National Clinical & Integrated Care Programmes
Person-centred, co-ordinated care

NEUROLOGY

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RELAPSING REMITTING MULTIPLE SCLEROSIS

New Diagnosis:

Given the delays in re-establishing outpatient clinics across the HSE, people with symptoms suggestive of MS may experience delays in accessing an expert neurologist and in accessing appropriate investigations.

There may be situations where those presenting with the most severe clinical events, such as transverse myelitis or bilateral optic neuritis where review in an emergency setting will be required, either in A+E, or in a designated day facility.

Early initiation of disease modifying treatment can reduce the chance of longer term progression in MS once a diagnosis has been established, and it remains important people with a first presentation of MS receive a timely diagnosis and access to appropriate therapy.

We recommend that virtual /telemedicine clinics should continue for patients while outpatient facilities are being re-established. However, all sites should have facilities to provide face to face meeting for those with significant / clinically concerning symptoms, taking into account the restriction surrounding social isolation, and balancing these requirements with the need to provide an accurate clinical diagnosis and appropriate management plan.

The diagnostic pathway should continue to be prioritized to occur within 8 weeks as per international guidelines.

This should include neurological examination, phlebotomy, neuroimaging and lumbar puncture where relevant. While this poses significant challenges given reduced access to imaging facilities and day cases, each centre should be encouraged to develop measures to expedite diagnosis, including dedicated access to neuroimaging, and waiting list initiatives for new patients.

People with Multiple Sclerosis on Disease Modifying Therapies:

Current advice is that people on DMT should continue their treatment. Neurologists starting people on *Alemtuzumab, Mavenclad, Ocrevus* or *Rituximab* were advised to consider alternative treatment until after the peak of COVID-19 infections has passed. Given that the issues surrounding COVID are likely to remain for at least 12 months, it is now the case that a risk /benefit analysis should be considered when assessing patients for new therapies, although consideration should be given as to

the indication for treatment. For example, the risks for those with primary progressive / secondary progressive MS may be higher than for those with Relapsing Remitting MS.

In general, it is now considered safe to commence or receive retreatment with *Mavenclad, Ocrevus* and *Tysabri* for those meeting the clinical indications for these compounds, and to *continue therapy* with *Alemtuzumab* and *Rituximab* where appropriate. A decision to commence on *Alemtuzumab* de novo should be considered carefully and a detailed risk benefit analysis performed.

Tysabri treatment interval should be extended to 6 weeks with appropriate monitoring, after the initial three infusions which should be delivered monthly.

If a patient is due re-treatment with any of these agents, it will be appropriate to proceed and advise regarding monitoring of lymphocyte count and cocooning.

People established on treatment should continue to have their safety blood monitoring performed and safety MRI scans coordinated by MS nurses, especially for the *Tysabri* treated population. Timing of safety blood tests could be modified during the course of the pandemic as detailed below (advice from The Association of British Neurologists, April 2020).

	Normal monitoring recommendation	Recommendation until risk of Covid 19 clarified or passed
Interferon Beta	3 months, 6 months, then 6 monthly	3 months after starting then none required
Glatiramer Acetate	None required	None
Teriflunomide	2 weekly for 6 months, then 2 monthly if stable	Monthly for 1st 6 months then 4 monthly if stable
Dimethyl Fumarate	3 monthly	6 monthly if stable and lymphocytes above 0.5
Fingolimod	1,3,6,12 months, then every 6-12 months	6 monthly in first year then 12 monthly if stable
Natalizumab	Every 3 months	6 monthly JCV
Ocrelizumab	Every 6 months	None
Alemtuzumab	Monthly	3 monthly FBC, C&E, LFTs, TFTs
Cladribine	2 months and 6 months after each course, 2 monthly if lymph <0.5	No change to 2-month test Delay 6-month test if 2-month bloods are stable and lymphocytes >0.5

Current recommendations continue to indicate that discontinuing DMT is appropriate in the case of a person with MS testing positive for COVID-19, and restarting after three negative tests.

Relapse management:

MS patients will require ongoing access to their usual neurology teams to report new symptoms and access appropriate advice for relapse management to prevent Emergency Room presentations.
As is the normal case, most hospitals have a point of contact for their patient **population via an MS nurse or Neurology team member** and it is recommended that this is maintained.

Summary for RRMS

Telephone triage and consultations by MS Nurses, SpRs and Consultants is essential to enable appropriate management of MS, including the provision of home-based care for relapses in the community. Patients should be admitted to a COVID free ward providing Neurology services where medically required.
Appropriate, socially distanced infusion capacity should be protected for those requiring hospital delivered DMTs.

SECONDARY PROGRESSIVE MS / HIGH DISABILITY

This cohort will require ongoing surveillance by the MS nurses (or Neurology teams where there is no MS nurse in post) to ensure that care does not break down within the community.
A continued prioritisation exercise will be required, and regular telephone follow up with the at risk patients required to facilitate rapid transfer to a care facility where necessary. Those with intercurrent illness (non COVID) may need admission to an Intermediate Care Facility within the community.

A number of patients with progressive MS may be on Rituximab or Ocrevus therapy. Consideration to the timing of retreatment could be based on assessment of B cell subsets and retreatment delayed if CD19 cells remain below 5% of the profile.

Table DMTs and risk of COVID-19

Agent	MOA[e16]	Risk of infectious disease	Potential beneficial effect by limiting immune responses mediating severe COVID-19 complication (e.g., ARDS)	Predicted potential to increase the risk of severe COVID-19 complication (e.g., ARDS)
Interferon β-1a and β-1b	Decreases immune cell activation through IFN receptor binding; decreased trafficking	No increased risk of infection[11]	Downregulation of proinflammatory cytokines[35]	None
Glatiramer acetate	Promotes Th1→Th2 shift; induces suppressor T cells and anti-inflammatory myeloid cells	No increased risk of infection[11]	Shift from Th1 and M1 (proinflammatory) to Th2 and M2 (anti-inflammatory)	None
Dimethyl fumarate	Promotes Th1-Th2 shift; induces mild apoptosis of memory T cells and B cells; neuroprotective effect by upregulation of Nrf2-dependent antioxidant response	Potential risk of PML[11]	Block proinflammatory cytokine production[e13] and inhibit macrophage function[e14]	Probably low
Teriflunomide	Inhibits proliferation of activated T and B lymphocytes by inhibiting DHODH	Potential reactivation of tuberculosis[11]	Downregulation of IL-1, IL-6, and TNFα from activated macrophage[e27,e28]	Probably low
S1P modulators	Prevent lymphocyte egress from lymph nodes by binding S1P receptor	Potential increased risk of some opportunistic infections (PML, *Cryptococcus*, VZV, and HPV); slight increased risk of lower respiratory infections[e33]	Block recruitment of monocytes and macrophages via S1P3 receptor modulation[e38] (only with nonspecific S1P modulator)	Probably low
Cladribine	Sustained reduction of T and B cells by interfering with DNA synthesis and repair	Slight increased risk of herpes infections with grade 3 or 4 lymphopenia[e44,e45]	Uncertain, main effects on lymphocytes	Probably low
Natalizumab	Prevents entry of T cells and others into the brain	Potential risk of PML[11]	Uncertain, probably none	Probably low
Anti-CD20 monoclonal antibodies	Binds CD20 resulting in B-cell cytotoxicity	Potential increased risk of URIs[e68]; reactivation of chronic hepatitis B	Uncertain; main effects on B cells/de novo plasmablasts	Probably low
Alemtuzumab	Depletes B and T cells by binding to CD52	Reactivated herpes infection (HSV and VZV)[e72,e78]; listeria[e79]; HPV[e78]	Uncertain	Probably low except during the first months after infusion[e80]

Abbreviations: ARDS = acute respiratory distress syndrome; COVID-19 = coronavirus 2019; DHODH = dihydroorotate dehydrogenase; DMT = disease-modifying therapy; HPV = human papillomavirus; PML = progressive multifocal leukoencephalopathy; URI = upper respiratory infection; VZV = varicella zoster virus.