RECOVERY

Standard Operating Procedure:

Measurement of additional early phase assessment outcomes

Revision History

Version	Issue Date	Author	Description
0.1	2021-02-17	Mark Campbell	Initial version (Dimethyl fumarate)
1.0	2021-02-20	Mark Campbell	First released version
1.1	2021-02-25	Mark Campbell	Additional clarification of participant's requiring outcome measurements
1.2	2021-03-10	Mark Campbell	Clarifications following site feedback
1.3	2021-03-22	Mark Campbell	Trauma mask oxygen rules clarified

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1 Glossary

Abbreviation	Description
DMF	Dimethyl fumarate – an immunomodulatory drug under early phase assessment as a potential intervention within RECOVERY
S/F_{94}	The primary outcome measure of the early phase assessment. The ratio of oxygen saturations to fraction of inspired oxygen when the oxygen saturations are <94%
SpO_2	Oxygen saturations of blood, measured by pulse oximetry
FiO_2	Fraction of inspired oxygen (% oxygen content)

2 Scope

This Standard Operating Procedure (SOP) describes the procedure for measuring the additional outcomes associated with early phase assessment of interventions within the RECOVERY trial.

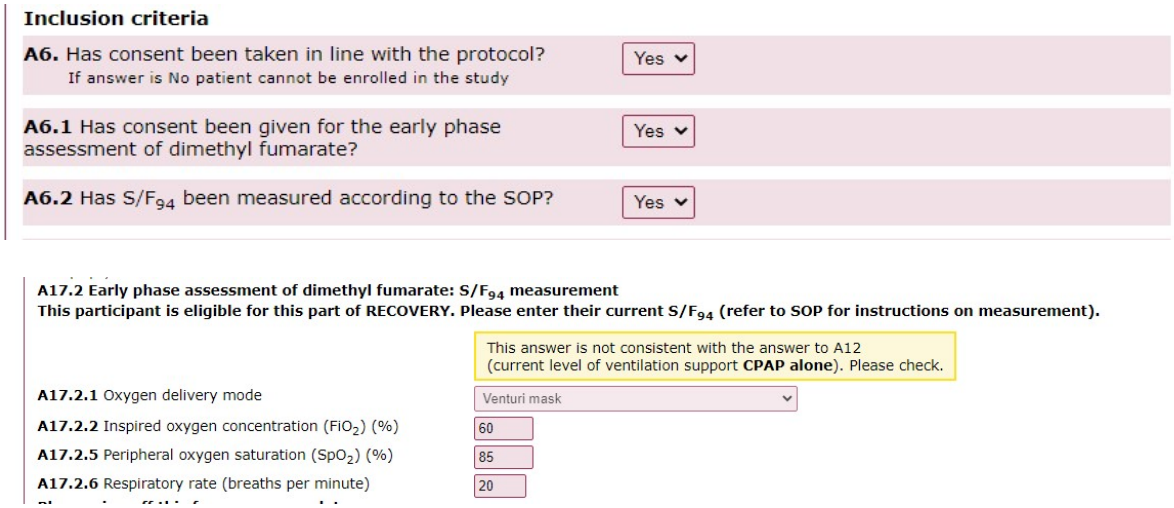
This SOP aims to act as a reference guide for study personnel measuring and/or recording the additional outcomes. It should also ensure consistency between personnel within, and between, study sites when measuring the outcomes.

It is designed to be used in conjunction with the latest version of the RECOVERY study protocol, which describes the appropriate inclusion criteria, consent, contraindications and dosing of study interventions.

3 Eligibility and Randomisation

3.1 Randomisation form

The randomisation form and website is the same as that used for all RECOVERY participants. There are a few extra questions pertinent to the dimethyl fumarate comparison:



Differences between current level of ventilation support and S/F$_{94}$ oxygen delivery method

It is permissible for the answers to Section A17.2 above to be different to those entered in Section A12. (current level of ventilation support) and Section A12.1 (latest oxygen saturation measurement).

Section A12 and A12.1 represent the current clinical measurements and should be completed as normal. Section A17.2 represents the new S/F$_{94}$ ratio measurement taken in line with the process described in this document. The oxygen delivery mode and oxygen saturations may necessarily be different to that entered earlier in the randomisation form.

Trauma/non-breather mask oxygen at randomisation

Trauma (non-rebreather) mask oxygen is not regarded as an acceptable mode of oxygen delivery at randomisation (as the estimate of FiO_2 is not very accurate). Participants should be switched to an alternative method of oxygen delivery or excluded from the comparison if this is not possible.

3.2 Drug administration

In accordance with manufacturer's recommendations, dimethyl fumarate can only be given as whole capsules via the oral route (i.e. routes such as nasogastric tube administration are not advised). Unfortunately, this may mean that patients for whom the oral route becomes unavailable (e.g. severe swallowing difficulties or on invasive mechanical ventilation with only nasogastric tube enteral access) may not be suitable for commencing or continuing dimethyl fumarate treatment.

4 Outcome Measurement

4.1 Participants who require outcome measurements to be completed

- **All participants who are allocated dimethyl fumarate (intervention group)**
- **All participants who are allocated usual care but were eligible for dimethyl fumarate (control group)**

4.2 S/F_{94} Ratio

4.2.1 Overview

The S/F_{94} ratio is defined as: the ratio of peripheral oxygen saturations (**S**pO_2) to fraction of inspired oxygen (**F**iO_2) when the oxygen saturations are <**94**%.

The SpO_2:FiO_2 ratio is a correction for the measured oxygen saturation (SpO_2) to account for how much oxygen the patient is receiving (FiO_2). If the measured SpO_2 is ≥94% the ratio is less accurate (because SpO2 cannot rise much further regardless of FiO_2). Therefore the SpO_2:FiO_2 ratio should be measured when the patien's SpO_2 is <94% (termed the S/F_{94} ratio).

It involves a simple measurement of peripheral oxygen saturations whilst the patient is on room air or receiving oxygen through a mask/system giving a known FiO_2. For an accurate measurement the peripheral oxygen saturations need to be <94% with the patient sat at 30 degrees not speaking for 5 minutes. This may mean that you need to change nasal cannula to an equivalent Venturi mask, or you may need to reduce the amount of oxygen/Venturi mask valve that you are giving the patient.

The S/F_{94} ratio should be measured at day 1 (**before** randomisation) and on days 3, 5 and 10 (unless discharged sooner).

4.2.2 Safety

Short periods of hypoxia (e.g. SpO_2 of 80% for less than 20 minutes) are not considered harmful. The participant should be monitored throughout and if they become breathless or distressed after a reduction in FiO_2 it should be immediately increased. After discussion with the participant, one further attempt can be made at reducing the FiO_2 with their agreement.

4.2.3 Instructions for Measurement

The following procedure describes the details for measurement of this outcome. It is estimated that this procedure could take anywhere between 10 and 30 minutes to complete, depending on the patient and environment.

Step One: Ensure oxygen therapy is being given at a measurable percentage of oxygen

This means using methods of oxygen delivery where a reliable FiO_2 can be determined. The most common modes that ***do not*** give a reliable measurable FiO_2 are nasal cannulae or simple (non-Venturi) face masks, which many hospitalised patients with COVID-19 may be using to receive oxygen therapy.

Note that FiO_2 is a different measure to the the oxygen flow rate (litres per minute of oxygen a patient is receiving).

Acceptable modes of oxygen therapy that give a measurable percentage of oxygen:

Acceptable oxygen mode	Description	FiO_2 delivered
Room air	SpO_2 on air is always acceptable if the patient has been breathing air for at least 5 minutes	21%
Venturi mask	Venturi masks have a changeable coloured attachment on the oxygen inflow stating an oxygen percentage	24% (Blue) 28% (White) 31% (Orange) 35% (Yellow) 40% (Red) 60% (Green)
HFNO	High-flow nasal oxygen e.g. Airvo	21-100%
Humidified O_2	A high-flow humidified system providing a specified oxygen percentage	21-100%
CPAP/NIV	Any kind of contiuous positive airway pressure or non-invasive respiratory support	21-100%
IPPV	Invasive positive pressure ventilation through an endotracheal tube or tracheostomy	21-100%

Trauma mask (non-rebreather mask):
A trauma mask (one with a reservoir bag) is often used to provide maximal oxygenation for a ward patient. This should be switched to a Venturi mask in order to define the FiO2 delivered for S/F_{94} measurement if at all possible.
At randomisation, the trauma mask is not an acceptable method of oxygen delivery for entry into the study due to the lack of accuracy in determing FiO_2.
However, on follow-up measures (at days 3, 5 and 10) if the patient is using a non-breather mask with flow rate >10L/min, oxygen saturations are already low and it is not felt safe to switch to a Venturi mask, then the FiO_2 should be recorded as 70% on the follow-up form. The value will default to this if non-rebreather mask is selected. This is regarded as preferable to having missing follow-up data.

If your patient is on an acceptable method of oxygen therapy proceed to **Step Two.**

If your patient is not on an acceptable method of oxygen therapy **change** to an acceptable oxygen mode as clinically appropriate. Some suggestions are below:

Previous Mode	SpO_2	Change to
Nasal cannulae less than 4L/min	>90%	Room air
	86-90%	Venturi mask 24%
Simple (Hudson) facemask less than 4L/min	Above 90%	Room air
	86-90%	Venturi mask 28%
Other masks with flow up to 15L/min	>90%	Venturi mask 40%
	86-90%	Venturi mask 60%
	<86% (if at or above 15L/min)	Do not reduce O_2 Record FiO_2 as 70%

Step Two: Ensure patient at rest, not talking, on the same oxygen therapy for at least 5 minutes.

The participant should be resting in bed with the head of the bed at 30° (or as close that as is comfortable) for at least 5 minutes.

The patient must not be talking or exercising during this time. Explain to the patient that talking may alter their oxygen levels and so they must remain calm and silent for 5 minutes.

Proning:
Patients who are being managed prone (awake or on IPPV) should have S/F_{94} measurements taken during the supine periods as part of standard care.

Delirium/dementia:
If patients are agitated this step may be difficult and so the requirement that the patient should be resting and not talking may need to be relaxed. As long as the other essential conditions are met (patient is receiving a measurable percentage of oxygen, and S_pO_2 is less than 94% or the patient is breathing air) the measurement can proceed. Please remember that increasing agitation may be a symptom of hypoxia.

Step Three: Ensure SpO_2 is less than 94% or the patient is breathing air

If SpO_2 is above 94%, reduce the FiO_2 and monitor SpO_2 continously for 5 minutes. If the patient remains comfortable, SpO_2 values as low as 80%, particularly for short periods (less than 20 minutes), are not thought to be harmful. If the patient becomes breathless, agitated or feels unwell after a change in oxygen therapy, immediately revert to the previous oxygen therapy.

Some suggestions for reducing FiO_2 are below:

Previous FiO_2	Change to FiO_2
≤30%	Room air
≤40%	28-30%
≤50%	40%
≤60%	50%
≤80%	60%
≤100%	80%

If the FiO_2 is reduced, wait for 5 minutes and observe the SpO_2. If still >94%, reduce the FiO_2 further (as above) and repeat until SpO_2 <94% (or the participant cannot tolerate further reductions

Step Four: Document outcome measurements

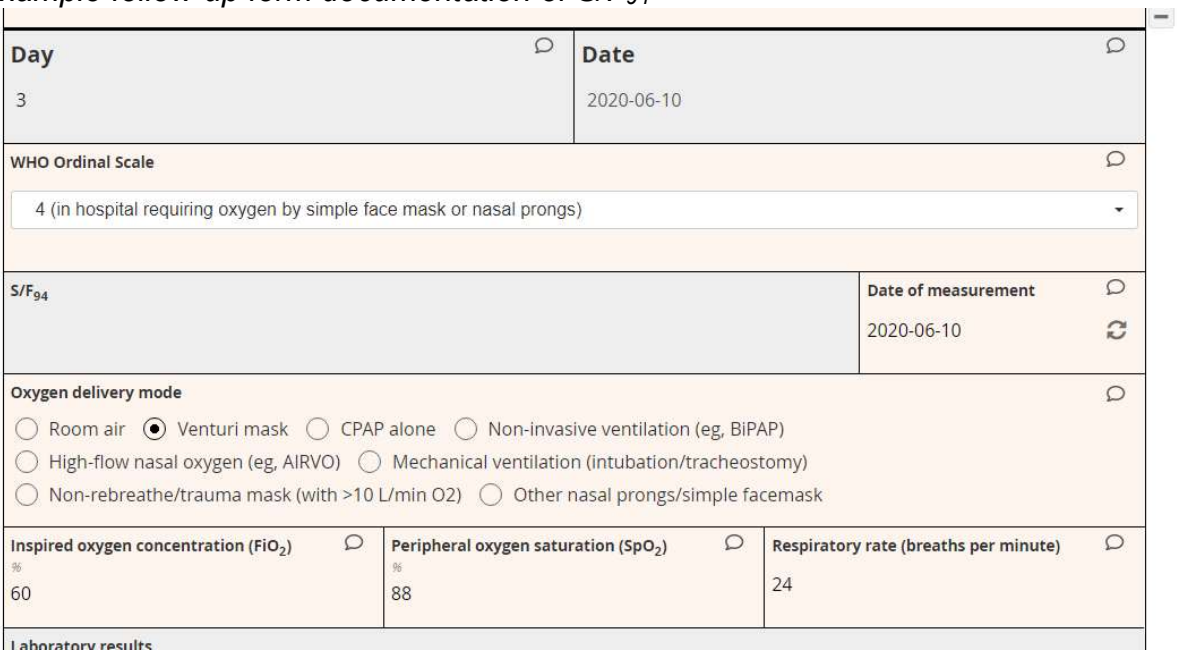
Once the above three steps are completed, the following parameters should be documented on the relevant Case Report Form:

- Oxygen delivery mode
- SpO_2
- FiO_2
- Respiratory rate (in breaths per minute)

If receiving specific modes of oxygen delivery an additional parameter should also be documented:

Oxygen delivery mode	Additional parameter
CPAP/NIV/IPPV	Peak end-expiratory pressure (PEEP) (in cm H_2O) This will be displayed on the machine or can be obtained by discussing with the responsible clinical staff. If receiving bi-level positive airway pressure (BiPAP) this may also be termed the EPAP (Expiratory Positive Airway Pressure).
High flow nasal oxygen	High flow nasal oxygen flow rate (in L/min) This will be displayed on the machine or can be obtained by discussing with the responsible clinical staff

Example follow-up form documentation of S/F_{94}



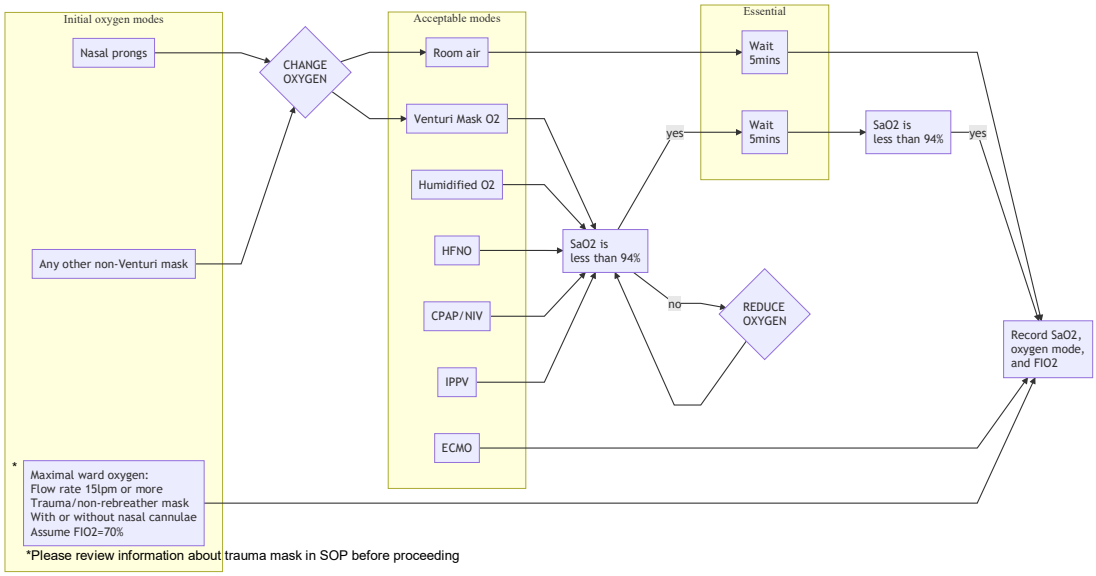
Please note that it is possible to record the oxygen delivery mode as “Other nasal prongs/simple facemask” on the follow-uo form. This is not an oxygen delivery method where an accurate FiO2 can be determined and should only be selected if it was not possible to switch to room air or a Venturi mask, together with a justificaition documented as to why this was the case.

NB Access to the OpenClinica DMF case report form may require an OpenClinica account if the researcher conducting the measurement does not have one. Please contact recoverytrial@ndph.ox.ac.uk in this case.

Step Five: Revert patient’s oxygen therapy to baseline

After completion of the study measurements, switch the patient’s oxygen delivery mode and FiO_2 back to those that they were on before any study procedures were carried out. Discuss with the responsible clinical staff if any concerns.

Overview flowchart



4.3 Ordinal Scale

The Ordinal Scale score is a clinical progression score allowing the measurement of clinically relevant improvement or deterioration.

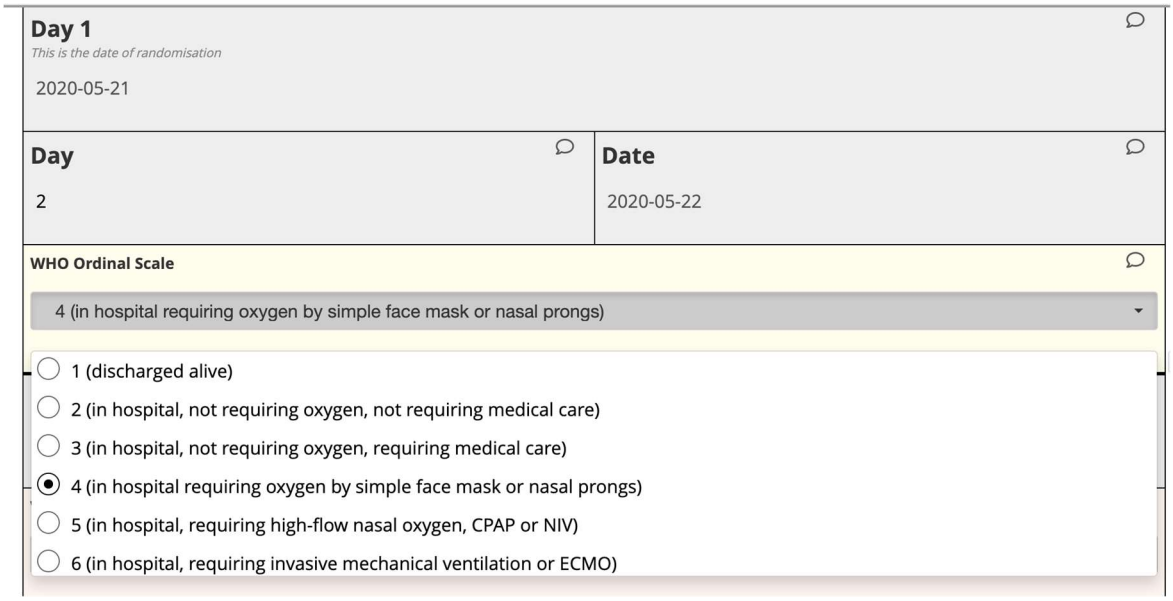
The Ordinal Scale score should be measured daily at ~12:00pm from study day 2 until day 10 (or discharge if sooner). It is appropriate to record from the medical records.

The Ordinal Scale score should be recorded as for the participant’s current clinical status rather than as for any change in oxygen therapy performed as part of measuring S/F_{94} within the study.

The Ordinal Scale score should be completed in accordance with the below:

Score	Descriptor
1	Discharged (alive)
2	Hospital admission, not requiring supplemental oxygen, no longer requiring medical care (hospitalisation extended for infection control or other nonmedical reasons e.g. social care. Sometimes documented as “medically fit for discharge” or “medically stable for discharge”)
3	Hospital admission, not requiring supplemental oxygen, but requiring ongoing medical care
4	Hospital admission, requiring supplemental oxygen (by face mask or nasal prongs)
5	Hospital admission, requiring high flow nasal oxygen, continuous positive airway pressure, non-invasive ventilation or both
6	Hospital admission, requiring invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
7	Death

Example follow-up form documentation recording Ordinal Scale score:



4.4 Laboratory results

Blood tests taken as part of routine clinical care on the required days (study days 3, 5 and 10) are entirely appropriate to be used for the data in order to avoid repeat blood tests for the patient. Otherwise, a blood test should be taken for study purposes on the relevant day and the sample processed and disposed of routinely in the local laboratory. If a result for the given day is not available, then one from the day before (or day after) may be substituted if available.

4.4.1 C-reactive protein

Blood C-reactive protein should be measured on days 3, 5 and 10 (unless discharged sooner).

Results should be documented (in mg/L) on the follow-up form and rounded to the nearest whole number. “Too high to measure” should be selected if above the limit of detection of the local assay.

4.4.2 Creatinine

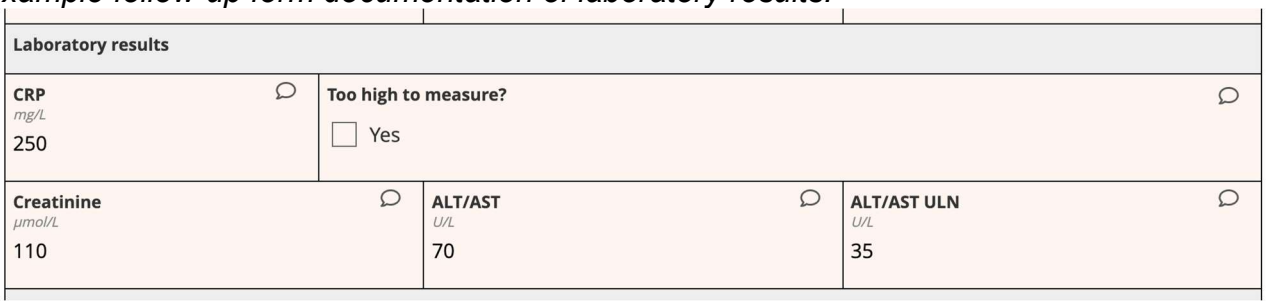
Blood creatinine level should be measured on days 3, 5 and 10 (unless discharged sooner) and the measurement completed on the follow-up form (documented in µmol/L)

4.4.3 Alanine (or aspartate) transaminase (ALT or AST)

Blood ALT and AST should be measured on days 3, 5 and 10 (unless discharged sooner) and the measurement completed on the follow-up form (documented in IU/L).

The upper limit of normal (ULN) should also be documented for the result for the local laboratory assay. This is usually found expressed in the form: Result X (Normal range Y-**Z**) where Z is the ULN.

Example follow-up form documentation of laboratory results:



4.5 Adverse Events and Adherence

4.5.1 Diarrhoea

Diarrhoea can be common with dimethyl fumarate (DMF) use. For the study, diarrhoea should be regarded as the passage of 3 or more loose or liquid stools in 24 hours (or more frequent passage than is normal for the individual)

The presence of *new* diarrhoea (since randomisation) should be recorded on the follow-up form on days 3, 5 and 10.

It can be documented as “None”, “Some” or “Severe”. Severe diarrhoea would be reported as per the patient’s own assessment or, if this is not possible, the opinion of the responsible clinical team.

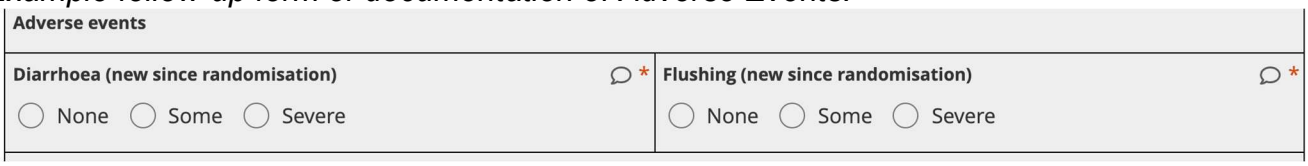
4.5.2 Flushing

Flushing can also be common with DMF use. For the study, flushing should be regarded as the uncomfortable experience of redness and warmth.

The presence of *new* flushing (since randomisation) should be recorded on the follow-up form on days 3, 5 and 10.

It can be documented as “None”, “Some” or “Severe”. Severe flushing would be reported as per the patient’s own assessment or, if this is not possible, the opinion of the responsible clinical team.

Example follow-up form of documentation of Adverse Events:



4.5.3 DMF Adherence [only for participants allocated DMF]

The following categories of questions appear on the follow-up form:

a) DMF dose in last 24 hours

On days 3, 5 and 10 the DMF dose should be documented (as received in the last 24 hours), with the options “Per protocol”, “reduced” or “discontinued” available.

If the drug has been reduced from a dose of 240mg 12-hourly to 120mg 12-hourly (or once daily) then the “reduced” option should be selected.

b) Reason for discontinuation

This is only asked if “discontinued” is selected for the question above and may be asked on days 3, 5 or 10.

The options “diarrhoea”, “flushing” or “Other” with a freetext box to input the reason for discontinuation are available.

c) Days dimethyl fumarate taken for

On day 10 the total number of days DMF was actually received by the patient should be completed (range 0-10 days).

5 Summary of timeline of additional outcome measures

Outcome measure	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
S/F_{94}	[ ]		[ ]		[ ]					[ ]
Ordinal Scale		[ ]	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]
Laboratory results (CRP, creatinine, ALT/AST)			[ ]		[ ]					[ ]
Adverse events			[ ]		[ ]					[ ]
Adherence			[ ]		[ ]					[ ]

Day 1 = Day of randomisation. S/F_{94} measurement as part of the randomisation form.
Outcome measurement stops at day 10 (or discharge if sooner)