Research Participant Information Statement

Research Study Title	**Phase III, multicentre, randomised, double-blinded, placebo-controlled, MAMS trial of SpironolacTone and famciclOvir in the treatment of Progressive MS to prevent disability progression (STOP-MS)**
Researcher's Names	Professor Simon Broadley (GCUH/GU) Professor Bruce Taylor (UTAS) Professor Michael Barnett (USyd) Professor Jeremy Chataway (UCL, London, UK) Professor Max Parmar (UCL, London, UK) Professor Lawrence Steinman (Stanford, CA, USA) Professor David Tscharke (ANU) Professor Tomas Kalincik (UMel) A/Prof Vilija Jokubaitis (Monash) Professor Corey Smith (QIMR/Berghofer Institute) Professor Jing Sun (GU) Dr Julie Campbell (UTAS) Dr Vivien Li (UMel) Dr Grant Parnell (USyd) A/Prof Sudarshini Ramanathan (USyd)

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(1) What is the study about?

The Epstein-Barr virus (EBV) that causes glandular fever has recently been identified as the likely primary cause of multiple sclerosis. Progressive forms of multiple sclerosis can have significant impact on quality of life and are currently less responsive to current therapies than relapsing-remitting MS. Following an intensive evaluation process with national and international EBV experts, we have selected two potential anti-EBV therapies (spironolactone and famciclovir) to test in an innovative multi-stage, multi-arm trial in order to identify the best potential treatment for progressive MS. Treatments will be compared to a placebo (dummy-treatment). It is hoped that by removing the primary cause of MS these therapies may slow the ongoing progression of disability.

If you decide to participate, we will organise for your enrolment into a placebo-controlled clinical trial which will be run in 2 stages. In Stage 1, you will be enrolled into a study where participants are randomly allocated to one of three treatment arms (the two active medications and the placebo). The three treatments will be identical looking capsules that are to be taken orally.

The first treatment arm is spironolactone, which is a Therapeutics Goods Administration (TGA) approved treatment used for congestive heart failure and sometimes liver failure or kidney failure. It is a diuretic (promotes increased urine production) through an effect on the kidneys. Spironolactone is known to disrupt the replication of EBV through a mechanism that is completely separate to its action on the kidneys.

The second treatment arm is famciclovir, which is a TGA approved drug routinely used for the treatment of other herpes viruses including herpes simplex virus 1 and 2 (the causes of cold sores and genital herpes) and varicella-zoster virus (the cause of

chickenpox and shingles). This anti-viral medication is known to be effective against EBV in animal models and has been used to treat serious EBV infections in immunocompromised people.

The third treatment arm will be a placebo (dummy treatment) that looks identical to the two active treatments but contains no medication. Treatment allocated in a 1:1:1 ratio. Thus, there is an equal chance of being randomised to spironolactone, famciclovir or placebo. This also means that 1 in 3 people will be taking placebo.

Stage 1 will run for 6 months and once 150 people have completed 6 months of these therapies, we will compare between these therapies to see which treatment most effectively reduces the activity of EBV when compared to the placebo arm.

EBV activity will be measured in two ways. The first will be levels of an antibody that people produce against EBV called EBNA1 antibody. Levels of EBNA1 antibody are known to be elevated in people with MS and lowering of levels is thought to indicate a lowering of EBV activity. The second measure of EBV activity will be through the detection of EBV DNA in saliva samples taken every 4 weeks for the first 24 weeks of treatment. People who carry EBV (which is essentially all people with MS) shed EBV in their saliva periodically and this is again thought to reflect EBV activity. A reduction in EBV DNA detection in saliva samples would suggest reduced EBV activity.

Following the analysis of the outcomes from Stage 1 we will determine which of spironolactone or famciclovir most successfully reduced the activity of EBV as measured by EBNA1 antibody levels and EBV DNA detection in saliva. Whichever drug performs the best will be chosen for continuance into Stage 2. If neither drug shows any beneficial effect the research team will consider introducing new therapies to repeat in Stage 1 or abandoning the trial.

There will be an interim stage where participants in Stage 1 will continue to take the same medication that they started on and new participants may be recruited to the same three arms prior to the results of Stage 1 being known. All participants in this interim stage will remain blinded to what treatment they are taking.

In Stage 2, participants from Stage 1 who were on either taking the more successful treatment or placebo will continue in the same treatment arms (without knowing which one they are taking still). Participants in the less effective treatment arm will be withdrawn from the study and invited to re-enrol under Stage 2 after a washout period of 30 days, if they wish. Participants enrolling into Stage 2 will be randomised to one of two treatment arms, the more successful treatment from Stage 1 or placebo. Treatment allocation will be on a 1:1 ratio basis and hence there is a 50% chance being on active treatment and 50% chance of being on placebo. Stage 2 will continue until the first participants from Stage 1 reach the 5 year mark and the last participants are at around the 2 year mark (average of around 3 years follow up). There will be 300 participants in Stage 2 (including 100 who have carried on from Stage 1).

(2) Why have I been invited to participate?

You have been invited to participate in this trial because your treating neurologist believes that you have a progressive form of MS. This can be either primary progressive (MS that is progressive from the outset) or secondary progressive (MS that has begun to progress after a period of relapses and remissions).

The inclusion criteria for the STOP-MS trial are:

- Age 25-70 years (inclusive)
- Diagnosed with primary or secondary progressive MS according to McDonald 2017 criteria
- EDSS of 4.0 – 8.0 (inclusive) at the time of randomisation
- Evidence of disability progression over the previous 24 months

- English speaking or non-English speaking but can ensure external interpreter assistance to attend all visits for the duration of the clinical trial
- Available to attend clinic visits.

The exclusion criteria are:

- A clinical relapse within 3 months of randomisation
- A significant concurrent disease that in the opinion of the principal investigator (PI) would negatively affect MS disease outcomes or preclude administration of spironolactone or famciclovir (including kidney failure)
- Currently taking medication or supplements known to cause high blood potassium levels
- Hypersensitivity to spironolactone or famciclovir
- Female participants who are pregnant
- Female participants who are breast-feeding
- Women of childbearing potential who are unwilling or unable to use an acceptable method of contraception whilst on trial treatment and for up to 30 days after the last dose of study drug
- Have received treatment with steroids (intravenous and/or oral) for MS relapse/progression within 3 months before randomisation
- Have received any trial therapy within the last 6 months (other than as part of the STOP-MS Stage 1 trial)
- Recent or current history of major depression, bipolar disorder, psychosis or suicidality
- Currently or recently taking any illicit substances (excluding cannabis products used for symptomatic relief).

(3) Who is carrying out the study?

The research is being led by Professor Simon Broadley an academic neurologist who works at Griffith University and the Gold Coast University Hospital on the Gold Coast. The trial is being overseen by a Steering Committee of prominent national and international MS researchers and people with MS chaired by Professor Pamela McCombe who works at the University of Queensland and the Royal Brisbane and Women's Hospital in Brisbane. The research is being conducted by the chief investigators listed on page 1 and the principal investigators at each trial site. The research team includes several people with MS and is being advised by a Consumer Engagement Committee of people with MS.

(4) What does the study involve?

As a participant in this study, you will be involved in activities such as reviews of your medical history and symptoms, clinical examinations, an electrocardiogram (ECG or heart tracing), online questionnaires and blood collections. You will also be asked to take the investigational medicine (spironolactone, famciclovir or placebo) for a period of between 2 and 5 years depending on what point you commence in the trial. Neither you nor your treating team will know which medication you are taking (this is called "double blinding").

There will be two longer visits 1-5 weeks apart at the beginning of the clinical trial where details of you past history of MS other past medical history will be recorded. Your age, sex and ethnicity will also be noted. Any other medications that you are taking will be noted and some screening tests will be performed to ensure that it is safe for you to enter the trial. These will include blood tests (blood cell counts, biochemistry test, liver tests and tests of kidney function) and an electrocardiogram (ECG). With your permission we will request results of relevant investigations to confirm your MS diagnosis such as MRI result and lumbar puncture results. You will not be required to undergo a lumbar puncture as part of this trial.

If you meet all of the inclusion and exclusion criteria and your screening tests are satisfactory you will be invited to enrol in the study at the second visit. This will involve being randomised and allocated to a treatment arm (although you will not know which arm) and being provided with a participant ID card and a list of medications that you should avoid whilst taking part in the study.

Throughout the trial you will be permitted to continue taking any existing treatment that you might be taking for your MS. You will also undergo MRI scans annually as part of your normal care. We will again, with your permission, ask for copies of these MRI scans to assist in monitoring your progress in the trial.

Following enrolment you will be prescribed study medication that you will take twice per day (morning and evening). For the first 4 weeks tablets will contain half of the full dose for both treatments. Provided all blood tests are satisfactory, the tablets will be replaced by full-dose medication at the dose-escalation visit (week 4). This dose will then be continued for the duration of the trial unless circumstances change (such as abnormal blood tests or side effects). If at any time blood results or side effect symptoms suggest an intolerance to the study medication or an increased risk of side effects, then at the discretion of the treating neurologist and in consultation with you, the following may occur:

1. The study medication may be discontinued.
2. The study medication may be reduced from full dose to half-dose.
3. The study medication may be continued at the full dose with more frequent monitoring.

You will be asked to undergo blood tests at 1, 3, 6 and 12 weeks and then every 12 weeks for the duration of the trial. You will be able to have these blood tests done at local pathology centres. You will receive a phone call after 12 weeks and then every 24 weeks until the end of the study from study staff at the trial site who will enquire about any significant changes in your health status. At week 24 and every 24 weeks thereafter until the end of the study, you will have a review visit at the trial site. You will be asked about any symptoms, changes in function, other health issues and any new medications. You will also undergo an assessment of your disability level (EDSS).

Prior to enrolment and then at the end of each year in the study you will be invited to complete a series of online questionnaires that evaluate patient reported outcomes and cover how your MS is affecting you overall, affecting your mobility, causing any pain, causing fatigue or affecting your quality of life. In order to facilitate this online collection of information we will request your first name and an email address, so that request to complete the surveys can be sent out to you. This data will be held in such a way that the researchers cannot see your first name and email address.

In addition to the above blood tests, participants in Stage 1 will be asked to provide two saliva samples prior to starting treatment then one saliva sample every 4 weeks for the first 24 weeks (8 samples in total). These samples can be collected either at the study site or at home and then posted to the analysis centre in Brisbane (QIMR/Berghofer Institute). We will provide all of the packaging and postage required to do this. A blood sample will also be collected prior to enrolment and again at 6 months for EBNA1 antibody testing which will also be done at QIMR/Berghofer in Brisbane. These sample will be collected at the study site. We estimate that the total amount of blood that will be collected will be as indicated in Table 1.

Table 1. Total blood volume to be collected for the STOP-MS trial each year

Stage	Timepoint	Volume of Blood per Year
Stage 1	Year 1	140 ml
	Subsequent years	60 ml
Stage 2	Year 1	120 ml
	Subsequent years	60 ml

This is considerably less than the 450 ml of a typical blood donation to the Red Cross which is permitted up to 6 times per year.

(5) Optional Studies

The following components of the trial are optional and to be involved in these you will be asked to tick a box on the consent page of this form. Your involvement in these studies is completely voluntary and your decision to be involved in them will in no way affect your treatment and care in the trial.

For all participants we will seek your specific permission to collect and store two types of blood sample for potential future studies for which funding has yet to be obtained. The first of these samples will be requested prior to treatment and will be used to extract DNA. This will be used to determine you genetic "fingerprint" and will be analysed to look for genetic differences that are associated with either a positive treatment response or worse outcomes over the duration of the trial (e.g. greater changes in disability level).

The second set of blood samples that we will request your specific consent for will be blood that can be separated into serum (fluid) and cells. We will only keep the serum portion. As part of consenting to this trial we have asked for your consent for the researchers to measure EBNA1 antibodies. However, you also have to option to consent for future additional tests of your serum sample, including markers of brain degeneration (e.g. serum neurofilament light protein), markers of immune function (e.g. cytokines) and other factors that might assist in understanding how particular treatments either do or don't work, and what might predict continued progression in MS.

You may also consent to your DNA and serum samples being used in future potential research that has yet to be defined.

The research team will hold these samples in a biobank that will be linked to your clinical information in a de-identified way (no information that could identify you will be included). Again, with your specific consent we would like to store these samples for potential future studies. Any such studies would need to have been approved by an ethics committee and would be reviewed by the research team. All analyses of your samples would be conducted in Australia, but results may be shared and combined with results from international collaborators. One example of such collaboration is the International MS Genetics Consortium which has successfully identified over 200 genes that make MS more likely.

These blood collections (DNA and serum) would increase the totals collected in the trial as shown in Table 2. This also remains much less than the 450 ml of a typical blood donation to the Red Cross which is permitted up to 6 times per year.

Table 2. Total blood volume to be collected for the STOP-MS trial each year if consent is given for all optional biobanking samples to be collected

Stage	Timepoint	Volume of Blood per Year
Stage 1	Year 1	200 ml*
	Subsequent years	80 ml
Stage 2	Year 1	180 ml*
	Subsequent years	80 ml

All participants are invited to participate in an additional method of data collection that involves playing a game on a web-based application called MSReactor. This app has been developed by our colleagues at Monash University and shows promise as a quick and more sensitive way to monitor both motor and cognitive functioning in people with MS. You will be asked to complete a series of three tasks that measure reaction tasks in simple game format. Your reaction times will be stored on server hosted by Monash University linked to your email address. This is an optional component of the trial and you will be required to provide your email address to register an account on the MSReactor app so that you can retrieve your password information if it is ever forgotten.

(6) How much time will the study take?

We have estimated that participants will spend a maximum of about 18 hours over 5 years undertaking activities in this study at the study site (not including time spent getting to and from appointments). This includes approximately 11 hours in clinic visits and 5 hours in MRI scanning time, with some additional time for blood and saliva collections. In addition, there will be a maximum of 5 hours in telephone reviews and 6 hours of blood collections in the community (local pathology lab). In total this amounts to about 29 hours of study participation over 5 years. This compares with perhaps 8-10 hours of time that would normally be spent in clinic visits, blood collections and MRI scans as part of normal care for someone on treatment for MS over this period of time.

(7) Are there any risks to participating in this study?

The two medications being trialled (spironolactone and famciclovir) are both existing therapies in Australia that have been approved by the TGA and are recommended by the Pharmaceutical Benefits Advisory Committee for funding through the Pharmaceutical Benefits Scheme. They are both widely used in Australia to treat people with the conditions for which they are primarily indicated (congestive heart failure for spironolactone and herpes virus infections for famciclovir). They are both generally regarded as safe, but like all medications they have known side effects and potential risks.

Spironolactone can cause increased potassium levels in the blood which can cause heart rhythm disturbances that could be fatal if left untreated. This principally occurs in settings where spironolactone is taken with other medications known to cause an increase in blood potassium levels, in people who have kidney failure or have diabetes. There are some other rarer conditions that can also make this more likely (cardiac failure, congenital adrenal hyperplasia, Addison's disease and post parathyroidectomy).

Unfortunately, there are usually no symptoms associated with an elevated potassium level. To reduce any risk of high potassium levels you will undergo an ECG at baseline to ensure that your heart is healthy before you commence the trial. You will be screened for and provided with a list of medications that you should avoid for the duration of the trial. If you are taking any of these medications you will be excluded from enrolling in

the trial and if you need to start any of them during the trial, we request that you inform the trial site staff and they will ask you to cease taking the study medication. We ask that you advise any doctor prescribing new medication that you are involved in this trial and show them you Participant ID Card and the list of medications to avoid. If they are in any doubt, they can contact the principal investigator at your trial site (indicated on the Participant ID Card) to seek further information.

Please note that some over the counter medications (e.g. anti-inflammatories such as Nurofen) and supplements (e.g. "Lily of the Valley") can cause increased potassium levels. It is requested that you check the list if you plan to start any new supplements or complementary medicine. If in doubt please check with your treating neurologist. As part of the study you will have checks of your potassium level in the blood prior to starting treatment and at regular intervals throughout the study, particularly in the first few weeks. We will also monitor your kidney function at the same time.

Kidney failure is not a specific risk from either spironolactone or famciclovir, but the coincidental development of kidney failure, as can occur with infection and other acute illnesses, increases the risk of increased blood potassium levels with spironolactone and the potential for toxicity from famciclovir (drowsiness and confusion). As indicated above kidney failure is an exclusion criteria for involvement in the trial and we will monitor your kidney function prior to starting and throughout the trial. It is important that if you fall ill for any reason and need to see a doctor or need to be admitted to hospital that you advise the treating doctors that you are in the STOP-MS trial and that is important that they should check you potassium level and kidney function.

Approximately 1 in 10 men taking spironolactone for more than 6 months may develop an abnormal swelling of breast tissue on the chest wall (called gynaecomastia). This side effect is reversible on stopping the drug. All male participants will be asked to report any breast swelling and will undergo an examination of the chest wall at each clinic visit. If evidence of gynaecomastia is found participants will be offered the option of discontinuing the study medication.

Spironolactone is potentially harmful to the foetus (known to cause malformations in animals) if taken during pregnancy or to the child (can cause increased potassium levels) if taken whilst breast feeding. There are no known risks with famciclovir in pregnancy or whilst breast feeding from animal studies, but there is insufficient data in humans to say that it is safe to take in these situations. Thus, both drugs are recommended to be avoided in pregnancy. Consequently, being pregnant or breast feeding are exclusion criteria to enrolment in the trial. Women of childbearing potential will undergo a pregnancy test prior to enrolment and will be required to use an acceptable method of contraception for the duration of the trial and for 30 days after discontinuation of the study medication. Acceptable methods of contraception are the oral contraceptive pill, implants, "depo" injections or an intrauterine device. Barrier methods alone are not acceptable.

There is no evidence of potential for harm to offspring of males conceived whilst taking either spironolactone or famciclovir and therefore there will be no requirement for male participants to use contraception during the trial.

(8) Will I incur any costs by participating in the study?

There will be no costs associated with your participation in this study. The trial treatment will be provided at no cost and your review visits and blood test costs will all be covered by the trial team. No remuneration is offered for your participation in this study but any reasonable out of pocket expenses (e.g. parking) associated with your participation can be claimed and will be reimbursed.

(9) Can I tell other people about the study?

You are free to discuss your participation in this study with others. When considering whether or not to participate in this study, we would encourage you to discuss your decision with friends, family and your general practitioner (GP).

(10) Do the investigators have any potential conflicts of interest?

The investigators declare that they have no potential conflicts of interest in conducting this research. The two treatments being trialled are both no longer subject to patent and are relatively inexpensive as generic alternatives are available for both. None of the research team have financial interests with regards to the manufacturers of these products.

The research team do declare a vested interest in trying to find effective therapies for progressive MS. In view of this we have been careful to design this study with inbuilt safety measures against potential sources of bias. These include the trial being randomised, placebo controlled and double-blinded. All participants and treating teams will not know who is receiving which treatment. Treatment allocations will not be uncovered (excepting in exceptional circumstances for individual participants) until all data has been collected and quality checked. At that point, the database will be locked and the data exported to an independent team not directly involved in running the trial to undertake the statistical analysis.

(11) Will I receive the results of the study?

No individual results from this study will be reported back to participants. However, participants in Stage 1 taking the least effective treatment will be advised of this at the end of the Stage 1 analysis. The interim and overall results of this study will be published in a medical journal and at that point the results will be summarised on the Griffith University Facebook page. If you would like to personally receive a copy of the findings, please indicate this on the consent form and provide an appropriate means of contact (email or postal address). These contact details will only be held at your local study site.

(12) Confidentiality and disclosure of information

Any information that is obtained in connection with this study that is able to be identified as being in connection with you will remain confidential and will be disclosed only with your permission, except as required by law. If you consent to participating in this study, we plan to publish the results in a medical journal and may present the results to the Therapeutic Goods Administration (and other relevant regulatory authorities). In any publication, information will be provided in such a way that you cannot be identified. Research data will be retained in a password protected electronic file at Griffith University for a period of 15 years from the date of the final publication before being destroyed.

The conduct of this research involves the collection, access, storage and/or use of your identified personal information. The information collected is confidential and will not be disclosed to third parties without your consent, except to meet government, legal or other regulatory authority requirements. A de-identified copy of this data may be used for other research purposes, including publishing openly (e.g. in an open access repository). However, your anonymity will at all times be safeguarded. For further information consult the University's Privacy Plan at

http://www.griffith.edu.au/about-griffith/plans-publications/griffith-university-privacy-plan or telephone (07) 3735 4375.

(13) Can I withdraw from the study?

Participation in this study is voluntary - you are not under any obligation to consent and - if you do consent - you can withdraw at any stage without affecting your relationship with the Principal Investigator responsible for your care. You can withdraw your consent by advising the researcher either verbally, via email, or by completing and returning the 'Participant Withdrawal of Consent Form' that is supplied herein.

(14) How can I obtain further information?

When you have read this information, the Principal Investigator will discuss it with you further and answer any questions you may have. If you would like to know more at any stage, please feel free to contact either the researcher or Professor Simon Broadley (Tel.: 07 5678 0174).

(15) What can I do if I have a complaint or a concern?

Griffith University and Gold Coast Hospital and Health Service conduct research in accordance with the National Statement on Ethical Conduct in Human Research (2023). If you have any concerns or complaints about the ethical conduct of this research project, you are encouraged to contact any or all of the following:

HREC Coordinator
Gold Coast University Hospital
1 Hospital Boulevard
SOUTHPORT QLD 4215
Email: GCHEthics@health.qld.gov.au
Phone: (07) 5687 3879

Any complaint will be investigated promptly and you will be informed of the outcome.

This information sheet is for you to keep.