6. Inclusion Criteria

- Individuals with Down Syndrome
- Over the age of 18 years
- Able to provide informed consent for themselves or have a representative to provide proxy consent on their behalf if they lack capacity
- Able to communicate with the investigator and to comply with requirements of the study
- Has carer support

7. Exclusion Criteria

- Individuals with contraindications to lithium treatment
- Individuals with contraindications to undergoing a magnetic resonance scan
- Non-compliance with taking of the tablets between baseline and the final assessment
- Treatment with lithium within the last 6 months
- Evidence of dementia
- Pregnancy

8. Duration of Treatment

3 – 4 weeks during titration phase and 4 weeks during maintenance phase. Total duration of each participant was approximately 7 - 8 weeks.

9. Study Results

Preliminary results suggest that there were no significant differences between the brain myo-inositol concentrations in the treatment vs the placebo group in either the DLPFC or Hippocampus.

The treatment group had more short term cognitive difficulties at the follow-up visit compared to the placebo group possibly as a result of the short term side effects of lithium carbonate.

10. Study population

Mean Age 34 years (range 20-51 years); 13 male: 6 female

11. Discussion

There were no reported SUSARs or SAEs during the study period and lithium carbonate was reasonably well tolerated by participants in the study.
There were no significant differences between the brain myo-inositol concentrations in the treatment vs the placebo group in either the DLPFC or Hippocampus.
The treatment group had more short term cognitive difficulties at the follow-up visit compared to the placebo group possibly as a result of the short term side effects of lithium carbonate.

12. Safety Evaluation

No safety issues have been raised in relation to this study.

No SUSARs, SAEs or SARs were reported.

13. Conclusions

This small pilot study did not show any effect of lithium on brain myo-inositol concentrations and there were short term cognitive side effects noted. The participants in the study did not report serious adverse effects and most were able to tolerate the study procedures suggesting that it may be feasible to replicate the study using larger samples in the future.

14. Declaration

Signature of Chief Investigator:	
Print name:	Professor Declan Murphy
Date of signature:	