BOX 1. RECOMMENDATIONS FOR UNRESOLVED ISSUES

1. **Anti-CD20s-treated patients without vaccine response: Should we optimize SARS-CoV-2 vaccination strategy and/or use SARS-CoV-2 preventive treatments?**

Based on the current literature, including the scarce evidence about timing of vaccines and boosters where more studies are needed, and our personal experience we propose some strategies for optimizing SARS-CoV-2 vaccination response in anti-CD20s therapies:

1. Vaccinating in advance of initiating therapy: For inactivated vaccines, at least 2 weeks prior to treatment, and for live-attenuated vaccines, at least 4 weeks before treatment.[4]
2. Personalizing the timing of vaccine administration: In terms of balancing the risks associated with delaying therapy for vaccination or a booster dose, it is important to consider individual patient characteristics, including age, disease severity, clinical or radiological activity, and anti-CD20 therapy duration. For many patients, especially those under 50 years-old with recent active disease, the risk of multiple sclerosis disease activity from delayed anti-CD20 therapy might outweigh the risk of severe SARS-CoV-2 infection. In these patients, vaccinating at least three months post-infusion and four to six weeks prior to infusion would be advisable. In those over 50 years-old without recent activity, increasing time since last anti-CD20 therapy infusion might be a good option.
3. Using mRNA-1273 vaccine over other vaccines for its higher antibody titres in head-to-head studies.[41]
4. Administering repeated annual booster doses annualy as recommended by WHO.[56]

In those people with multiple sclerosis who remain seronegative regardless of SARS-CoV-2 vaccination, novel anti-SARS-CoV-2 monoclonal antibodies or antiviral agents with activity against new SARS-CoV-2 subvariants might become a preventive option.

2. **S1PRM-treated patients: Which is the best approach for vaccination?**

As vaccine responses in sphingosine 1-phosphate receptor modulators responses are closely linked to peripheral lymphocyte counts, it has been suggested that discontinuing fingolimod until lymphocyte count recovers (around one or two months) might help boost vaccine responses.[48] However, this slow recovery due to fingolimod's long half-life might increase the risk of rebound multiple sclerosis disease activity associated with prolonged cessation of

fingolimod. In contrast, ponesimod and siponimod facilitate a quicker lymphocyte reconstitution after withdrawal (seven to ten days), which could potentially mitigate the risk of rebound as this risk increases with cessation for more than one month, but more data is needed to confirm this.[47] In this sense, the EAN/ECTRIMS guidelines for people with multiple sclerosis do not provide specific strategies for improving vaccine responses in people being treated with sphingosine 1-phosphate receptor modulators, as this topic remains a matter of ongoing research.[4] In our opinion, discontinuation of fingolimod primarily for vaccination may be neither advisable nor necessary.