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# BMJ Open

## Safety and Efficacy of Mycophenolate Mofetil in Treating NMOSD : a protocol for systematic review and meta-analysis.

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4 Safety and Efficacy of Mycophenolate Mofetil in Treating NMOSD : a protocol  
5 for systematic review and meta-analysis.

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21  
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25 The authors have no conflicts of interest to disclose.

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29 Hospital, No. 2, Yinghua Donglu, Chaoyang District, Beijing 100029, China (e-mail:  
30 jinmingyk@163.com).

### 31 32 33 **Abstract**

34  
35 **Introduction** Neuromyelitis optica spectrum disorders (NMOSD) is an inflammatory  
36 and heterogeneous astrocyte disorder of the central nervous system (CNS) with the  
37 characteristic of higher incidence in women and Asian. Most patients with NMOSD  
38 have a course of recurrence and remission, which are prone to cause paralysis and  
39 blindness. A number of studies have confirmed the efficacy and promising prospect of  
40 mycophenolate mofetil (MMF) in the treatment of NMOSD. However, there are  
41 controversial about its therapeutic effect and safety. The purpose of this study is to  
42 conduct a systematic review and meta-analysis to assess the efficacy and safety of MMF  
43 in treating NMOSD.

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53 **Methods and analysis** This systematic review will include all comparative researches,  
54 from randomized controlled trials (RCTs) to cohort studies, and case-control study. A  
55 relevant literature search will be conducted in PubMed, Web of Science, EMBASE, the  
56 Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang  
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4 Database, China Science and Technology Journal database (VIP) and CBM. We will  
5 also search registers of clinical trials, potential gray literature, and conference abstracts.  
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7 There are no limits on language and publication status. The reporting quality and risk  
8 of bias will be assessed by two researchers independently. Expanded disability status  
9 scales (EDSS), annualized relapse rate (ARR) will be evaluated as the primary outcome.  
10  
11 The secondary outcomes will include the frequency and extent of adverse events (AEs),  
12 best-corrected visual acuity (BCVA), relapse-free rate and time to the next attack.  
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14 Meta-analysis will be performed using RevMan5.3 software provided by the Cochrane  
15 Collaboration and Stata 12.0.  
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21 **Ethics and dissemination** Because the data used for this systematic review will be  
22 exclusively extracted from published studies, ethical approval and informed consent of  
23 patients will not be required. The systematic review will be published in a peer-  
24 reviewed journal, presented at conferences and will be shared on social media platforms.  
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29 **PROSPERO registration number:** PROSPERO CRD42020164179.  
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### 31 **Strengths and limitations of this study:**

- 32  
33 ▶ This study is the first to conduct an exhaustive literature search to identify studies  
34 aimed to assess the effectiveness and safety of MMF in treating NMOSD.
- 35  
36 ▶ One limitation of this study is that differences in patients, interventions and primary  
37 outcomes may mean that meta-analysis cannot be conducted, and narrative and meta-  
38 analytical syntheses are planned.
- 39  
40 ▶ Although we will include studies published in any language, translation difficulties  
41 may arise, which will result in the exclusion of these studies.
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43 ▶ The analysis of different sources of heterogeneity and the assessment of risk of bias  
44 of the included studies is a key point for extracting and synthesising evidence-based  
45 conclusions.  
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52 **Keywords:** mycophenolate mofetil, neuromyelitis optica spectrum disorders, protocol,  
53 systematic review, meta-analysis.  
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## 56 **1. Introduction**

57 Neuromyelitis optica (NMO), also known as Devic disease, is currently considered to  
58 be a rare autoimmune astrocyte disease of the central nervous system mediated by  
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4 autoantibodies, dominated by humoral immunity and involving multiple immune cells  
5 and factors, with optic neuritis(ON) and acute transverse myelitis as typical clinical  
6 manifestations.<sup>1</sup> NMO has been recognized as a subtype of multiple sclerosis (MS) for  
7 more than 100 years since it was first described and reported.<sup>2</sup> Until 2004, the discovery  
8 and confirmation of anti-aquaporin-4 immunoglobulin G (AQP4-IgG) made significant  
9 progress in pathogenesis, diagnosis and treatment of NMO.<sup>3</sup> <sup>4</sup> The concept of  
10 neuromyelitis optica spectrum disorders (NMOSD) was first proposed based on the  
11 widespread clinical use of specific AQP4-IgG,<sup>4</sup> which mainly referred to the limited  
12 NMO of positive AQP4-IgG. However, with the gradual improvement of the specificity  
13 of AQP4-IgG clinical testing, the shortcomings of the diagnostic criteria of NMO in  
14 2006 and NMOSD in 2007 became prominent. In 2015, the international NMO  
15 diagnostic team proposed a new international diagnostic standard for NMOSD.<sup>5</sup>  
16 NMOSD includes NMO, ON, longitudinally extensive transverse myelitis and other  
17 typical demyelinating brain syndrome.<sup>5</sup> Up to now, there is no solid data on the  
18 incidence and prevalence of NMOSD in the world. According to the existing  
19 epidemiological data of small samples, middle-aged and young women are the high  
20 incidence of this disease, with the onset age ranging from 32 to 41 years old, and the  
21 incidence of female is about 10 times that of male.<sup>5</sup> The incidence and prevalence vary  
22 from region to region, with the incidence and prevalence being about 0.05-0.40 and  
23 0.52-4.40/100,000, respectively.<sup>6</sup> The areas with a large Asian population are the region  
24 with high incidence of NMOSD.<sup>7-9</sup> Most patients with NMOSD have a course of  
25 recurrence and remission, including ON, myelitis and lesions in special parts of the  
26 brain, which are prone to cause paralysis and blindness.<sup>5</sup> NMOSD has become one of  
27 the most common causes of non-traumatic disability and blindness in young and  
28 middle-aged people, bringing heavy burdens on the life, work and study of patients, as  
29 well as the society and economy of various countries.<sup>10</sup> Relevant clinical data show that  
30 after an average of 5 years of NMO, about 1/4 of the patients will be unable to walk  
31 independently, about 10% will be wheelchair-dependent, and more than half of the  
32 patients will develop severe visual impairment in at least one eye.<sup>11</sup> In particular, ON  
33 associated with NMO (NMO-ON) has poor recovery of visual impairment even after  
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4 conventional treatment. They often develop into severe bilateral visual impairment in  
5 the long term, leaving behind varying degrees of optic atrophy, which is different from  
6 MS.<sup>12 13</sup>

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9 Currently, there are no uniform guidelines for the clinical management of NMOSD.  
10 The class of drugs in treating NMOSD is collectively referred to as disease modifying  
11 drugs,<sup>14</sup> and the treatment is divided into two stages: acute phase and remission phase.  
12 The former is based on corticosteroids to reduce the severity of acute attacks. Treatment  
13 options include intravenous corticosteroids (IVCSs), plasma exchange (PLEX) and  
14 immunoglobulin. Immunosuppressive agents are often used in the latter to prevent  
15 recurrence and reduce the progression of neurological disability.<sup>15</sup> Common drugs  
16 include mycophenolate mofetil (MMF), azathioprine (AZA), tacrolimus, cyclosporine,  
17 and monoclonal antibodies, etc.<sup>15</sup> Although AZA and rituximab are suggested as first-  
18 line treatments based on observational studies and expert opinion from the published  
19 guidelines for NMOSD recommending,<sup>16</sup> there are still AEs such as disease recurrence  
20 and myelosuppression, which lead to drug withdrawal in patients with MMF.<sup>17</sup> In recent  
21 years, rituximab has also been reports of infusion reactions, infection, and even death,<sup>18-  
22 20</sup> and its clinical application has been limited by factors such as high price.<sup>18 21</sup>  
23 Therefore, we urgently need to find new immunoregulatory drugs for the treatment of  
24 NMOSD. The application of MMF in NMOSD is still in the exploration stage and is  
25 recommended as second-line treatments,<sup>16</sup> but a number of studies have confirmed the  
26 efficacy and promising prospect of MMF in the treatment of NMOSD,<sup>21-24</sup> and only a  
27 few adverse events (AEs) have been reported.<sup>21 22</sup> Further studies also suggested that  
28 MMF was more effective and caused fewer AEs than AZA.<sup>25 26</sup>

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31 Although MMF is increasingly used in NMOSD, its therapeutic effect and safety are  
32 still controversial. There are no systematic reviews and meta-analysis yet that evaluated  
33 the effects of MMF against other therapies in patients with NMOSD. It is therefore  
34 timely to perform a systematic review and meta-analysis to assess the efficacy and  
35 safety of MMF on current research for its potential use in clinical practice in treating  
36 NMOSD.

## 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 **2. Methods**

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4 This protocol has been registered on PROSPERO (registration number: CRD  
5 42020164179). Our protocol will follow the Meta-analysis of Observational Studies in  
6 Epidemiology (MOOSE),<sup>27</sup> the Cochrane Handbook for Systematic Reviews of  
7 Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-  
8 Analysis Protocol (PRISMA-P) statement guidelines.<sup>28 29</sup>

## 13 **2.1 Inclusion criteria for study selection**

### 15 **2.1.1 Types of studies**

17 All comparative researches, from randomized controlled trials (RCTs) to cohort studies,  
18 and case-control study, covering at least two interventions, will be included. The current  
19 clinical trial results will be objectively integrated, which is conducive to the evaluation  
20 of the efficacy and safety of MMF for NMOSD. We will exclude reviews, qualitative  
21 studies, animal trials, laboratory studies and studies only involving one intervention.

### 27 **2.1.2 Types of patients**

29 Patients diagnosed as having NMOSD will be included in the study.<sup>5 30</sup> There will be  
30 no restrictions based on other conditions, such as age at onset, sex, ethnicity,  
31 educational or economic status, number of relapses prior to treatment, previous  
32 treatment, duration of illness, disease severity, and baseline expanded disability status  
33 scales (EDSS), AQP4-IgG serological status.

### 39 **2.1.3 Types of interventions**

40 Trials comparing MMF to placebo or to any other active drugs will be considered.  
41 Besides, the types, dosage, and frequency of MMF were not limited. Studies that MMF  
42 with combination therapy fail to objectively evaluate the efficacy and safety of MMF  
43 will be excluded. The control interventions will include AZA, tacrolimus, cyclosporine,  
44 and monoclonal antibody drugs, placebo, etc.

### 50 **2.1.4 Types of outcome measures**

#### 52 **2.1.4.1 Primary outcomes**

54 (1) EDSS: Disability progression was defined as an increase of at least 1 point above  
55 the pre-treatment score if baseline score < 5.5, and of at least a half point if baseline  
56 score > 5.5, of the Kurtzke EDSS. Outcome measured was the mean change in the  
57 EDSS from before and after MMF treatment.<sup>31 32</sup>



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4 (2) Annualized relapse rate (ARR): A relapse is defined as neurologic symptoms  
5 lasting for > 24 h, which occur at least 30 days after the onset of a preceding event.  
6 ARR is computed as a function of the number of relapse over the number of days  
7 (years) in observation. Post-treatment ARR were compared to pre-treatment ARR.  
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#### 13 **2.1.4.2 Secondary outcomes**

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15 (1) The frequency and extent of Adverse events (AEs): Any symptomatic events which  
16 had a possible, probable or definite causal relationship with MMF treatment were  
17 defined as AEs during the treatment and follow-up periods.  
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19 (2) Relapse-free rate: the absence of relapse during the observation period of the study  
20 reported as percentage per study.<sup>32</sup>  
21  
22 (3) Best-corrected visual acuity (BCVA): measured according to a validated measure  
23 such as the ETDRS chart, Snellen chart or a similar tool, other measures of visual  
24 acuity would be considered if outcomes could be justified and validated in relation  
25 to accepted relevant standard measures. Outcome measured was the mean change  
26 in the BCVA from before and after MMF treatment.<sup>34</sup>  
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28 (4) Time to the next attack.  
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30 (5) Relapse-free rates.  
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#### 33 **2.1.4.3 Security index**

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35 The safety was assessed by the occurrence of AEs. Any unexpected events that occurred  
36 during the studies will be recorded on an adverse event report form, including:<sup>35</sup>  
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39 (1) General physical examination (temperature, pulse, respiration, blood pressure).  
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41 (2) Routine examination of blood, urine and stool.  
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43 (3) Liver and kidney function examination.  
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45 (4) Gastrointestinal discomfort.  
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47 (5) Hair loss or Alopecia.  
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49 (6) Allergic or Anaphylactoid reactions.  
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51 (7) Drug discontinued due to drug-related AEs.  
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53 (8) Possible AEs and related detection indicators.  
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#### 60 **2.2 Search methods for the identification of studies**

### 2.2.1 Electronic searches

A relevant literature search by sensitive search strategies was conducted using the the following electronic databases from their inception to December 31, 2019: PubMed, Web of Science, EMBASE, the Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang Database, China Science and Technology Journal database (VIP)and CBM. Search methods of MeSH terms with free words were applied in English databases. The related terms are as follows: Participants (neuromyelitis optica, neuromyelitis optica spectrum disorders, Devic Neuromyelitis Optica, Devic's Neuromyelitis Optica, Devic's Syndrome, NMO spectrum disorders), Intervention (mycophenolic acid, mycophenolate mofetil, “mofetil, mycophenolate”, cellcept, myfortic, RS61443). The search strategy for PubMed is listed in Table 1, which including all search terms, and other searches will be conducted based on these results. This will be appropriately adapted for search in the other databases. There are no limits on language and publication status.

### 2.2.2 Searching other resources

we will also search PROSPERO, the International Clinical Trials Registry Platform (ICTRP), ClinicalTrials.gov, dissertations, and gray literature to identify systematic reviews or clinical trials related to mycophenolate mofetil and neuromyelitis optica spectrum disorders. Relevant journals and conference processes will be manual searched. We will also review papers and bibliographies included in the trials.

## 2.3 Data collection and analysis

### 2.3.1 Selection of studies

Two reviewers (MYH and ZQL) will independently browse the titles and abstracts of all of the retrieved records to distinguish and exclude any obviously irrelevant articles. Studies only related to human subjects will be included. Any disagreements will be resolved by discussion between the 2 authors and an arbiter (MJ). The study selection procedure is presented in a PRISMA flow chart (Fig. 1).

### 2.3.2 Data extraction and management

Based on the inclusion criteria, a standard data collection form will be produced prior to data extraction. Search results will be entered into an EndNote X9 database and

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4 duplicate entries removed. Two authors (MYH and ZQL) will extract the data of  
5 interest from the eligible study and enter the following information in the data  
6 extraction sheet: The basic characteristics of each study (study design or methods ,  
7 author, title, source/journal, time of publication, country, hospital setting); participants  
8 characteristics (average age, gender, sample size, inclusion and exclusion criteria,  
9 baseline situation); Interventions (type, duration, frequency and dosage of MMF,  
10 randomization, allocation concealment, blinding methods); Comparators (AZA,  
11 tacrolimus, cyclosporine, monoclonal antibodies, and placebo, etc); Outcomes  
12 (measures, main outcomes, security indexes, and follow up); If funded, it will also be  
13 recorded. When the consensus on data extraction is not available through discussion,  
14 the third reviewer (MJ) will make a decision.

### 25 **2.3.3 Assessment of risk of bias**

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27 Two authors (Yang Chen and LQN) will independently evaluate the risk and bias using  
28 the Cochrane risk of bias (ROB) assessment tool for RCTs.<sup>36</sup> Methodological quality  
29 assessment of the included observational studies will be performed using the  
30 Newcastle–Ottawa Scale (NOS).<sup>37</sup> The RevMan software program (V.5.3) will record  
31 the selected details of each study.<sup>38</sup>

### 32 **2.3.4 Measures of treatment effect**

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34 The risk ratio (RR) and 95% confidence interval (CI) will be used to analyze  
35 dichotomous data and measure the treatment effect. A weighted mean difference  
36 (WMD) or a standard mean difference (SMD) with 95% CIs will be used to analyze  
37 continuous outcomes.

### 38 **2.3.5 Unit of analysis issue**

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40 We will only extract the 1st experimental period data of crossover trials to avoid  
41 carryover effects. Meanwhile, considering that there are multiple intervention groups  
42 in trials, we will combine all analogous groups into a single pairwise comparison to  
43 prevent a unit of analysis issue.

### 44 **2.3.6 Management of missing data**

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46 Reviewer (YLQ) will contact the appropriate author of the included trials for  
47 clarification or more details via email and telephone if necessary. The missing data will  
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4 be deleted, if there is no response from the author. In this case, this will be addressed  
5 in the discussion. Qualitative analysis would be used if relevant data was not available.

### 7 **2.3.7 Assessment of heterogeneity and data synthesis**

9 We will use the complete case data as the analysis data. Heterogeneity will be tested  
10 with a standard Chisquare test.<sup>39</sup> In order to quantify the impact of the statistical  
11 heterogeneity on the systematic review, the  $I^2$  value will be applied to calculate and  
12 present the heterogeneity degree. When  $P > 0.1$ ,  $I^2 < 50\%$ , it is considered that there is no  
13 heterogeneity between the trials, and the fixed effect model will be used, otherwise, the  
14 random effect model will be adopted. All statistical analyses will be performed using  
15 RevMan5.3 software provided by the Cochrane Collaboration. Using the software to  
16 obtain forest plots and test the heterogeneity between the included studies. The Grades  
17 of Recommendation, Assessment, Development and Evaluation (GRADE) will be use  
18 to assess the meta-analysis findings and determine the quality of evidence. Narrative  
19 comprehensive synthesis will be adopted, if meta-analysis is not possible due to lack of  
20 clinical studies or heterogeneity.  
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### 33 **2.3.8 Assessment of reporting biases**

34 When 10 or more studies are included in a meta-analysis, we will assess funnel plot  
35 asymmetry for reporting biases and small study effects using Egger's method.<sup>40</sup> For  
36 Egger's test, P value of greater than 0.05 was determined as no considerable publication  
37 bias or small-study effects in studies. As funnel plot asymmetry does not necessarily  
38 suggest reporting bias, we will try to distinguish possible reasons for the asymmetry,  
39 including poor methodological quality and true heterogeneity of studies.  
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### 47 **2.3.9 Subgroup analysis**

48 When heterogeneity is detected, a subgroup analysis will be conducted to judge the  
49 source of heterogeneity. The criteria for a subgroup analysis are as follows:  
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- 51 (1) Age.
- 52 (2) Type of MMF.
- 53 (3) Research type.
- 54 (4) Participation population.
- 55 (5) Type of control interventions.
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4 (6) Intervention dosage, frequency and duration.

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6 (7) AQP4-IgG serological status.

### 7 8 **2.3.10 Sensitivity analysis**

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10 In the case of sufficient trials data, the ROB tool will be used to assess methodological  
11 quality. Sensitivity analysis will be performed to assess the robustness of aggregate  
12 estimates and to detect whether any single study accounts for a significant proportion  
13 of heterogeneity by removing the included studies one by one from the summary  
14 analysis. If low-quality articles are deleted, a second meta-analysis will be performed.  
15 The results and effect size of the two meta-analyses will be compared and discussed.<sup>41</sup>

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21 **2.4 Patient and public involvement** Patients and/or the public will not participate in  
22 the study. However, once our findings are disseminated by scientific publications, they  
23 are shared through social networks, so that our conclusions can influence the behavior  
24 of neuro-ophthalmologist and health policy makers.

## 25 26 27 28 **3 Discussion**

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31 NMOSD is an inflammatory and heterogeneous astrocyte disorder of the CNS with the  
32 characteristic of higher incidence in women and Asian, concerned because of its high  
33 pathogenicity, high risk of recurrence and poor prognosis.<sup>1</sup> Most patients with NMOSD  
34 have a course of recurrence and remission, which are prone to cause paralysis and  
35 blindness,<sup>5</sup> bringing heavy burdens on the life, work and study of patients, as well as  
36 the society and economy of various countries. At present, the treatment of NMOSD is  
37 divided into two stages: acute phase (IVCSs, PLEX, and immunoglobulin) and  
38 remission phase (MMF, AZA, tacrolimus, cyclosporine, monoclonal antibodies, etc.).<sup>15</sup>  
39 AEs associated with AZA were seemingly frequent and may contribute to patient  
40 nonadherence to prescribed medication.<sup>16 17</sup> In recent years, rituximab has been  
41 recommended to prevent recurrence of NMOSD, but there have also been reports of  
42 infusion reactions, infection, and even death,<sup>18-20</sup> and its clinical application has been  
43 limited by factors such as high price.<sup>18 21</sup> Therefore, we urgently need to find new  
44 immunoregulatory drugs for the treatment of NMOSD.

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A number of studies have confirmed the efficacy and promising prospect of MMF in  
the treatment of NMOSD,<sup>21-24</sup> and only a few adverse events (AEs) have been reported.

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4 21 22 Further studies also suggested that MMF was more effective and caused fewer AEs  
5 than AZA. 25 26 However, there are controversial about its therapeutic effect and safety.  
6  
7 The primary objective of this systematic review is to evaluate the clinical efficacy and  
8 safety of MMF in the treatment of NMO. We will conduct qualitative and quantitative  
9 analysis of the overall data included in each study. The presented evidences were  
10 collected from RCTs and observational studies with different evidence strengths to  
11 provide more comprehensive analysis. Therefore, the heterogeneity of the methodology  
12 will be a major limitation in this systematic review, which may lead to some results not  
13 being analyzed. We expect that this systematic review will benefit patients with  
14 NMOSD, clinicians, healthcare managers and policy-makers.  
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#### 25 **Author contributions**

26 MYH conceived and designed the protocol, and MYH drafted the protocol manuscript.  
27 MYH developed the search strategy, with input from ZQL and LQN. MYH and ZQL  
28 planned the data extraction. MYH, Yang Chen and ZJW planned the quality appraisal  
29 of all included studies. MYH, ZQL, LQN, Yang Chen, HM, YC, ZJW, YLQ and MJ  
30 critically revised the manuscript for methodological and intellectual content. All  
31 authors approved the final version.  
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37 **Conceptualization:** Meng-Yu Han, Zi-Qiang Liu, Zhi-Jun Wang, Ming Jin.

38 **Data curation:** Meng-Yu Han, Zi-Qiang Liu, Lu-Qi Nong, Huan Meng.

39 **Formal analysis:** Meng-Yu Han, Zi-Qiang Liu.

40 **Funding acquisition:** Meng-Yu Han.

41 **Investigation:** Ming Jin.

42 **Methodology:** Meng-Yu Han, Zi-Qiang Liu, Lu-Qi Nong, You Chen.

43 **Project administration:** Ming Jin.

44 **Resources:** Meng-Yu Han, Zi-Qiang Liu, Lu-Qi Nong, Ming Jin.

45 **Software:** Meng-Yu Han, Zi-Qiang Liu, Lu-Qi Nong.

46 **Supervision:** Meng-Yu Han, Zhi-Jun Wang, Ming Jin.

47 **Validation:** Huan Meng, Yang Chen, Ya-li Qin, Ming Jin.

48 **Visualization:** Huan Meng, Yang Chen, Ya-li Qin, Ming Jin.

49 **Writing – original draft:** Meng-Yu Han, Zi-Qiang Liu, Lu-Qi Nong, Ming Jin.  
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4 **Writing – review & editing:** Meng-Yu Han, Zi-Qiang Liu, Lu-Qi Nong, Ming Jin.  
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## SUPPLEMENTARY MATERIAL

Table 1 Search strategy used in PubMed database.

Number	Search terms
#1	("Neuromyelitis Optica"[Mesh]) OR (((((neuromyelitis optica spectrum disorders [Title/Abstract]) OR Devic Neuromyelitis Optica [Title/Abstract]) OR Devic's Neuromyelitis Optica [Title/Abstract]) OR Devic's Syndrome [Title/Abstract]) OR NMO spectrum disorders [Title/Abstract])
#2	("Mycophenolic Acid"[Mesh]) OR (((((Mycophenolate Mofetil [Title/Abstract]) OR "Mofetil,Mycophenolate" [Title/Abstract]) OR

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4	Cellcept [Title/Abstract]) OR Myfortic [Title/Abstract]) OR RS61443
5	[Title/Abstract])
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7	#3
8	((("Randomized Controlled Trial" [Publication Type]) OR
9	RCT[Title/Abstract])) OR (("Cohort Studies"[Mesh]) OR ((cohort
10	study[Title/Abstract]) OR "studies, cohort"[Title/Abstract]))) OR
11	(((Case-Referrent Studies[Title/Abstract]) OR Case-Base
12	Studies[Title/Abstract])) OR (("Case-Control Studies"[Mesh]) OR
13	Case-Comparison Studies[Title/Abstract]))
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19	#4
20	#1 and #2 and #3

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Figure1. The PRISMA flow chart of the selection process.

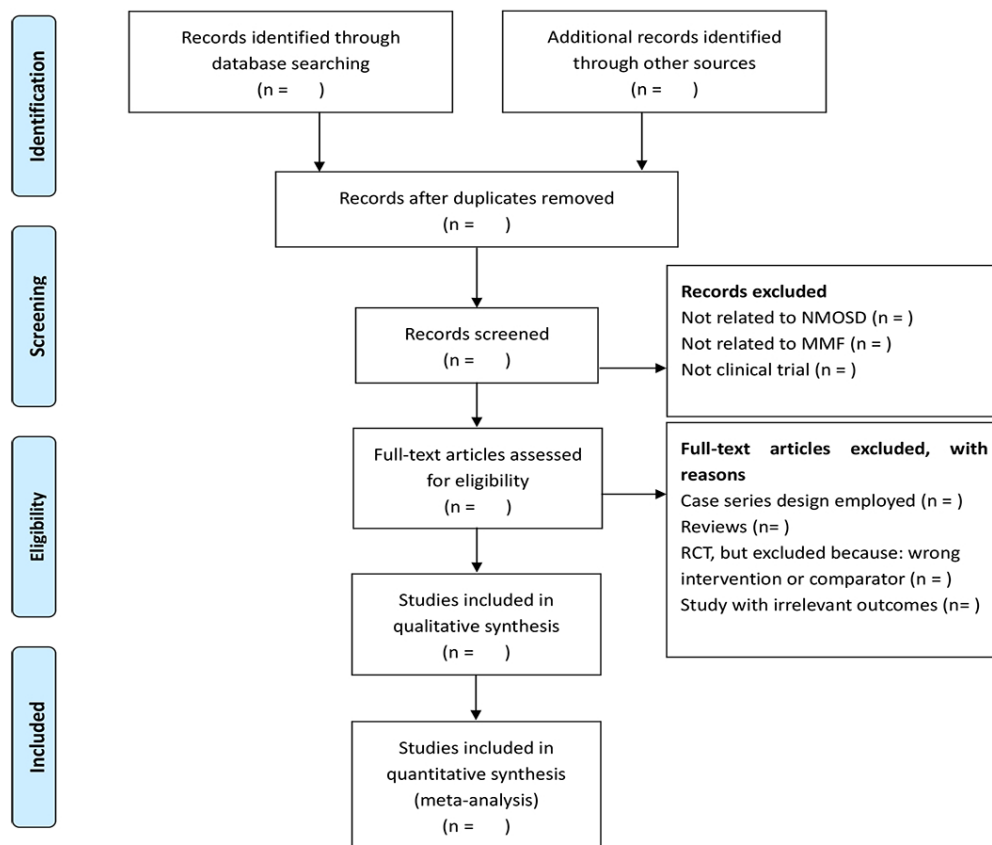


Figure1. The PRISMA flow chart of the selection process.

# Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

			Page
			Number
Title	Reporting Item		
Identification	<a href="#">#1a</a>	Identify the report as a protocol of a systematic review	Page 1
Update	<a href="#">#1b</a>	If the protocol is for an update of a previous systematic review, identify as such	

## 1 Registration

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4 [#2](#) If registered, provide the name of the registry (such as Page 2  
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6 PROSPERO) and registration number  
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## 9 Authors

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13 Contact [#3a](#) Provide name, institutional affiliation, e-mail address of all Page 1  
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15 protocol authors; provide physical mailing address of  
16  
17 corresponding author  
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20 Contribution [#3b](#) Describe contributions of protocol authors and identify the Page1,11,12  
21  
22 guarantor of the review  
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## 25 Amendments

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29 [#4](#) If the protocol represents an amendment of a previously  
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31 completed or published protocol, identify as such and list  
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33 changes; otherwise, state plan for documenting important  
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35 protocol amendments  
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## 38 Support

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42 Sources [#5a](#) Indicate sources of financial or other support for the review Page 1  
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45 Sponsor [#5b](#) Provide name for the review funder and / or sponsor Page 1  
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48 Role of sponsor or [#5c](#) Describe roles of funder(s), sponsor(s), and / or Page 1  
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50 funder institution(s), if any, in developing the protocol  
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## 53 Introduction

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56 Rationale [#6](#) Describe the rationale for the review in the context of what Page 2,3,4  
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1		is already known	
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4	Objectives	<a href="#">#7</a> Provide an explicit statement of the question(s) the review	Page 5,6
5		will address with reference to participants, interventions,	
6		comparators, and outcomes (PICO)	
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11	<b>Methods</b>		
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14	Eligibility criteria	<a href="#">#8</a> Specify the study characteristics (such as PICO, study	Page 7,8
15		design, setting, time frame) and report characteristics	
16		(such as years considered, language, publication status) to	
17		be used as criteria for eligibility for the review	
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24	Information	<a href="#">#9</a> Describe all intended information sources (such as	Page 7,8
25		electronic databases, contact with study authors, trial	
26	sources	registers or other grey literature sources) with planned	
27		dates of coverage	
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34	Search strategy	<a href="#">#10</a> Present draft of search strategy to be used for at least one	Page 7
35		electronic database, including planned limits, such that it	
36		could be repeated	
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42	Study records -	<a href="#">#11a</a> Describe the mechanism(s) that will be used to manage	Page7,8
43	data management	records and data throughout the review	
44			
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47	Study records -	<a href="#">#11b</a> State the process that will be used for selecting studies	Page 7,8
48		(such as two independent reviewers) through each phase	
49	selection process	of the review (that is, screening, eligibility and inclusion in	
50		meta-analysis)	
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57	Study records -	<a href="#">#11c</a> Describe planned method of extracting data from reports	Page 7,8,9
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1	data collection		(such as piloting forms, done independently, in duplicate),	
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3	process		any processes for obtaining and confirming data from	
4				
5			investigators	
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8	Data items	<a href="#">#12</a>	List and define all variables for which data will be sought	Page 8
9				
10			(such as PICO items, funding sources), any pre-planned	
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12			data assumptions and simplifications	
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15	Outcomes and	<a href="#">#13</a>	List and define all outcomes for which data will be sought,	Page5,6
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17	prioritization		including prioritization of main and additional outcomes,	
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19			with rationale	
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23	Risk of bias in	<a href="#">#14</a>	Describe anticipated methods for assessing risk of bias of	Page 8
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25	individual studies		individual studies, including whether this will be done at	
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27			the outcome or study level, or both; state how this	
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29			information will be used in data synthesis	
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33	Data synthesis	<a href="#">#15a</a>	Describe criteria under which study data will be	Page 9
34				
35			quantitatively synthesised	
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38	Data synthesis	<a href="#">#15b</a>	If data are appropriate for quantitative synthesis, describe	Page 9
39				
40			planned summary measures, methods of handling data	
41				
42			and methods of combining data from studies, including any	
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44			planned exploration of consistency (such as I <sup>2</sup> , Kendall's	
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50	Data synthesis	<a href="#">#15c</a>	Describe any proposed additional analyses (such as	Page 9,10
51				
52			sensitivity or subgroup analyses, meta-regression)	
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56	Data synthesis	<a href="#">#15d</a>	If quantitative synthesis is not appropriate, describe the	Page 9
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1 type of summary planned

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4 Meta-bias(es) [#16](#) Specify any planned assessment of meta-bias(es) (such Page 8,9  
5 as publication bias across studies, selective reporting  
6 within studies)  
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11 Confidence in [#17](#) Describe how the strength of the body of evidence will be Page 9  
12 cumulative assessed (such as GRADE)  
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15 evidence

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18 None The PRISMA-P checklist is distributed under the terms of the Creative Commons Attribution

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21 made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)  
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# BMJ Open

## Safety and Efficacy of Mycophenolate Mofetil in Treating NMOSD : a protocol for systematic review and meta-analysis.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-040371.R1
Article Type:	Protocol
Date Submitted by the Author:	14-Jul-2020
Complete List of Authors:	han, mengyu; Beijing University of Chinese Medicine; China-Japan Friendship Hospital, Ophthalmology Nong, Luqi; Beijing University of Chinese Medicine, Graduate School ; China-Japan Friendship Hospital, Ophthalmology Liu, Ziqiang; Beijing University of Chinese Medicine, Graduate School ; China-Japan Friendship Hospital, Ophthalmology Chen, You; China-Japan Friendship Hospital Chen, Yang; Beijing University of Chinese Medicine Meng, Huan; Beijing University of Chinese Medicine, Graduate School; China-Japan Friendship Hospital, Ophthalmology Qin, Yali; Sun Yat-Sen University Zhongshan Ophthalmic Center Wang, Zhijun; China-Japan Friendship Hospital, ophthalmology department Jin, Ming; China-Japan Friendship Hospital, Ophthalmology
<b>Primary Subject Heading</b>:	Ophthalmology
Secondary Subject Heading:	Neurology, Evidence based practice
Keywords:	OPHTHALMOLOGY, NEUROLOGY, IMMUNOLOGY, Neuro-ophthalmology < NEUROLOGY

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4 Safety and Efficacy of Mycophenolate Mofetil in Treating NMOSD : a protocol  
5 for systematic review and meta-analysis.

6 Mengyu Han, PhD<sup>a,b</sup>, Luqi Nong, MD<sup>a,b</sup>, Ziqiang Liu, MD<sup>a,b</sup>, You Chen<sup>b</sup>, Yang  
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8 Jin MD<sup>b\*</sup>

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## 22 23 24 25 **Abstract**

26  
27 **Introduction** Neuromyelitis optica spectrum disorders (NMOSD) is an inflammatory  
28 and heterogeneous astrocyte disorder of the central nervous system (CNS) with the  
29 characteristic of higher incidence in women and Asian. Most patients with NMOSD  
30 have a course of recurrence and remission that is prone to cause paralysis and blindness.  
31 Several studies have confirmed the efficacy and promising prospect of mycophenolate  
32 mofetil (MMF) in the treatment of NMOSD. Yet its therapeutic effect and safety are  
33 controversial. This research aims to perform a systematic review and meta-analysis to  
34 evaluate MMF's effectiveness and safety in treating NMOSD.

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42 **Methods and analysis** This systematic review will cover all comparative researches,  
43 from randomized controlled trials (RCTs) to cohort studies, and case-control study. A  
44 relevant literature search will be conducted in PubMed, Web of Science, EMBASE, the  
45 Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang  
46 Database, China Science and Technology Journal database (VIP) and Chinese  
47 Biomedical Literature database (CBM). We will also search registers of clinical trials,  
48 potential gray literature, and abstracts from conferences. There are no limits on  
49 language and publication status. The reporting quality and risk of bias will be assessed  
50 by two researchers independently. Expanded disability status scales (EDSS),  
51 annualized relapse rate (ARR) will be evaluated as the primary outcome. The secondary  
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4 outcomes will consist of the frequency and severity of adverse events (AEs), best-  
5 corrected visual acuity (BCVA), relapse-free rate and time to the next attack. A meta-  
6 analysis will be performed using RevMan5.3 software provided by the Cochrane  
7 Collaboration and Stata 12.0.  
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11 **Ethics and dissemination** Because the data used for this systematic review will be  
12 exclusively extracted from published studies, ethical approval and informed consent of  
13 patients will not be required. The systematic review will be published in a peer-  
14 reviewed journal, presented at conferences and will be shared on social media platforms.  
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17 **PROSPERO registration number:** PROSPERO CRD42020164179.  
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21 **Strengths and limitations of this study:**  
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23 ▶ This study will carry out an exhaustive literature search to identify studies aimed at  
24 evaluating the efficacy and safety of MMF in treating NMOSD.  
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26 ▶ One limitation of this study is that differences in patients, interventions and primary  
27 outcomes may mean that meta-analysis cannot be performed and there are plans for  
28 narrative and meta-analytical syntheses.  
29

30 ▶ Although we will include studies published in any language, translation difficulties  
31 may arise, which will result in the exclusion of these studies.  
32

33 ▶ The analysis of various sources of heterogeneity and the assessment of risk of bias  
34 of the included studies is a critical point for extracting and synthesizing evidence-based  
35 conclusions.  
36

37  
38 **Keywords:** mycophenolate mofetil, neuromyelitis optica spectrum disorders, protocol,  
39 systematic review, meta-analysis.  
40

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42 **1. Introduction**  
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44 Neuromyelitis Optica (NMO), also known as Devic disease, is generally considered to  
45 be a rare autoimmune astrocyte disorder of the central nervous system (CNS), induced  
46 by autoantibodies, dominated by humoral immunity and involving numerous immune  
47 cells and factors, with optic neuritis(ON) and acute transverse myelitis as typical  
48 clinical manifestations.<sup>1</sup> NMO has been known as a subtype of multiple sclerosis (MS)  
49 for over 100 years since it was first described and reported.<sup>2</sup> Until 2004, the discovery  
50 and confirmation of anti-aquaporin-4 immunoglobulin G (AQP4-IgG) had made  
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4 substantial progress in pathogenesis, diagnosis, and treatment of NMO.<sup>3 4</sup> The notion  
5 of neuromyelitis optica spectrum disorders (NMOSD) was first proposed based on the  
6 wide clinical use of specific AQP4-IgG,<sup>4</sup> which mainly referred to the minimal AQP4-  
7 IgG positive NMO. However, the deficiencies of the diagnostic criteria of NMO in  
8 2006 and NMOSD in 2007 became prominent with the incremental improvement of the  
9 specificity of clinical AQP4-IgG tests. In 2015, a groundbreaking international  
10 diagnostic protocol for NMOSD was put forward by the global NMO diagnostic team.<sup>5</sup>  
11 NMOSD consists of NMO, ON, longitudinally extensive transverse myelitis and other  
12 common cerebral demyelinating syndromes.<sup>5</sup> There are so far no reliable statistics on  
13 the worldwide incidence and prevalence of NMOSD. According to the current  
14 epidemiological evidence of small samples, the high incidence of this disease is among  
15 middle-aged and young women, with the onset age varying from 32 to 41 years old,  
16 and the incidence in females is about 10 times that of males.<sup>5</sup> The incidence and  
17 prevalence of approximately 0.05-0.40 and 0.52-4.40/100,000 vary from region to  
18 region.<sup>6</sup> A populous region of Asia is the region with a high incidence of NMOSD.<sup>7-9</sup>  
19 Most NMOSD patients have a recurrence and remission including ON, myelitis, and  
20 lesions in special parts of the brain that are vulnerable to cause paralysis and blindness.<sup>5</sup>  
21 NMOSD has become one of the most common causes of non-traumatic disability and  
22 blindness in young and middle-aged individuals, putting heavy burdens on the life,  
23 work and study, as well as the society and economy of various countries.<sup>10</sup> Clinical  
24 studies indicate that approximately 1/4 of patients will not be able to walk  
25 independently after an average of 5 years of NMO, approximately 10% will be  
26 wheelchair-dependent, and more than half of patients will have serious vision loss in at  
27 least one eye.<sup>11</sup> In particular, ON associated with NMO (NMO-ON) possesses poor  
28 recovery even after traditional therapy, which often progresses into significant bilateral  
29 visual loss in the long term, leaving behind varying degrees of optic atrophy, which is  
30 different from MS.<sup>12 13</sup>

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Currently, there are no standardized guidelines for the clinical management of NMOSD.  
The class of NMOSD drugs is commonly referred to as disease-modifying drugs,<sup>14</sup> and  
the treatment is split into two stages: the acute phase and the period of remission. The

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4 former is based on corticosteroids to reduce the severity and frequency of acute attacks  
5 that include intravenous corticosteroids (IVCSs), plasma exchange (PLEX), and  
6 immunoglobulin. Immunosuppressive agents, including mycophenolate mofetil  
7 (MMF), azathioprine (AZA), cyclophosphamide, methotrexate, mitoxantrone,  
8 tacrolimus, cyclosporine, and monoclonal antibodies, are frequently used during the  
9 process of recovery to avoid recurrence and to mitigate the progression of neurological  
10 impairment.<sup>15 16</sup> Although AZA and rituximab are recommended as first-line therapies  
11 obtained from clinical trials and expert opinion from the published guidelines for  
12 NMOSD,<sup>16</sup> there are still adverse events (AEs) such as disease recurrence and  
13 myelosuppression that result in drug withdrawal or replacement of patients with  
14 NMOSD.<sup>17</sup> Rituximab has also been reported in recent years as infusion reactions,  
15 infection, and even death,<sup>18-20</sup> and its clinical application has been constrained by such  
16 factors as high price.<sup>18 21</sup> Therefore, a better immunosuppressant for the treatment of  
17 NMOSD is urgently needed. The application of MMF in NMOSD is still under  
18 investigation and is recommended as second-line treatments,<sup>16</sup> but some studies have  
19 verified MMF's efficacy and promising potential,<sup>21-24</sup> and only a few AEs were  
20 published.<sup>21 22</sup> Especially, additional studies have also indicated that MMF was more  
21 effective and triggered less AEs than AZA.<sup>25 26</sup> In patients experiencing AEs or poor  
22 response to AZA, MMF is recommended as an alternative therapy.<sup>16</sup>

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24 Although MMF is increasingly employed in NMOSD, there is still controversy about  
25 its related harms and benefits. At present, only low evidence exists concerning  
26 comparative treatment efficacy of MMF with other drugs. Based on current clinical  
27 trials, it is therefore timely to perform a systematic review and meta-analysis to  
28 elucidate the efficacy and safety of MMF in treating NMOSD.

## 2. Methods

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30 This protocol has been registered on PROSPERO (registration number: CRD  
31 42020164179). Our protocol will follow the Meta-analysis of Observational Studies in  
32 Epidemiology (MOOSE),<sup>27</sup> the Cochrane Handbook for Systematic Reviews of  
33 Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-  
34 Analysis Protocol (PRISMA-P) statement guidelines.<sup>28 29</sup>

## 2.1 Inclusion criteria for study selection

### 2.1.1 Types of studies

All comparative researches, from randomized controlled trials (RCTs) to cohort studies, and case-control study, covering at least two interventions, will be included. The current clinical trial results will be objectively integrated, which is conducive to the evaluation of the efficacy and safety of MMF for NMOSD. We will exclude reviews, qualitative studies, animal trials, laboratory studies and studies only involving one intervention.

### 2.1.2 Types of patients

Patients diagnosed as having NMOSD will be included in this study.<sup>5 30</sup> There will be no restrictions based on other conditions, such as age at onset, sex, ethnicity, educational or economic status, number of pre-treatment relapses, previous treatment, duration of illness, disease severity, and baseline expanded disability status scales (EDSS), AQP4-IgG serological status.

### 2.1.3 Types of interventions

Trials comparing MMF to placebo or any other active substances, including AZA, cyclophosphamide, methotrexate, mitoxantrone, tacrolimus, cyclosporine, and monoclonal antibodies, will be considered. Besides, the types, dosage, and frequency of MMF were not limited. Studies that MMF with combination therapy fail to objectively evaluate the efficacy and safety of MMF will be eliminated.

### 2.1.4 Types of outcome measures

#### 2.1.4.1 Primary outcomes

- (1) EDSS: Disability progression was characterized as an increase in the Kurtzke EDSS by at least 1 point above the pre-treatment score if baseline score < 5.5, and by at least half-point if baseline score > 5.5. Outcome measured was the mean changes of EDSS before and after MMF treatment.<sup>31 32</sup>
- (2) Annualized relapse rate (ARR): Relapse is equivalent to a neurologic symptom lasting for > 24 h, which occurs at least 30 days after the onset of a preceding event. ARR is computed as the number of relapses divided by the time in years (days). Post-treatment ARR was contrasted with pre-treatment ARR.<sup>33</sup>

#### 2.1.4.2 Secondary outcomes



- (1) The frequency and extent of AEs: During treatment and follow-up periods, any symptomatic events which had a possible, probable or definite causal relationship to MMF treatment were defined as AEs.
- (2) Relapse-free rate: The absence of relapse during the observation period of the study reported as percentage per study.<sup>32</sup>
- (3) Best-corrected visual acuity (BCVA): BCVA was measured using a standardized test, such as the ETDRS chart, Snellen chart or similar method, and other visual acuity measures would be allowed if findings could be justified as well as validated concerning accepted relevant standard measures. Outcome measured was the mean change of BCVA from before and after MMF treatment.<sup>34</sup>
- (4) Time to the next attack.

#### ***2.1.4.3 Security index***

The safety was assessed by the occurrence of AEs. Any unexpected events that occurred during the studies will be recorded on an AEs report form, including:<sup>35</sup>

- (1) General physical examination (temperature, pulse, respiration, blood pressure).
- (2) Routine examination of blood, urine and stool.
- (3) Liver and kidney function examination.
- (4) Gastrointestinal discomfort.
- (5) Hair loss or Alopecia.
- (6) Allergic or Anaphylactoid reactions.
- (7) Drug discontinued due to drug-related AEs.
- (8) Possible AEs and related detection indicators.

## **2.2 Search methods for the identification of studies**

### **2.2.1 Electronic searches**

A relevant literature search by sensitive search strategies was conducted using the following electronic databases from their inception to June 31, 2020: PubMed, Web of Science, EMBASE, the Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang Database, China Science and Technology Journal database (VIP) and Chinese Biomedical Literature database (CBM). Search methods of MeSH terms with free words were applied in English databases. The related terms are as follows:

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4 Participants (neuromyelitis optica, neuromyelitis optica spectrum disorders, Devic  
5 Neuromyelitis Optica, Devic's Neuromyelitis Optica, Devic's Syndrome, NMO  
6 spectrum disorders), Intervention (mycophenolic acid, mycophenolate mofetil, “mofetil,  
7 mycophenolate”, cellcept, myfortic, RS61443). The search strategy for PubMed is  
8 described in Table 1, which will include all search terms, and other searches will be  
9 carried out based on those results. This will be suitably adapted to search in the other  
10 databases. There are no limits on language and publication status.

### 17 **2.2.2 Searching other resources**

18 we will also search PROSPERO, the International Clinical Trials Registry Platform  
19 (ICTRP), ClinicalTrials.gov, dissertations, and gray literature to identify systematic  
20 reviews or clinical trials related to mycophenolate mofetil and neuromyelitis optica  
21 spectrum disorders. Manual searches will be conducted for related journals and  
22 conference processes. We will also review papers and bibliographies included in the  
23 trials.

## 31 **2.3 Data collection and analysis**

### 33 **2.3.1 Selection of studies**

34 Two reviewers (MYH and ZQL) will independently browse the titles and abstracts of  
35 all of the retrieved records to distinguish and exclude any irrelevant articles. Studies  
36 only related to human subjects are to be included. Any discord will be resolved by  
37 discussion between the two authors and an arbiter (MJ). The selection procedure for the  
38 study is shown in a PRISMA flow chart (Fig. 1).

### 45 **2.3.2 Data extraction and management**

46 Based on the inclusion criteria, a standard form of data collection will be produced prior  
47 to data extraction. Search results will be entered into an EndNote X9 database and  
48 duplicate entries removed. Two authors (MYH and ZQL) will extract the data of  
49 interest from the eligible study and enter the data extraction sheet as follows: The basic  
50 characteristics of each study (study design or methods, author, title, source/journal, time  
51 of publication, country, hospital setting); participants characteristics (average age,  
52 gender, sample size, inclusion and exclusion criteria, baseline situation); Interventions  
53 (type, duration, frequency and dosage of MMF, randomization, allocation concealment,  
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4 blinding methods); Comparators (AZA, tacrolimus, cyclosporine, monoclonal  
5 antibodies, and placebo, etc); Outcomes (measures, main outcomes, security indexes,  
6 and follow up); If funded, it will also be recorded. When the consensus on data  
7 extraction is not available through discussion, the third reviewer (MJ) will make a  
8 decision.  
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### 13 **2.3.3 Assessment of risk of bias**

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15 Two authors (Yang Chen and LQN) will independently estimate the risk and bias using  
16 the Cochrane risk of bias (ROB) assessment tool for RCTs.<sup>36</sup> Methodological quality  
17 evaluation of the included observational studies will be carried out using the  
18 Newcastle–Ottawa Scale (NOS).<sup>37</sup> The RevMan software program (V.5.3) will  
19 document the selected details of each study.<sup>38</sup>  
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### 25 **2.3.4 Measures of treatment effect**

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27 The risk ratio (RR) and 95% confidence interval (CI) will be used to analyze  
28 dichotomous data and calculate the treatment effect. A weighted mean difference  
29 (WMD) or a standard mean difference (SMD) with 95% CIs will be used to analyze  
30 continuous outcomes.  
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### 35 **2.3.5 Unit of analysis issue**

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37 We will only extract the 1st experimental period data of crossover trials to avoid  
38 carryover effects. In the meantime, given that there are multiple intervention groups in  
39 trials, we will combine all analogous groups into a single pairwise comparison to avoid  
40 the issue of a unit of analysis.  
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### 45 **2.3.6 Management of missing data**

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47 Reviewer (YLQ and You Chen) will contact the appropriate author of the included trials  
48 for clarification or more details via email and telephone if necessary. The missing data  
49 will be deleted, if there is no response from the author. That will be addressed in the  
50 discussion in this case. If quantitative data were not available, then the qualitative  
51 analysis should be used.  
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### 56 **2.3.7 Assessment of heterogeneity and data synthesis**

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58 We will use all of the case data for the analysis data. Heterogeneity will be tested with  
59 a standard Chisquare test.<sup>39</sup> To quantify the impact of the statistical heterogeneity on  
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4 the systematic review, the  $I^2$  value will be applied to calculate and present the  
5 heterogeneity degree. If  $P > 0.1$ ,  $I^2 < 50\%$ , it is considered that there is no heterogeneity  
6 between the trials, and the model of fixed effect will be used, otherwise, the model of  
7 random effect will be adopted. All statistical analyzes will be performed using the  
8 RevMan5.3 software provided by the Cochrane Collaboration. Using the software to  
9 obtain forest plots and test the heterogeneity between the included studies. The Grades  
10 of Recommendation, Assessment, Development and Evaluation (GRADE) will be used  
11 to assess the meta-analysis findings and determine the quality of evidence. Where meta-  
12 analysis is not feasible due to lack of clinical trials or heterogeneity, systematic  
13 narrative synthesis is adopted.

### 23 **2.3.8 Assessment of reporting biases**

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25 When 10 or more studies are included in a meta-analysis, we will evaluate funnel plot  
26 asymmetry for reporting biases and small-study effects using Egger's method.<sup>40</sup> For  
27 Egger's test, P value of greater than 0.05 was determined as no significant publishing  
28 bias or small-study effects in studies. As funnel plot asymmetry does not necessarily  
29 suggest reporting bias, we will attempt to recognize potential causes for the asymmetry,  
30 including poor methodological quality and true heterogeneity of studies.

### 37 **2.3.9 Subgroup analysis**

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39 Upon detection of heterogeneity, a subgroup analysis will be carried out to judge the  
40 source of heterogeneity. The criteria for a subgroup analysis are as follows:

- 42 (1) Age.
- 44 (2) Type of MMF.
- 46 (3) Research type.
- 48 (4) Participation population.
- 50 (5) Type of control interventions.
- 52 (6) Intervention dosage, frequency and duration.
- 54 (7) AQP4-IgG serological status.

### 56 **2.3.10 Sensitivity analysis**

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58 The ROB tool will be used to estimate methodological quality in the case of sufficient  
59 data from trials. Sensitivity analysis will be performed to determine the robustness of  
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4 aggregate estimates and to detect whether any single study accounts for a substantial  
5 proportion of heterogeneity by eliminating the included studies from the summary  
6 review one by one. If low-quality articles are deleted, then a second meta-analysis will  
7 be carried out. Comparison and discussion of the results and effect size of the two meta-  
8 analyses will be held. <sup>41</sup>

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13 **2.4 Patient and public involvement** Patients and/or the public will not participate in  
14 the study. However, once scientific publications disseminate our findings, they are  
15 circulated across social networks so that our conclusions will affect the actions of  
16 neuro-ophthalmologists and health policymakers.

### 21 **3 Discussion**

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23 Pathogenesis, diagnosis and treatment of NMO are rapidly growing areas of research  
24 as AQP4-IgG were first identified. Patients with NMOSD should receive standardized  
25 and personalized immunotherapy as soon as possible, as any further acute episodes may  
26 result in severe and often irreversible disability. The challenges in discovering new and  
27 better drugs for NMO are the rareness of the disease and the unfavorable prognosis in  
28 many cases, which make clinical studies with placebo groups difficult.<sup>16</sup> Many studies  
29 have confirmed the efficacy and promising prospect of MMF in the treatment of  
30 NMOSD,<sup>21-24</sup> and only a few AEs were reported.<sup>21 22</sup> Additional studies have also  
31 indicated that MMF was more effective and triggered less AEs than AZA.<sup>25 26</sup> However,  
32 its therapeutic effect and safety remain controversial. The primary aim of this  
33 systematic review is to determine MMF's clinical effectiveness and safety in treating  
34 NMOSD. The overall data used in each analysis will be evaluated qualitatively and  
35 quantitatively. To provide a more detailed review, the evidence provided was obtained  
36 from RCTs and observational studies with different evidence strengths. Hence, the  
37 methodology's variability would be a significant weakness of this systematic analysis,  
38 which may result in certain results not being evaluated. We expect that this systematic  
39 review will benefit patients with NMOSD, physicians, health care administrators and  
40 policy-makers.

### 56 **Author contributions**

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3 MYH conceived and designed the protocol, and MYH drafted the protocol manuscript.  
4 MYH developed the search strategy, with input from ZQL and LQN. MYH and ZQL  
5 planned data extraction. MYH, Yang Chen and ZJW planned the quality appraisal of  
6 all included studies. MYH, ZQL, LQN, Yang Chen, HM, You Chen, ZJW, YLQ and  
7 MJ critically revised the manuscript for methodological and intellectual content. All  
8 authors approved the final version.  
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13 **Conceptualization:** Meng-Yu Han, Zi-Qiang Liu, Zhi-Jun Wang, Ming Jin.

14 **Data curation:** Meng-Yu Han, Zi-Qiang Liu, Lu-Qi Nong, Huan Meng.

15 **Formal analysis:** Meng-Yu Han, Zi-Qiang Liu.

16 **Funding acquisition:** Meng-Yu Han.

17 **Investigation:** Ming Jin.

18 **Methodology:** Meng-Yu Han, Zi-Qiang Liu, Lu-Qi Nong, You Chen.

19 **Project administration:** Ming Jin.

20 **Resources:** Meng-Yu Han, Zi-Qiang Liu, Lu-Qi Nong, Ming Jin.

21 **Software:** Meng-Yu Han, Zi-Qiang Liu, Lu-Qi Nong.

22 **Supervision:** Meng-Yu Han, Zhi-Jun Wang, Ming Jin.

23 **Validation:** Huan Meng, Yang Chen, Ya-li Qin, Ming Jin.

24 **Visualization:** Huan Meng, Yang Chen, Ya-li Qin, Ming Jin.

25 **Writing – original draft:** Meng-Yu Han, Zi-Qiang Liu, Lu-Qi Nong, Ming Jin.

26 **Writing – review & editing:** Meng-Yu Han, Zi-Qiang Liu, Lu-Qi Nong, Ming Jin.

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33 **Competing interests:** None declared.  
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Table 1 Search strategy used in PubMed database.

Number	Search terms
#1	("Neuromyelitis Optica"[Mesh]) OR (((((neuromyelitis optica spectrum disorders [Title/Abstract]) OR Devic Neuromyelitis Optica [Title/Abstract]) OR Devic's Neuromyelitis Optica [Title/Abstract]) OR Devic's Syndrome [Title/Abstract]) OR NMO spectrum disorders [Title/Abstract])
#2	("Mycophenolic Acid"[Mesh]) OR (((((Mycophenolate Mofetil [Title/Abstract]) OR "Mofetil,Mycophenolate" [Title/Abstract]) OR Cellcept [Title/Abstract]) OR Myfortic [Title/Abstract]) OR RS61443 [Title/Abstract])
#3	#1 and #2

Figure1. The PRISMA flow chart of the selection process.

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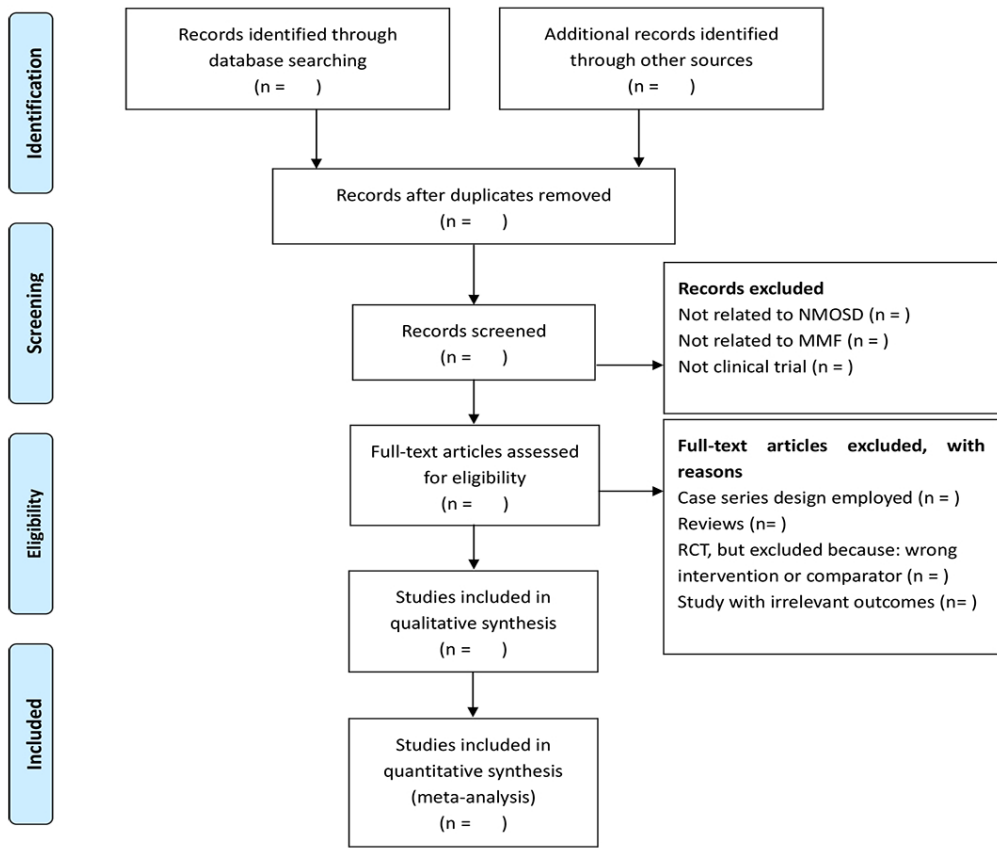


Figure1. The PRISMA flow chart of the selection process.

# Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the PRISMA-Reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

			Page
		Reporting Item	Number
<b>Title</b>			
Identification	<a href="#">#1a</a>	Identify the report as a protocol of a systematic review	Page 1
Update	<a href="#">#1b</a>	If the protocol is for an update of a previous systematic review, identify as such	

## 1 Registration

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4 [#2](#) If registered, provide the name of the registry (such as Page 2  
5  
6 PROSPERO) and registration number  
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## 9 Authors

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13 Contact [#3a](#) Provide name, institutional affiliation, e-mail address of all Page 1  
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15 protocol authors; provide physical mailing address of  
16  
17 corresponding author  
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20 Contribution [#3b](#) Describe contributions of protocol authors and identify the Page 1,11  
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22 guarantor of the review  
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## 25 Amendments

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29 [#4](#) If the protocol represents an amendment of a previously  
30  
31 completed or published protocol, identify as such and list  
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33 changes; otherwise, state plan for documenting important  
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35 protocol amendments  
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## 38 Support

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42 Sources [#5a](#) Indicate sources of financial or other support for the review Page 1  
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45 Sponsor [#5b](#) Provide name for the review funder and / or sponsor Page 1  
46

47  
48 Role of sponsor or [#5c](#) Describe roles of funder(s), sponsor(s), and / or institution(s), Page 1  
49  
50 funder if any, in developing the protocol  
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## 53 Introduction

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56 Rationale [#6](#) Describe the rationale for the review in the context of what is Page  
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1		already known	2,3,4
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4	Objectives	<a href="#">#7</a> Provide an explicit statement of the question(s) the review	Page 5,6
5		will address with reference to participants, interventions,	
6		comparators, and outcomes (PICO)	
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11	<b>Methods</b>		
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14	Eligibility criteria	<a href="#">#8</a> Specify the study characteristics (such as PICO, study	Page 7,8
15		design, setting, time frame) and report characteristics (such	
16		as years considered, language, publication status) to be	
17		used as criteria for eligibility for the review	
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24	Information	<a href="#">#9</a> Describe all intended information sources (such as electronic	Page 7,8
25		databases, contact with study authors, trial registers or other	
26	sources	grey literature sources) with planned dates of coverage	
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32	Search strategy	<a href="#">#10</a> Present draft of search strategy to be used for at least one	Page 7
33		electronic database, including planned limits, such that it	
34		could be repeated	
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39	Study records -	<a href="#">#11a</a> Describe the mechanism(s) that will be used to manage	Page7,8
40		records and data throughout the review	
41	data management		
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45	Study records -	<a href="#">#11b</a> State the process that will be used for selecting studies (such	Page 7,8
46		as two independent reviewers) through each phase of the	
47	selection process	review (that is, screening, eligibility and inclusion in meta-	
48		analysis)	
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54	Study records -	<a href="#">#11c</a> Describe planned method of extracting data from reports	Page
55		(such as piloting forms, done independently, in duplicate),	7,8,9
56	data collection		
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1	process		any processes for obtaining and confirming data from	
2			investigators	
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6	Data items	<a href="#">#12</a>	List and define all variables for which data will be sought	Page 8
7			(such as PICO items, funding sources), any pre-planned	
8			data assumptions and simplifications	
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13	Outcomes and	<a href="#">#13</a>	List and define all outcomes for which data will be sought,	Page 5,6
14	prioritization		including prioritization of main and additional outcomes, with	
15			rationale	
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21	Risk of bias in	<a href="#">#14</a>	Describe anticipated methods for assessing risk of bias of	Page 7,8
22	individual studies		individual studies, including whether this will be done at the	
23			outcome or study level, or both; state how this information	
24			will be used in data synthesis	
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31	Data synthesis	<a href="#">#15a</a>	Describe criteria under which study data will be quantitatively	Page 9
32			synthesised	
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36	Data synthesis	<a href="#">#15b</a>	If data are appropriate for quantitative synthesis, describe	Page 9
37			planned summary measures, methods of handling data and	
38			methods of combining data from studies, including any	
39			planned exploration of consistency (such as I <sup>2</sup> , Kendall's $\tau$ )	
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46	Data synthesis	<a href="#">#15c</a>	Describe any proposed additional analyses (such as	Page 9,10
47			sensitivity or subgroup analyses, meta-regression)	
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51	Data synthesis	<a href="#">#15d</a>	If quantitative synthesis is not appropriate, describe the type	Page 9
52			of summary planned	
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57	Meta-bias(es)	<a href="#">#16</a>	Specify any planned assessment of meta-bias(es) (such as	Page 8,9
58				
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1 publication bias across studies, selective reporting within  
2  
3 studies)  
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6 Confidence in [#17](#) Describe how the strength of the body of evidence will be Page 9  
7  
8 cumulative assessed (such as GRADE)  
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10 evidence  
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13 None The PRISMA-P checklist is distributed under the terms of the Creative Commons Attribution  
14 License CC-BY 4.0. This checklist can be completed online using <https://www.goodreports.org/>, a tool  
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16 made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)  
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# BMJ Open

## Safety and Efficacy of Mycophenolate Mofetil in Treating NMOSD : a protocol for systematic review and meta-analysis.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-040371.R2
Article Type:	Protocol
Date Submitted by the Author:	07-Sep-2020
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<b>Primary Subject Heading</b>:	Ophthalmology
Secondary Subject Heading:	Neurology, Evidence based practice
Keywords:	OPHTHALMOLOGY, NEUROLOGY, IMMUNOLOGY, Neuro-ophthalmology < NEUROLOGY

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4 Safety and Efficacy of Mycophenolate Mofetil in Treating NMOSD : a protocol  
5 for systematic review and meta-analysis.

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21 [jinmingyk@163.com](mailto:jinmingyk@163.com)).

## 22 23 24 25 **Abstract**

26  
27 **Introduction** Neuromyelitis optica spectrum disorders (NMOSD) is an inflammatory  
28 and heterogeneous astrocyte disorder of the central nervous system (CNS) with the  
29 characteristic of higher incidence in women and Asian people. Most patients with  
30 NMOSD have a course of recurrence and remission that is prone to cause paralysis and  
31 blindness. Several studies have confirmed the efficacy and promising prospect of  
32 mycophenolate mofetil (MMF) in the treatment of NMOSD. Yet its therapeutic effect  
33 and safety are controversial. Although there has been two published literature that is  
34 relevant to the topic of this study, both of them have certain defects, and they can only  
35 provide answers about the efficacy or safety of MMF in the treatment of NMOSD from  
36 partial perspectives or conclusions. This research aims to perform a direct and  
37 comprehensive systematic review and meta-analysis to evaluate MMF's effectiveness  
38 and safety in treating NMOSD.

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51 **Methods and analysis** This systematic review will cover all comparative researches,  
52 from randomized controlled trials (RCTs) to cohort studies, and case-control study. A  
53 relevant literature search will be conducted in PubMed, Web of Science, EMBASE, the  
54 Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang  
55 Database, China Science and Technology Journal database (VIP) and Chinese  
56 Biomedical Literature database (CBM). We will also search registers of clinical trials,  
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4 potential gray literature, and abstracts from conferences. There are no limits on  
5 language and publication status. The reporting quality and risk of bias will be assessed  
6 by two researchers independently. Expanded disability status scales (EDSS),  
7 annualized relapse rate (ARR) will be evaluated as the primary outcome. The secondary  
8 outcomes will consist of the frequency and severity of adverse events (AEs), best-  
9 corrected visual acuity (BCVA), relapse-free rate and time to the next attack. A meta-  
10 analysis will be performed using RevMan5.3 software provided by the Cochrane  
11 Collaboration and Stata 12.0.  
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19 **Ethics and dissemination** Because the data used for this systematic review will be  
20 exclusively extracted from published studies, ethical approval and informed consent of  
21 patients will not be required. The systematic review will be published in a peer-  
22 reviewed journal, presented at conferences and will be shared on social media platforms.  
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27 **PROSPERO registration number:** PROSPERO CRD42020164179.  
28

#### 29 **Strengths and limitations of this study:**

30  
31 ► This study will carry out an exhaustive literature search to identify studies aimed at  
32 evaluating the efficacy and safety of MMF in treating NMOSD.  
33

34 ► One limitation of this study is that differences in patients, interventions and primary  
35 outcomes may mean that meta-analysis cannot be performed and there are plans for  
36 narrative and meta-analytical syntheses.  
37  
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39 ► Although we will include studies published in any language, translation difficulties  
40 may arise, which will result in the exclusion of these studies.  
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43 ► The analysis of various sources of heterogeneity and the assessment of risk of bias  
44 of the included studies is a critical point for extracting and synthesizing evidence-based  
45 conclusions.  
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49  
50 **Keywords:** mycophenolate mofetil, neuromyelitis optica spectrum disorders, protocol,  
51 systematic review, meta-analysis.  
52

#### 53 **1. Introduction**

54 Neuromyelitis Optica (NMO), also known as Devic disease, is generally considered to  
55 be a rare autoimmune astrocyte disorder of the central nervous system (CNS), induced  
56 by autoantibodies, dominated by humoral immunity and involving numerous immune  
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4 cells and factors, with optic neuritis(ON) and acute transverse myelitis as typical  
5 clinical manifestations.<sup>1</sup> NMO has been known as a subtype of multiple sclerosis (MS)  
6 for over 100 years since it was first described and reported.<sup>2</sup> Until 2004, the discovery  
7 and confirmation of anti-aquaporin-4 immunoglobulin G (AQP4-IgG) had made  
8 substantial progress in pathogenesis, diagnosis, and treatment of NMO.<sup>3 4</sup> The notion  
9 of neuromyelitis optica spectrum disorders (NMOSD) was first proposed based on the  
10 wide clinical use of specific AQP4-IgG,<sup>4</sup> which mainly referred to the minimal AQP4-  
11 IgG positive NMO. However, the deficiencies of the diagnostic criteria of NMO in  
12 2006 and NMOSD in 2007 became prominent with the incremental improvement of the  
13 specificity of clinical AQP4-IgG tests. In 2015, a groundbreaking international  
14 diagnostic protocol for NMOSD was put forward by the global NMO diagnostic team.<sup>5</sup>  
15 NMOSD consists of NMO, ON, longitudinally extensive transverse myelitis and other  
16 common cerebral demyelinating syndromes.<sup>5</sup> There are so far no reliable statistics on  
17 the worldwide incidence and prevalence of NMOSD. According to the current  
18 epidemiological evidence of small samples, the high incidence of this disease is among  
19 middle-aged and young women, with the onset age varying from 32 to 41 years old,  
20 and the incidence in females is about 10 times that of males.<sup>5</sup> The incidence and  
21 prevalence of approximately 0.05-0.40 and 0.52-4.40/100,000 vary from region to  
22 region.<sup>6</sup> A populous region of Asia is the region with a high incidence of NMOSD.<sup>7-9</sup>  
23 Most NMOSD patients have a recurrence and remission including ON, myelitis, and  
24 lesions in special parts of the brain that are vulnerable to cause paralysis and blindness.<sup>5</sup>  
25 NMOSD has become one of the most common causes of non-traumatic disability and  
26 blindness in young and middle-aged individuals, putting heavy burdens on the life,  
27 work and study, as well as the society and economy of various countries.<sup>10</sup> Clinical  
28 studies indicate that approximately 1/4 of patients will not be able to walk  
29 independently after an average of 5 years of NMO, approximately 10% will be  
30 wheelchair-dependent, and more than half of patients will have serious vision loss in at  
31 least one eye.<sup>11</sup> In particular, ON associated with NMO (NMO-ON) possesses poor  
32 recovery even after traditional therapy, which often progresses into significant bilateral  
33 visual loss in the long term, leaving behind varying degrees of optic atrophy, which is  
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4 different from MS.<sup>12 13</sup>

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6 Currently, there are no standardized guidelines for the clinical management of NMOSD.  
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8 The class of NMOSD drugs is commonly referred to as disease-modifying drugs,<sup>14</sup> and  
9  
10 the treatment is split into two stages: the acute phase and the period of remission. The  
11  
12 former is based on corticosteroids to reduce the severity and frequency of acute attacks  
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14 that include intravenous corticosteroids (IVCSs), plasma exchange (PLEX), and  
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16 immunoglobulin. Immunosuppressive agents, including mycophenolate mofetil  
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18 (MMF), azathioprine (AZA), cyclophosphamide, methotrexate, mitoxantrone,  
19  
20 tacrolimus, cyclosporine, and monoclonal antibodies, are frequently used during the  
21  
22 process of recovery to avoid recurrence and to mitigate the progression of neurological  
23  
24 impairment.<sup>15 16</sup> Although AZA and rituximab are recommended as first-line therapies  
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26 obtained from clinical trials and expert opinion from the published guidelines for  
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28 NMOSD,<sup>16</sup> there are still adverse events (AEs) such as disease recurrence and  
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30 myelosuppression that results in drug withdrawal or replacement of these drugs in  
31  
32 patients with NMOSD.<sup>17</sup> Other AEs for Rituximab have also been reported in recent  
33  
34 years such as infusion reactions, infection, and even death,<sup>18-20</sup> and its clinical  
35  
36 application has been constrained by such factors as high price.<sup>18 21</sup> Therefore, a better  
37  
38 immunosuppressant for the treatment of NMOSD is urgently needed. The application  
39  
40 of MMF in NMOSD is still under investigation and is recommended as second-line  
41  
42 treatments,<sup>16</sup> but some studies have verified MMF's efficacy and promising potential,<sup>21-</sup>  
43  
44 <sup>24</sup> and only a few AEs were published.<sup>21 22</sup> Especially, additional studies have also  
45  
46 indicated that MMF was more effective and triggered less AEs than AZA.<sup>25 26</sup> In  
47  
48 patients experiencing AEs or poor response to AZA, MMF is recommended as an  
49  
50 alternative therapy.<sup>16</sup>

51  
52 Although MMF is increasingly employed in NMOSD, there is still controversy about  
53  
54 its related harms and benefits. At present, there are mainly two published articles that  
55  
56 are relevant to the topic and purpose of our research.<sup>27 28</sup> Nevertheless, these two studies  
57  
58 have some imperfections in the direct evaluation of the efficacy and safety of MMF in  
59  
60 the treatment of NMOSD patients. For example, the Espiritu and Pasco paper did not  
quantitatively evaluate the efficacy of MMF in the treatment of NMOSD and did not

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4 compare the AEs of MMF with other drugs in the treatment of NMOSD. Additionally,  
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6 Huang et al. 's research was a network meta-analysis and the literature related to MMF  
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8 in this paper was three observational studies that made the number of included studies  
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10 and closed loops per comparison were few, which might lower the reliability of the  
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12 findings. In our study, the database we searched includes not only the English database  
13  
14 but also the Chinese database. The retrieval time is limited to June 2020, and we will  
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16 add 3 retrospective studies involving 471 patients with NMOSD,<sup>29-31</sup> which makes the  
17  
18 retrieval literature more comprehensive. At the same time, the conclusions of the  
19  
20 previously published literature about the clinical effect of MMF were inconsistent.  
21  
22 Poupart argued that RTX was clinically better tolerated than MMF.<sup>30</sup> But Huang et al  
23  
24 argued that MMF had the best drug tolerance and was superior to RTX.<sup>31</sup> We expect  
25  
26 our research to help solve this problem as well.

## 27 **2. Methods**

28  
29 This protocol has been registered on PROSPERO (registration number: CRD  
30  
31 42020164179). Our protocol will follow the Meta-analysis of Observational Studies in  
32  
33 Epidemiology (MOOSE),<sup>32</sup> the Cochrane Handbook for Systematic Reviews of  
34  
35 Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-  
36  
37 Analysis Protocol (PRISMA-P) statement guidelines.<sup>33 34</sup>

### 38 **2.1 Inclusion criteria for study selection**

#### 39 **2.1.1 Types of studies**

40  
41 All comparative researches, from randomized controlled trials (RCTs) to cohort studies,  
42  
43 and case-control study, covering at least two interventions, will be included. The current  
44  
45 clinical trial results will be objectively integrated, which is conducive to the evaluation  
46  
47 of the efficacy and safety of MMF for NMOSD. We will exclude reviews, qualitative  
48  
49 studies, animal trials, laboratory studies and studies only involving one intervention.  
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#### 52 **2.1.2 Types of patients**

53  
54 Patients diagnosed as having NMOSD will be included in this study.<sup>5 35</sup> There will be  
55  
56 no restrictions based on other conditions, such as age at onset, sex, ethnicity,  
57  
58 educational or economic status, number of pre-treatment relapses, previous treatment,  
59  
60 duration of illness, disease severity, and baseline expanded disability status scales

(EDSS), AQP4-IgG serological status.

### 2.1.3 Types of interventions

Trials comparing MMF to placebo or any other active substances, including AZA, cyclophosphamide, methotrexate, mitoxantrone, tacrolimus, cyclosporine, and monoclonal antibodies, will be considered. Besides, the types, dosage, and frequency of MMF were not limited. Studies that MMF with combination therapy fail to objectively evaluate the efficacy and safety of MMF will be eliminated.

### 2.1.4 Types of outcome measures

#### 2.1.4.1 Primary outcomes

- (1) EDSS: Disability progression was characterized as an increase in the Kurtzke EDSS by at least 1 point above the pre-treatment score if baseline score  $< 5.5$ , and by at least half-point if baseline score  $> 5.5$ . Outcome measured was the mean changes of EDSS before and after MMF treatment.<sup>36 37</sup>
- (2) Annualized relapse rate (ARR): Relapse is equivalent to a neurologic symptom lasting for  $> 24$  h, which occurs at least 30 days after the onset of a preceding event. ARR is computed as the number of relapses divided by the time in years (days). Post-treatment ARR was contrasted with pre-treatment ARR.<sup>38</sup>

#### 2.1.4.2 Secondary outcomes

- (1) The frequency and extent of AEs: During treatment and follow-up periods, any symptomatic events which had a possible, probable or definite causal relationship to MMF treatment were defined as AEs.
- (2) Relapse-free rate: The absence of relapse during the observation period of the study reported as percentage per study.<sup>35</sup>
- (3) Best-corrected visual acuity (BCVA): BCVA was measured using a standardized test, such as the ETDRS chart, Snellen chart or similar method, and other visual acuity measures would be allowed if findings could be justified as well as validated concerning accepted relevant standard measures. Outcome measured was the mean change of BCVA from before and after MMF treatment.<sup>39</sup>
- (4) Time to the next attack.

#### 2.1.4.3 Security index



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4 The safety was assessed by the occurrence of AEs. Any unexpected events that occurred  
5 during the studies will be recorded on an AEs report form, including:<sup>28</sup>  
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- 7  
8 (1) General physical examination (temperature, pulse, respiration, blood pressure).  
9  
10 (2) Routine examination of blood, urine and stool.  
11  
12 (3) Liver and kidney function examination.  
13  
14 (4) Gastrointestinal discomfort.  
15  
16 (5) Hair loss or Alopecia.  
17  
18 (6) Allergic or Anaphylactoid reactions.  
19  
20 (7) Drug discontinued due to drug-related AEs.  
21  
22 (8) Possible AEs and related detection indicators.

## 23 **2.2 Search methods for the identification of studies**

### 24 **2.2.1 Electronic searches**

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26 A relevant literature search by sensitive search strategies was conducted using the  
27 following electronic databases from their inception to June 31, 2020: PubMed, Web of  
28 Science, EMBASE, the Cochrane Library, China National Knowledge Infrastructure  
29 (CNKI), Wanfang Database, China Science and Technology Journal database (VIP)  
30 and Chinese Biomedical Literature database (CBM). Search methods of MeSH terms  
31 with free words were applied in English databases. The related terms are as follows:  
32 Participants (neuromyelitis optica, neuromyelitis optica spectrum disorders, Devic  
33 Neuromyelitis Optica, Devic's Neuromyelitis Optica, Devic's Syndrome, NMO  
34 spectrum disorders), Intervention (mycophenolic acid, mycophenolate mofetil, "mofetil,  
35 mycophenolate", cellcept, myfortic, RS61443). The search strategy for PubMed is  
36 described in Table 1, which will include all search terms, and other searches will be  
37 carried out based on those results. This will be suitably adapted to search in the other  
38 databases. There are no limits on language and publication status.

### 39 **2.2.2 Searching other resources**

40 we will also search PROSPERO, the International Clinical Trials Registry Platform  
41 (ICTRP), ClinicalTrials.gov, dissertations, and gray literature to identify systematic  
42 reviews or clinical trials related to mycophenolate mofetil and neuromyelitis optica  
43 spectrum disorders. Manual searches will be conducted for related journals and  
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conference processes. We will also review papers and bibliographies included in the trials.

## **2.3 Data collection and analysis**

### **2.3.1 Selection of studies**

Two reviewers (MYH and ZQL) will independently browse the titles and abstracts of all of the retrieved records to distinguish and exclude any irrelevant articles. Studies only related to human subjects are to be included. Any discord will be resolved by discussion between the two authors and an arbiter (MJ). The selection procedure for the study is shown in a PRISMA flow chart (Fig. 1).

### **2.3.2 Data extraction and management**

Based on the inclusion criteria, a standard form of data collection will be produced prior to data extraction. Search results will be entered into an EndNote X9 database and duplicate entries removed. Two authors (MYH and ZQL) will extract the data of interest from the eligible study and enter the data extraction sheet as follows: The basic characteristics of each study (study design or methods, author, title, source/journal, time of publication, country, hospital setting); participants characteristics (average age, gender, sample size, inclusion and exclusion criteria, baseline situation); Interventions (type, duration, frequency and dosage of MMF, randomization, allocation concealment, blinding methods); Comparators (AZA, tacrolimus, cyclosporine, monoclonal antibodies, and placebo, etc); Outcomes (measures, main outcomes, security indexes, and follow up); If funded, it will also be recorded. When the consensus on data extraction is not available through discussion, the third reviewer (MJ) will make a decision.

### **2.3.3 Assessment of risk of bias**

Two authors (Yang Chen and LQN) will independently estimate the risk and bias using the Cochrane risk of bias (ROB) assessment tool for RCTs.<sup>40</sup> Methodological quality evaluation of the included observational studies will be carried out using the Newcastle–Ottawa Scale (NOS).<sup>41</sup> The RevMan software program (V.5.3) will document the selected details of each study.<sup>42</sup>

### **2.3.4 Measures of treatment effect**

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4 The risk ratio (RR) and 95% confidence interval (CI) will be used to analyze  
5 dichotomous data and calculate the treatment effect. A weighted mean difference  
6 (WMD) or a standard mean difference (SMD) with 95% CIs will be used to analyze  
7 continuous outcomes.  
8  
9

### 11 **2.3.5 Unit of analysis issue**

12  
13 We will only extract the 1st experimental period data of crossover trials to avoid  
14 carryover effects. In the meantime, given that there are multiple intervention groups in  
15 trials, we will combine all analogous groups into a single pairwise comparison to avoid  
16 a unit of analysis issue.  
17  
18

### 21 **2.3.6 Management of missing data**

22  
23 Reviewer (YLQ and You Chen) will contact the appropriate author of the included trials  
24 for clarification or more details via email and telephone if necessary. The missing data  
25 will be deleted, if there is no response from the author. That will be addressed in the  
26 discussion in this case. If quantitative data were not available, then the qualitative  
27 analysis should be used.  
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### 33 **2.3.7 Assessment of heterogeneity and data synthesis**

34  
35 We will use all of the case data for the analysis data. Heterogeneity will be tested with  
36 a standard Chisquare test.<sup>43</sup> To quantify the impact of the statistical heterogeneity on  
37 the systematic review, the  $I^2$  value will be applied to calculate and present the  
38 heterogeneity degree. If  $P > 0.1$ ,  $I^2 < 50\%$ , it is considered that there is no heterogeneity  
39 between the trials, and the model of fixed effect will be used, otherwise, the model of  
40 random effect will be adopted. All statistical analyzes will be performed using the  
41 RevMan5.3 software provided by the Cochrane Collaboration. Using the software to  
42 obtain forest plots and test the heterogeneity between the included studies. The Grades  
43 of Recommendation, Assessment, Development and Evaluation (GRADE) will be used  
44 to assess the meta-analysis findings and determine the quality of evidence. Where meta-  
45 analysis may not be not feasible due to lack of clinical trials or heterogeneity, systematic  
46 narrative synthesis will be adopted.  
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### 58 **2.3.8 Assessment of reporting biases**

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60 When 10 or more studies are included in a meta-analysis, we will evaluate funnel plot

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4 asymmetry for reporting biases and small-study effects using Egger's method.<sup>44</sup> For  
5 Egger's test, P value of greater than 0.05 was determined as no significant publishing  
6 bias or small-study effects in studies. As funnel plot asymmetry does not necessarily  
7 suggest reporting bias, we will attempt to recognize potential causes for the asymmetry,  
8 including poor methodological quality and true heterogeneity of studies.  
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### 13 **2.3.9 Subgroup analysis**

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15 Upon detection of heterogeneity, a subgroup analysis will be carried out to judge the  
16 source of heterogeneity. The criteria for a subgroup analysis are as follows:  
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- 18 (1) Age.
- 19 (2) Type of MMF.
- 20 (3) Research type.
- 21 (4) Participation population.
- 22 (5) Type of control interventions.
- 23 (6) Intervention dosage, frequency and duration.
- 24 (7) AQP4-IgG serological status.

### 25 **2.3.10 Sensitivity analysis**

26  
27 The ROB tool will be used to estimate methodological quality in the case of sufficient  
28 data from trials. Sensitivity analysis will be performed to determine the robustness of  
29 aggregate estimates and to detect whether any single study accounts for a substantial  
30 proportion of heterogeneity by eliminating the included studies from the summary  
31 review one by one. If low-quality articles are deleted, then a second meta-analysis will  
32 be carried out. Comparison and discussion of the results and effect size of the two meta-  
33 analyses will be held.<sup>45</sup>  
34

35  
36 **2.4 Patient and public involvement** Patients and/or the public will not participate in  
37 the study. However, once scientific publications disseminate our findings, they are  
38 circulated across social networks so that our conclusions will affect the actions of  
39 neuro-ophthalmologists and health policymakers.  
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## 48 **3 Discussion**

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50 Pathogenesis, diagnosis and treatment of NMO are rapidly growing areas of research  
51 as AQP4-IgG were first identified. Patients with NMOSD should receive standardized  
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4 and personalized immunotherapy as soon as possible, as any further acute episodes may  
5 result in severe and often irreversible disability. The challenges in discovering new and  
6 better drugs for NMO are the rareness of the disease and the unfavorable prognosis in  
7 many cases, which make clinical studies with placebo groups difficult.<sup>16</sup> Many studies  
8 have confirmed the efficacy and promising prospect of MMF in the treatment of  
9 NMOSD,<sup>21-24</sup> and only a few AEs were reported.<sup>21 22</sup> Additional studies have also  
10 indicated that MMF was more effective and triggered less AEs than AZA.<sup>25 26</sup> However,  
11 its therapeutic effect and safety remain controversial. Although there has been two  
12 published literature that is relevant to the topic of this study,<sup>27 28</sup> both of them have  
13 certain defects, and they can only provide answers about the efficacy or safety of MMF  
14 in the treatment of NMOSD from partial perspectives or conclusions. If our paper is  
15 completed, it will be a currently searchable protocol for a traditional meta-and  
16 systematic review that directly and synthetically evaluates the efficacy and safety of  
17 MMF in the treatment of NMOSD. One of the strengths of this protocol will use a  
18 comprehensive search strategy of published literature. The overall data used in each  
19 analysis will be evaluated qualitatively and quantitatively. The sources of heterogeneity  
20 and different subgroups of the articles will be analyzed to comprehensively evaluate  
21 the efficacy and safety of MMF in the treatment of NMOSD, and to increase the  
22 credibility of the article content and conclusions. We expect that this systematic review  
23 will benefit patients with NMOSD, physicians, health care administrators and policy-  
24 makers.

### 45 46 **Author contributions**

47 MYH conceived and designed the protocol, and MYH drafted the protocol manuscript.  
48 MYH developed the search strategy, with input from ZQL and LQN. MYH and ZQL  
49 planned data extraction. MYH, Yang Chen and ZJW planned the quality appraisal of  
50 all included studies. MYH, ZQL, LQN, Yang Chen, HM, You Chen, ZJW, YLQ and  
51 MJ critically revised the manuscript for methodological and intellectual content. All  
52 authors approved the final version.

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4 **Conceptualization:** Meng-Yu Han, Zi-Qiang Liu, Zhi-Jun Wang, Ming Jin.

5 **Data curation:** Meng-Yu Han, Zi-Qiang Liu, Lu-Qi Nong, Huan Meng.

6  
7 **Formal analysis:** Meng-Yu Han, Zi-Qiang Liu.

8  
9 **Funding acquisition:** Meng-Yu Han.

10  
11 **Investigation:** Ming Jin.

12  
13 **Methodology:** Meng-Yu Han, Zi-Qiang Liu, Lu-Qi Nong, You Chen.

14  
15 **Project administration:** Ming Jin.

16  
17 **Resources:** Meng-Yu Han, Zi-Qiang Liu, Lu-Qi Nong, Ming Jin.

18  
19 **Software:** Meng-Yu Han, Zi-Qiang Liu, Lu-Qi Nong.

20  
21 **Supervision:** Meng-Yu Han, Zhi-Jun Wang, Ming Jin.

22  
23 **Validation:** Huan Meng, Yang Chen, Ya-li Qin, Ming Jin.

24  
25 **Visualization:** Huan Meng, Yang Chen, Ya-li Qin, Ming Jin.

26  
27 **Writing – original draft:** Meng-Yu Han, Zi-Qiang Liu, Lu-Qi Nong, Ming Jin.

28  
29 **Writing – review & editing:** Meng-Yu Han, Zi-Qiang Liu, Lu-Qi Nong, Ming Jin.

30  
31  
32  
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35 study.  
36  
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Table 1 Search strategy used in PubMed database.

Number	Search terms
#1	("Neuromyelitis Optica"[Mesh]) OR (((((neuromyelitis optica spectrum disorders [Title/Abstract]) OR Devic Neuromyelitis Optica [Title/Abstract]) OR Devic's Neuromyelitis Optica [Title/Abstract]) OR Devic's Syndrome [Title/Abstract]) OR NMO spectrum disorders [Title/Abstract])
#2	("Mycophenolic Acid"[Mesh]) OR (((((Mycophenolate Mofetil [Title/Abstract]) OR "Mofetil,Mycophenolate" [Title/Abstract]) OR Cellcept [Title/Abstract]) OR Myfortic [Title/Abstract]) OR RS61443 [Title/Abstract])

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#3	#1 and #2
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Figure 1. The PRISMA flow chart of the selection process.

For peer review only

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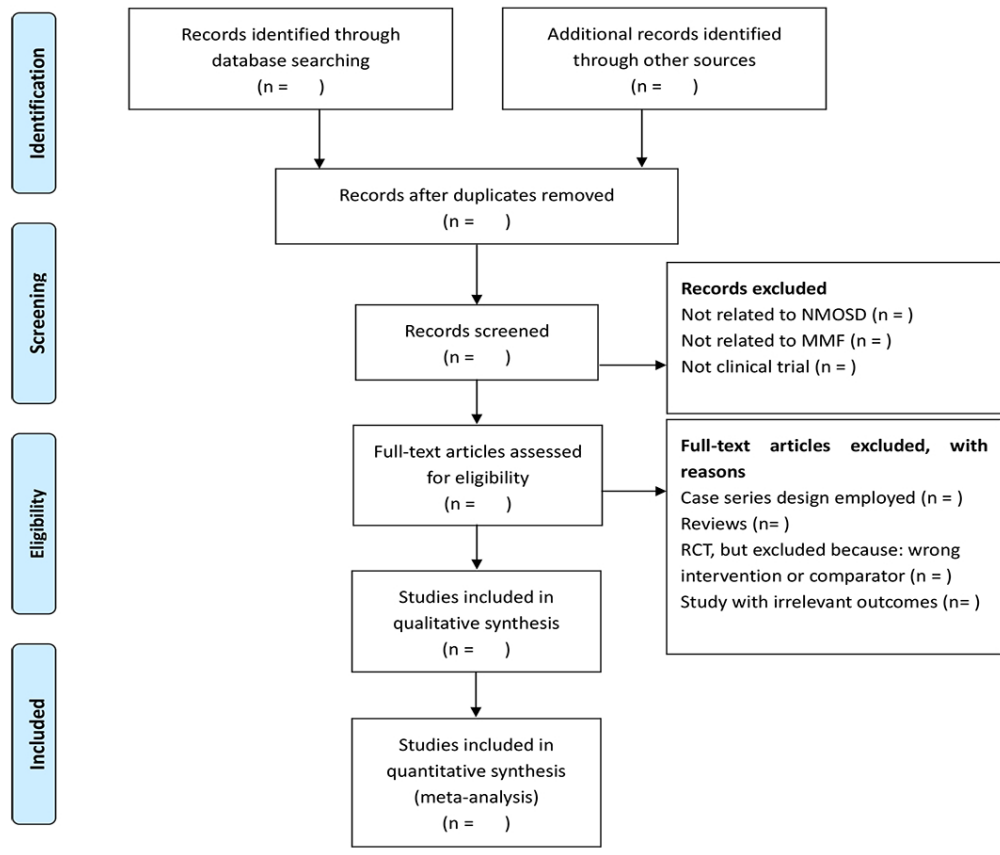


Figure1. The PRISMA flow chart of the selection process.

# Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

			Page
		Reporting Item	Number
<b>Title</b>			
Identification	<a href="#">#1a</a>	Identify the report as a protocol of a systematic review	Page 1
Update	<a href="#">#1b</a>	If the protocol is for an update of a previous systematic review, identify as such	

## 1 Registration

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4 [#2](#) If registered, provide the name of the registry (such as Page 2  
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6 PROSPERO) and registration number  
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## 9 Authors

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13 Contact [#3a](#) Provide name, institutional affiliation, e-mail address of all Page 1  
14  
15 protocol authors; provide physical mailing address of  
16  
17 corresponding author  
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20 Contribution [#3b](#) Describe contributions of protocol authors and identify the Page1,11,12  
21  
22 guarantor of the review  
23  
24

## 25 Amendments

26  
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28  
29 [#4](#) If the protocol represents an amendment of a previously  
30  
31 completed or published protocol, identify as such and list  
32  
33 changes; otherwise, state plan for documenting important  
34  
35 protocol amendments  
36  
37

## 38 Support

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42 Sources [#5a](#) Indicate sources of financial or other support for the review Page 12  
43  
44

45 Sponsor [#5b](#) Provide name for the review funder and / or sponsor Page 12  
46  
47

48 Role of sponsor or [#5c](#) Describe roles of funder(s), sponsor(s), and / or Page 12  
49  
50 funder institution(s), if any, in developing the protocol  
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## 53 Introduction

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55  
56 Rationale [#6](#) Describe the rationale for the review in the context of what Page 2,3,4,5  
57  
58

1		is already known	
2			
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4	Objectives	<a href="#">#7</a> Provide an explicit statement of the question(s) the review	Page 5,6,7
5		will address with reference to participants, interventions,	
6		comparators, and outcomes (PICO)	
7			
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10			
11	<b>Methods</b>		
12			
13			
14	Eligibility criteria	<a href="#">#8</a> Specify the study characteristics (such as PICO, study	Page 7,8
15		design, setting, time frame) and report characteristics	
16		(such as years considered, language, publication status) to	
17		be used as criteria for eligibility for the review	
18			
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24	Information	<a href="#">#9</a> Describe all intended information sources (such as	Page 7,8
25		electronic databases, contact with study authors, trial	
26	sources	registers or other grey literature sources) with planned	
27		dates of coverage	
28			
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34	Search strategy	<a href="#">#10</a> Present draft of search strategy to be used for at least one	Page 7
35		electronic database, including planned limits, such that it	
36		could be repeated	
37			
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40			
41	Study records -	<a href="#">#11a</a> Describe the mechanism(s) that will be used to manage	Page 8
42		records and data throughout the review	
43	data management		
44			
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46			
47	Study records -	<a href="#">#11b</a> State the process that will be used for selecting studies	Page 8
48		(such as two independent reviewers) through each phase	
49	selection process	of the review (that is, screening, eligibility and inclusion in	
50		meta-analysis)	
51			
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57	Study records -	<a href="#">#11c</a> Describe planned method of extracting data from reports	Page 8,9
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60			

1	data collection		(such as piloting forms, done independently, in duplicate),	
2				
3	process		any processes for obtaining and confirming data from	
4				
5			investigators	
6				
7				
8	Data items	<a href="#">#12</a>	List and define all variables for which data will be sought	Page 8
9				
10			(such as PICO items, funding sources), any pre-planned	
11				
12			data assumptions and simplifications	
13				
14				
15	Outcomes and	<a href="#">#13</a>	List and define all outcomes for which data will be sought,	Page 6,7
16				
17	prioritization		including prioritization of main and additional outcomes,	
18				
19			with rationale	
20				
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22				
23	Risk of bias in	<a href="#">#14</a>	Describe anticipated methods for assessing risk of bias of	Page 8
24				
25	individual studies		individual studies, including whether this will be done at	
26				
27			the outcome or study level, or both; state how this	
28				
29			information will be used in data synthesis	
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33	Data synthesis	<a href="#">#15a</a>	Describe criteria under which study data will be	Page 9
34				
35			quantitatively synthesised	
36				
37				
38	Data synthesis	<a href="#">#15b</a>	If data are appropriate for quantitative synthesis, describe	Page 9
39				
40			planned summary measures, methods of handling data	
41				
42			and methods of combining data from studies, including any	
43				
44			planned exploration of consistency (such as I <sup>2</sup> , Kendall's	
45				
46			τ)	
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49				
50	Data synthesis	<a href="#">#15c</a>	Describe any proposed additional analyses (such as	Page 9,10
51				
52			sensitivity or subgroup analyses, meta-regression)	
53				
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55				
56	Data synthesis	<a href="#">#15d</a>	If quantitative synthesis is not appropriate, describe the	Page 9
57				
58				
59				
60				



1 type of summary planned

2  
3  
4 Meta-bias(es) [#16](#) Specify any planned assessment of meta-bias(es) (such Page 8,9,10  
5 as publication bias across studies, selective reporting  
6 within studies)  
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8

9  
10  
11 Confidence in [#17](#) Describe how the strength of the body of evidence will be Page 9  
12 cumulative assessed (such as GRADE)  
13 evidence  
14  
15

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17  
18 None The PRISMA-P checklist is distributed under the terms of the Creative Commons Attribution  
19 License CC-BY 4.0. This checklist can be completed online using <https://www.goodreports.org/>, a tool  
20 made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)  
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# BMJ Open

## Safety and Efficacy of Mycophenolate Mofetil in Treating Neuromyelitis Optica Spectrum Disorders : a protocol for systematic review and meta-analysis.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-040371.R3
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Date Submitted by the Author:	12-Oct-2020
Complete List of Authors:	han, mengyu; Beijing University of Chinese Medicine; China-Japan Friendship Hospital, Ophthalmology Nong, Luqi; Beijing University of Chinese Medicine, Graduate School ; China-Japan Friendship Hospital, Ophthalmology Liu, Ziqiang; Beijing University of Chinese Medicine, Graduate School ; China-Japan Friendship Hospital, Ophthalmology Chen, You; China-Japan Friendship Hospital Chen, Yang; Beijing University of Chinese Medicine Meng, Huan; Beijing University of Chinese Medicine, Graduate School; China-Japan Friendship Hospital, Ophthalmology Qin, Yali; Sun Yat-Sen University Zhongshan Ophthalmic Center Wang, Zhijun; China-Japan Friendship Hospital, ophthalmology department Jin, Ming; China-Japan Friendship Hospital, Ophthalmology
<b>Primary Subject Heading</b>:	Ophthalmology
Secondary Subject Heading:	Neurology, Evidence based practice
Keywords:	OPHTHALMOLOGY, NEUROLOGY, IMMUNOLOGY, Neuro-ophthalmology < NEUROLOGY

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3 Safety and Efficacy of Mycophenolate Mofetil in Treating Neuromyelitis Optica  
4 Spectrum Disorders : a protocol for systematic review and meta-analysis.  
5

6  
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22  
23

## 24 25 **Abstract**

26  
27 **Introduction** Neuromyelitis optica spectrum disorders (NMOSD) is an inflammatory  
28 and heterogeneous astrocyte disorder of the central nervous system (CNS) with the  
29 characteristic of higher incidence in women and Asian people. Most patients with  
30 NMOSD have a course of recurrence and remission that is prone to cause paralysis and  
31 blindness. Several studies have confirmed the efficacy and promising prospect of  
32 mycophenolate mofetil (MMF) in the treatment of NMOSD. Yet its therapeutic effect  
33 and safety are controversial. Although there has been two published literature that is  
34 relevant to the topic of this study, both of them have certain defects, and they can only  
35 provide answers about the efficacy or safety of MMF in the treatment of NMOSD from  
36 partial perspectives or conclusions. This research aims to perform a direct and  
37 comprehensive systematic review and meta-analysis to evaluate MMF's effectiveness  
38 and safety in treating NMOSD.  
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51 **Methods and analysis** This systematic review will cover all comparative researches,  
52 from randomized controlled trials (RCTs) to cohort studies, and case-control study. A  
53 relevant literature search will be conducted in PubMed, Web of Science, EMBASE, the  
54 Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang  
55 Database, China Science and Technology Journal database (VIP) and Chinese  
56 Biomedical Literature database (CBM) from their inception to June 31, 2020. We will  
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4 also search registers of clinical trials, potential gray literature, and abstracts from  
5 conferences. There are no limits on language and publication status. The reporting  
6 quality and risk of bias will be assessed by two researchers independently. Expanded  
7 disability status scales (EDSS), annualized relapse rate (ARR) will be evaluated as the  
8 primary outcome. The secondary outcomes will consist of the frequency and severity  
9 of adverse events (AEs), best-corrected visual acuity (BCVA), relapse-free rate and  
10 time to the next attack. A meta-analysis will be performed using RevMan5.3 software  
11 provided by the Cochrane Collaboration and Stata 12.0.  
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19 **Ethics and dissemination** Because the data used for this systematic review will be  
20 exclusively extracted from published studies, ethical approval and informed consent of  
21 patients will not be required. The systematic review will be published in a peer-  
22 reviewed journal, presented at conferences and will be shared on social media platforms.  
23  
24

25  
26  
27 **PROSPERO registration number:** PROSPERO CRD42020164179.  
28

### 29 **Strengths and limitations of this study:**

30  
31 ▶ This study will carry out an exhaustive literature search to identify studies aimed at  
32 evaluating the efficacy and safety of MMF in treating NMOSD.  
33

34 ▶ One limitation of this study is that differences in patients, interventions and primary  
35 outcomes may mean that meta-analysis cannot be performed and there are plans for  
36 narrative and meta-analytical syntheses.  
37  
38

39 ▶ Although we will include studies published in any language, translation difficulties  
40 may arise, which will result in the exclusion of these studies.  
41  
42

43 ▶ The analysis of various sources of heterogeneity and the assessment of risk of bias  
44 of the included studies is a critical point for extracting and synthesizing evidence-based  
45 conclusions.  
46  
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48

49  
50 **Keywords:** mycophenolate mofetil, neuromyelitis optica spectrum disorders, protocol,  
51 systematic review, meta-analysis.  
52

## 53 **1. Introduction**

54 Neuromyelitis Optica (NMO), also known as Devic disease, is generally considered to  
55 be a rare autoimmune astrocyte disorder of the central nervous system (CNS), induced  
56 by autoantibodies, dominated by humoral immunity and involving numerous immune  
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4 cells and factors, with optic neuritis(ON) and acute transverse myelitis as typical  
5 clinical manifestations.<sup>1</sup> NMO has been known as a subtype of multiple sclerosis (MS)  
6 for over 100 years since it was first described and reported.<sup>2</sup> Until 2004, the discovery  
7 and confirmation of anti-aquaporin-4 immunoglobulin G (AQP4-IgG) had made  
8 substantial progress in pathogenesis, diagnosis, and treatment of NMO.<sup>3 4</sup> The notion  
9 of neuromyelitis optica spectrum disorders (NMOSD) was first proposed based on the  
10 wide clinical use of specific AQP4-IgG,<sup>4</sup> which mainly referred to the minimal AQP4-  
11 IgG positive NMO. However, the deficiencies of the diagnostic criteria of NMO in  
12 2006 and NMOSD in 2007 became prominent with the incremental improvement of the  
13 specificity of clinical AQP4-IgG tests. In 2015, a groundbreaking international  
14 diagnostic protocol for NMOSD was put forward by the global NMO diagnostic team.<sup>5</sup>  
15 NMOSD consists of NMO, ON, longitudinally extensive transverse myelitis and other  
16 common cerebral demyelinating syndromes.<sup>5</sup> There are so far no reliable statistics on  
17 the worldwide incidence and prevalence of NMOSD. According to the current  
18 epidemiological evidence of small samples, the high incidence of this disease is among  
19 middle-aged and young women, with the onset age varying from 32 to 41 years old,  
20 and the incidence in females is about 10 times that of males.<sup>5</sup> The incidence and  
21 prevalence of approximately 0.05-0.40 and 0.52-4.40/100,000 vary from region to  
22 region.<sup>6</sup> A populous region of Asia is the region with a high incidence of NMOSD.<sup>7-9</sup>  
23 Most NMOSD patients have a recurrence and remission including ON, myelitis, and  
24 lesions in special parts of the brain that are vulnerable to cause paralysis and blindness.<sup>5</sup>  
25 NMOSD has become one of the most common causes of non-traumatic disability and  
26 blindness in young and middle-aged individuals, putting heavy burdens on the life,  
27 work and study, as well as the society and economy of various countries.<sup>10</sup> Clinical  
28 studies indicate that approximately 1/4 of patients will not be able to walk  
29 independently after an average of 5 years of NMO, approximately 10% will be  
30 wheelchair-dependent, and more than half of patients will have serious vision loss in at  
31 least one eye.<sup>11</sup> In particular, ON associated with NMO (NMO-ON) possesses poor  
32 recovery even after traditional therapy, which often progresses into significant bilateral  
33 visual loss in the long term, leaving behind varying degrees of optic atrophy, which is  
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4 different from MS.<sup>12 13</sup>

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6 Currently, there are no standardized guidelines for the clinical management of NMOSD.  
7  
8 The class of NMOSD drugs is commonly referred to as disease-modifying drugs,<sup>14</sup> and  
9  
10 the treatment is split into two stages: the acute phase and the period of remission. The  
11  
12 former is based on corticosteroids to reduce the severity and frequency of acute attacks  
13  
14 that include intravenous corticosteroids (IVCSs), plasma exchange (PLEX), and  
15  
16 immunoglobulin. Immunosuppressive agents, including mycophenolate mofetil  
17  
18 (MMF), azathioprine (AZA), cyclophosphamide, methotrexate, mitoxantrone,  
19  
20 tacrolimus, cyclosporine, and monoclonal antibodies, are frequently used during the  
21  
22 process of recovery to avoid recurrence and to mitigate the progression of neurological  
23  
24 impairment.<sup>15 16</sup> Although AZA and rituximab are recommended as first-line therapies  
25  
26 obtained from clinical trials and expert opinion from the published guidelines for  
27  
28 NMOSD,<sup>16</sup> there are still adverse events (AEs) such as disease recurrence and  
29  
30 myelosuppression that results in drug withdrawal or replacement of these drugs in  
31  
32 patients with NMOSD.<sup>17</sup> Other AEs for Rituximab have also been reported in recent  
33  
34 years such as infusion reactions, infection, and even death,<sup>18-20</sup> and its clinical  
35  
36 application has been constrained by such factors as high price.<sup>18 21</sup> Therefore, a better  
37  
38 immunosuppressant for the treatment of NMOSD is urgently needed. The application  
39  
40 of MMF in NMOSD is still under investigation and is recommended as second-line  
41  
42 treatments,<sup>16</sup> but some studies have verified MMF's efficacy and promising potential,<sup>21-</sup>  
43  
44 <sup>24</sup> and only a few AEs were published.<sup>21 22</sup> Especially, additional studies have also  
45  
46 indicated that MMF was more effective and triggered less AEs than AZA.<sup>25 26</sup> In  
47  
48 patients experiencing AEs or poor response to AZA, MMF is recommended as an  
49  
50 alternative therapy.<sup>16</sup>

51  
52 Although MMF is increasingly employed in NMOSD, there is still controversy about  
53  
54 its related harms and benefits. At present, there are mainly two published articles that  
55  
56 are relevant to the topic and purpose of our research.<sup>27 28</sup> Nevertheless, these two studies  
57  
58 have some imperfections in the direct evaluation of the efficacy and safety of MMF in  
59  
60 the treatment of NMOSD patients. For example, the Espiritu and Pasco paper did not  
quantitatively evaluate the efficacy of MMF in the treatment of NMOSD and did not

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4 compare the AEs of MMF with other drugs in the treatment of NMOSD. Additionally,  
5  
6 Huang et al. 's research was a network meta-analysis and the literature related to MMF  
7  
8 in this paper was three observational studies that made the number of included studies  
9  
10 and closed loops per comparison were few, which might lower the reliability of the  
11  
12 findings. In our study, the database we searched includes not only the English database  
13  
14 but also the Chinese database. The retrieval time is limited to June 2020, and we will  
15  
16 add 3 retrospective studies involving 471 patients with NMOSD,<sup>29-31</sup> which makes the  
17  
18 retrieval literature more comprehensive. At the same time, the conclusions of the  
19  
20 previously published literature about the clinical effect of MMF were inconsistent.  
21  
22 Poupart argued that RTX was clinically better tolerated than MMF.<sup>30</sup> But Huang et al  
23  
24 argued that MMF had the best drug tolerance and was superior to RTX.<sup>31</sup> We expect  
25  
26 our research to help solve this problem as well.

## 27 **2. Methods**

28  
29 This protocol has been registered on PROSPERO (registration number: CRD  
30  
31 42020164179). Our protocol will follow the Meta-analysis of Observational Studies in  
32  
33 Epidemiology (MOOSE),<sup>32</sup> the Cochrane Handbook for Systematic Reviews of  
34  
35 Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-  
36  
37 Analysis Protocol (PRISMA-P) statement guidelines.<sup>33 34</sup>

### 38 **2.1 Inclusion criteria for study selection**

#### 39 **2.1.1 Types of studies**

40  
41 All comparative researches, from randomized controlled trials (RCTs) to cohort studies,  
42  
43 and case-control study, covering at least two interventions, will be included. The current  
44  
45 clinical trial results will be objectively integrated, which is conducive to the evaluation  
46  
47 of the efficacy and safety of MMF for NMOSD. We will exclude reviews, qualitative  
48  
49 studies, animal trials, laboratory studies and studies only involving one intervention.  
50  
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#### 52 **2.1.2 Types of patients**

53  
54 Patients diagnosed as having NMOSD will be included in this study.<sup>5 35</sup> There will be  
55  
56 no restrictions based on other conditions, such as age at onset, sex, ethnicity,  
57  
58 educational or economic status, number of pre-treatment relapses, previous treatment,  
59  
60 duration of illness, disease severity, and baseline expanded disability status scales



(EDSS), AQP4-IgG serological status.

### 2.1.3 Types of interventions

Trials comparing MMF to placebo or any other active substances, including AZA, cyclophosphamide, methotrexate, mitoxantrone, tacrolimus, cyclosporine, and monoclonal antibodies, will be considered. Besides, the types, dosage, and frequency of MMF were not limited. Studies that MMF with combination therapy fail to objectively evaluate the efficacy and safety of MMF will be eliminated.

### 2.1.4 Types of outcome measures

#### 2.1.4.1 Primary outcomes

- (1) EDSS: Disability progression was characterized as an increase in the Kurtzke EDSS by at least 1 point above the pre-treatment score if baseline score < 5.5, and by at least half-point if baseline score > 5.5. Outcome measured was the mean changes of EDSS before and after MMF treatment.<sup>36 37</sup>
- (2) Annualized relapse rate (ARR): Relapse is equivalent to a neurologic symptom lasting for > 24 h, which occurs at least 30 days after the onset of a preceding event. ARR is computed as the number of relapses divided by the time in years (days). Post-treatment ARR was contrasted with pre-treatment ARR.<sup>38</sup>

#### 2.1.4.2 Secondary outcomes

- (1) The frequency and extent of AEs: During treatment and follow-up periods, any symptomatic events which had a possible, probable or definite causal relationship to MMF treatment were defined as AEs.
- (2) Relapse-free rate: The absence of relapse during the observation period of the study reported as percentage per study.<sup>35</sup>
- (3) Best-corrected visual acuity (BCVA): BCVA was measured using a standardized test, such as the ETDRS chart, Snellen chart or similar method, and other visual acuity measures would be allowed if findings could be justified as well as validated concerning accepted relevant standard measures. Outcome measured was the mean change of BCVA from before and after MMF treatment.<sup>39</sup>
- (4) Time to the next attack.

#### 2.1.4.3 Security index

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3  
4 The safety was assessed by the occurrence of AEs. Any unexpected events that occurred  
5 during the studies will be recorded on an AEs report form, including:<sup>28</sup>  
6

- 7 (1) General physical examination (temperature, pulse, respiration, blood pressure).  
8  
9 (2) Routine examination of blood, urine and stool.  
10  
11 (3) Liver and kidney function examination.  
12  
13 (4) Gastrointestinal discomfort.  
14  
15 (5) Hair loss or Alopecia.  
16  
17 (6) Allergic or Anaphylactoid reactions.  
18  
19 (7) Drug discontinued due to drug-related AEs.  
20  
21 (8) Possible AEs and related detection indicators.  
22

## 23 **2.2 Search methods for the identification of studies**

### 24 **2.2.1 Electronic searches**

25  
26 A relevant literature search by sensitive search strategies was conducted using the  
27 following electronic databases from their inception to June 31, 2020: PubMed, Web of  
28 Science, EMBASE, the Cochrane Library, China National Knowledge Infrastructure  
29 (CNKI), Wanfang Database, China Science and Technology Journal database (VIP)  
30 and Chinese Biomedical Literature database (CBM). Search methods of MeSH terms  
31 with free words were applied in English databases. The related terms are as follows:  
32 Participants (neuromyelitis optica, neuromyelitis optica spectrum disorders, Devic  
33 Neuromyelitis Optica, Devic's Neuromyelitis Optica, Devic's Syndrome, NMO  
34 spectrum disorders), Intervention (mycophenolic acid, mycophenolate mofetil, “mofetil,  
35 mycophenolate”, cellcept, myfortic, RS61443). The search strategy for PubMed is  
36 described in Table 1, which will include all search terms, and other searches will be  
37 carried out based on those results. This will be suitably adapted to search in the other  
38 databases. There are no limits on language and publication status.  
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### 52 **2.2.2 Searching other resources**

53  
54 we will also search PROSPERO, the International Clinical Trials Registry Platform  
55 (ICTRP), ClinicalTrials.gov, dissertations, and gray literature to identify systematic  
56 reviews or clinical trials related to mycophenolate mofetil and neuromyelitis optica  
57 spectrum disorders. Manual searches will be conducted for related journals and  
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4 conference processes. We will also review papers and bibliographies included in the  
5 trials.  
6

## 7 **2.3 Data collection and analysis**

### 8 **2.3.1 Selection of studies**

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10  
11 Two reviewers (MYH and ZQL) will independently browse the titles and abstracts of  
12 all of the retrieved records to distinguish and exclude any irrelevant articles. Studies  
13 only related to human subjects are to be included. Any discord will be resolved by  
14 discussion between the two authors and an arbiter (MJ). The selection procedure for the  
15 study is shown in a PRISMA flow chart (Fig. 1).  
16  
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### 21 **2.3.2 Data extraction and management**

22  
23 Based on the inclusion criteria, a standard form of data collection will be produced prior  
24 to data extraction. Search results will be entered into an EndNote X9 database and  
25 duplicate entries removed. Two authors (MYH and ZQL) will extract the data of  
26 interest from the eligible study and enter the data extraction sheet as follows: The basic  
27 characteristics of each study (study design or methods, author, title, source/journal, time  
28 of publication, country, hospital setting); participants characteristics (average age,  
29 gender, sample size, inclusion and exclusion criteria, baseline situation); Interventions  
30 (type, duration, frequency and dosage of MMF, randomization, allocation concealment,  
31 blinding methods); Comparators (AZA, tacrolimus, cyclosporine, monoclonal  
32 antibodies, and placebo, etc); Outcomes (measures, main outcomes, security indexes,  
33 and follow up); If funded, it will also be recorded. When the consensus on data  
34 extraction is not available through discussion, the third reviewer (MJ) will make a  
35 decision.  
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### 48 **2.3.3 Assessment of risk of bias**

49  
50 Two authors (Yang Chen and LQN) will independently estimate the risk and bias using  
51 the Cochrane risk of bias (ROB) assessment tool for RCTs.<sup>40</sup> Methodological quality  
52 evaluation of the included observational studies will be carried out using the  
53 Newcastle–Ottawa Scale (NOS).<sup>41</sup> The RevMan software program (V.5.3) will  
54 document the selected details of each study.<sup>42</sup>  
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### **2.3.4 Measures of treatment effect**

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4 The risk ratio (RR) and 95% confidence interval (CI) will be used to analyze  
5 dichotomous data and calculate the treatment effect. A weighted mean difference  
6 (WMD) or a standard mean difference (SMD) with 95% CIs will be used to analyze  
7 continuous outcomes.  
8  
9

### 11 **2.3.5 Unit of analysis issue**

12  
13 We will only extract the 1st experimental period data of crossover trials to avoid  
14 carryover effects. In the meantime, given that there are multiple intervention groups in  
15 trials, we will combine all analogous groups into a single pairwise comparison to avoid  
16 a unit of analysis issue.  
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18

### 21 **2.3.6 Management of missing data**

22  
23 Reviewer (YLQ and You Chen) will contact the appropriate author of the included trials  
24 for clarification or more details via email and telephone if necessary. The missing data  
25 will be deleted, if there is no response from the author. That will be addressed in the  
26 discussion in this case. If quantitative data were not available, then the qualitative  
27 analysis should be used.  
28  
29

### 33 **2.3.7 Assessment of heterogeneity and data synthesis**

34  
35 We will use all of the case data for the analysis data. Heterogeneity will be tested with  
36 a standard Chisquare test.<sup>43</sup> To quantify the impact of the statistical heterogeneity on  
37 the systematic review, the  $I^2$  value will be applied to calculate and present the  
38 heterogeneity degree. If  $P > 0.1$ ,  $I^2 < 50\%$ , it is considered that there is no heterogeneity  
39 between the trials, and the model of fixed effect will be used, otherwise, the model of  
40 random effect will be adopted. All statistical analyzes will be performed using the  
41 RevMan5.3 software provided by the Cochrane Collaboration. Using the software to  
42 obtain forest plots and test the heterogeneity between the included studies. The Grades  
43 of Recommendation, Assessment, Development and Evaluation (GRADE) will be used  
44 to assess the meta-analysis findings and determine the quality of evidence. Where meta-  
45 analysis may not be not feasible due to lack of clinical trials or heterogeneity, systematic  
46 narrative synthesis will be adopted.  
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### 58 **2.3.8 Assessment of reporting biases**

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60 When 10 or more studies are included in a meta-analysis, we will evaluate funnel plot

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4 asymmetry for reporting biases and small-study effects using Egger's method.<sup>44</sup> For  
5 Egger's test, P value of greater than 0.05 was determined as no significant publishing  
6 bias or small-study effects in studies. As funnel plot asymmetry does not necessarily  
7 suggest reporting bias, we will attempt to recognize potential causes for the asymmetry,  
8 including poor methodological quality and true heterogeneity of studies.  
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### 13 **2.3.9 Subgroup analysis**

14  
15 Upon detection of heterogeneity, a subgroup analysis will be carried out to judge the  
16 source of heterogeneity. The criteria for a subgroup analysis are as follows:  
17

- 18 (1) Age.
- 19 (2) Type of MMF.
- 20 (3) Research type.
- 21 (4) Participation population.
- 22 (5) Type of control interventions.
- 23 (6) Intervention dosage, frequency and duration.
- 24 (7) AQP4-IgG serological status.

### 25 **2.3.10 Sensitivity analysis**

26  
27 The ROB tool will be used to estimate methodological quality in the case of sufficient  
28 data from trials. Sensitivity analysis will be performed to determine the robustness of  
29 aggregate estimates and to detect whether any single study accounts for a substantial  
30 proportion of heterogeneity by eliminating the included studies from the summary  
31 review one by one. If low-quality articles are deleted, then a second meta-analysis will  
32 be carried out. Comparison and discussion of the results and effect size of the two meta-  
33 analyses will be held.<sup>45</sup>  
34

35  
36 **2.4 Patient and public involvement** Patients and/or the public will not participate in  
37 the study. However, once scientific publications disseminate our findings, they are  
38 circulated across social networks so that our conclusions will affect the actions of  
39 neuro-ophthalmologists and health policymakers.  
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49 **2.5 Ethics and dissemination** Because the data used for this systematic review will be  
50 exclusively extracted from published studies, ethical approval and informed consent of  
51 patients will not be required. The systematic review will be published in a peer-  
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4 reviewed journal, presented at conferences and will be shared on social media platforms.  
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### 7 **3 Discussion**

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9 Pathogenesis, diagnosis and treatment of NMO are rapidly growing areas of research  
10 as AQP4-IgG were first identified. Patients with NMOSD should receive standardized  
11 and personalized immunotherapy as soon as possible, as any further acute episodes may  
12 result in severe and often irreversible disability. The challenges in discovering new and  
13 better drugs for NMO are the rareness of the disease and the unfavorable prognosis in  
14 many cases, which make clinical studies with placebo groups difficult.<sup>16</sup> Many studies  
15 have confirmed the efficacy and promising prospect of MMF in the treatment of  
16 NMOSD,<sup>21-24</sup> and only a few AEs were reported.<sup>21 22</sup> Additional studies have also  
17 indicated that MMF was more effective and triggered less AEs than AZA.<sup>25 26</sup> However,  
18 its therapeutic effect and safety remain controversial. Although there has been two  
19 published literature that is relevant to the topic of this study,<sup>27 28</sup> both of them have  
20 certain defects, and they can only provide answers about the efficacy or safety of MMF  
21 in the treatment of NMOSD from partial perspectives or conclusions. If our paper is  
22 completed, it will be a currently searchable protocol for a traditional meta-and  
23 systematic review that directly and synthetically evaluates the efficacy and safety of  
24 MMF in the treatment of NMOSD. One of the strengths of this protocol will use a  
25 comprehensive search strategy of published literature. The overall data used in each  
26 analysis will be evaluated qualitatively and quantitatively. The sources of heterogeneity  
27 and different subgroups of the articles will be analyzed to comprehensively evaluate  
28 the efficacy and safety of MMF in the treatment of NMOSD, and to increase the  
29 credibility of the article content and conclusions. We expect that this systematic review  
30 will benefit patients with NMOSD, physicians, health care administrators and policy-  
31 makers.  
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### 54 **Author contributions**

55  
56 MYH conceived and designed the protocol, and MYH drafted the protocol manuscript.  
57  
58 MYH developed the search strategy, with input from ZQL and LQN. MYH and ZQL  
59  
60

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4 planned data extraction. MYH, Yang Chen and ZJW planned the quality appraisal of  
5 all included studies. MYH, ZQL, LQN, Yang Chen, HM, You Chen, ZJW, YLQ and  
6 MJ critically revised the manuscript for methodological and intellectual content. All  
7 authors approved the final version.  
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13 **Conceptualization:** Meng-Yu Han, Zi-Qiang Liu, Zhi-Jun Wang, Ming Jin.

14 **Data curation:** Meng-Yu Han, Zi-Qiang Liu, Lu-Qi Nong, Huan Meng.

15 **Formal analysis:** Meng-Yu Han, Zi-Qiang Liu.

16 **Funding acquisition:** Meng-Yu Han.

17 **Investigation:** Ming Jin.

18 **Methodology:** Meng-Yu Han, Zi-Qiang Liu, Lu-Qi Nong, You Chen.

19 **Project administration:** Ming Jin.

20 **Resources:** Meng-Yu Han, Zi-Qiang Liu, Lu-Qi Nong, Ming Jin.

21 **Software:** Meng-Yu Han, Zi-Qiang Liu, Lu-Qi Nong.

22 **Supervision:** Meng-Yu Han, Zhi-Jun Wang, Ming Jin.

23 **Validation:** Huan Meng, Yang Chen, Ya-li Qin, Ming Jin.

24 **Visualization:** Huan Meng, Yang Chen, Ya-li Qin, Ming Jin.

25 **Writing – original draft:** Meng-Yu Han, Zi-Qiang Liu, Lu-Qi Nong, Ming Jin.

26 **Writing – review & editing:** Meng-Yu Han, Zi-Qiang Liu, Lu-Qi Nong, Ming Jin.

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35 study.  
36

37 **Competing interests:** None declared.  
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Table 1 Search strategy used in PubMed database.

Number	Search terms
#1	("Neuromyelitis Optica"[Mesh]) OR (((((neuromyelitis optica spectrum disorders [Title/Abstract]) OR Devic Neuromyelitis Optica [Title/Abstract]) OR Devic's Neuromyelitis Optica [Title/Abstract]) OR Devic's Syndrome [Title/Abstract]) OR NMO spectrum disorders

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	[Title/Abstract])
#2	("Mycophenolic Acid"[Mesh]) OR (((((Mycophenolate Mofetil [Title/Abstract]) OR "Mofetil,Mycophenolate" [Title/Abstract]) OR Cellcept [Title/Abstract]) OR Myfortic [Title/Abstract]) OR RS61443 [Title/Abstract])
#3	#1 and #2

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Figure1. The PRISMA flow chart of the selection process.

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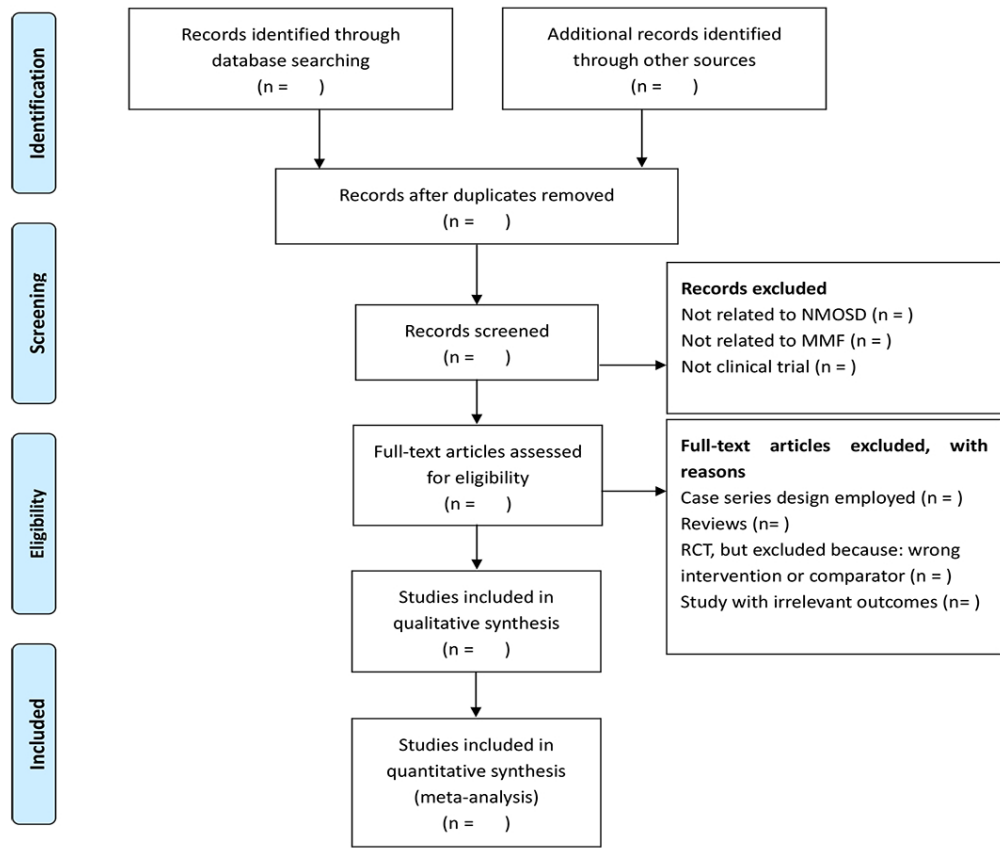


Figure1. The PRISMA flow chart of the selection process.

# Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

			Page
		Reporting Item	Number
<b>Title</b>			
Identification	<a href="#">#1a</a>	Identify the report as a protocol of a systematic review	Page 1
Update	<a href="#">#1b</a>	If the protocol is for an update of a previous systematic review, identify as such	

## 1 Registration

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4 [#2](#) If registered, provide the name of the registry (such as Page 2  
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6 PROSPERO) and registration number  
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## 9 Authors

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13 Contact [#3a](#) Provide name, institutional affiliation, e-mail address of all Page 1  
14  
15 protocol authors; provide physical mailing address of  
16  
17 corresponding author  
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19  
20 Contribution [#3b](#) Describe contributions of protocol authors and identify the Page1,11,12  
21  
22 guarantor of the review  
23  
24

## 25 Amendments

26  
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29 [#4](#) If the protocol represents an amendment of a previously  
30  
31 completed or published protocol, identify as such and list  
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33 changes; otherwise, state plan for documenting important  
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35 protocol amendments  
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## 38 Support

39  
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42 Sources [#5a](#) Indicate sources of financial or other support for the review Page 12  
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45 Sponsor [#5b](#) Provide name for the review funder and / or sponsor Page 12  
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48 Role of sponsor or [#5c](#) Describe roles of funder(s), sponsor(s), and / or Page 12  
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50 funder institution(s), if any, in developing the protocol  
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## 53 Introduction

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56 Rationale [#6](#) Describe the rationale for the review in the context of what Page 2,3,4,5  
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1		is already known	
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4	Objectives	<a href="#">#7</a> Provide an explicit statement of the question(s) the review	Page 5,6,7
5		will address with reference to participants, interventions,	
6		comparators, and outcomes (PICO)	
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11	<b>Methods</b>		
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14	Eligibility criteria	<a href="#">#8</a> Specify the study characteristics (such as PICO, study	Page 7,8
15		design, setting, time frame) and report characteristics	
16		(such as years considered, language, publication status) to	
17		be used as criteria for eligibility for the review	
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24	Information	<a href="#">#9</a> Describe all intended information sources (such as	Page 7,8
25		electronic databases, contact with study authors, trial	
26	sources	registers or other grey literature sources) with planned	
27		dates of coverage	
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34	Search strategy	<a href="#">#10</a> Present draft of search strategy to be used for at least one	Page 7
35		electronic database, including planned limits, such that it	
36		could be repeated	
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41	Study records -	<a href="#">#11a</a> Describe the mechanism(s) that will be used to manage	Page 8
42		records and data throughout the review	
43	data management		
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47	Study records -	<a href="#">#11b</a> State the process that will be used for selecting studies	Page 8
48		(such as two independent reviewers) through each phase	
49	selection process	of the review (that is, screening, eligibility and inclusion in	
50		meta-analysis)	
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57	Study records -	<a href="#">#11c</a> Describe planned method of extracting data from reports	Page 8,9
58			
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1	data collection		(such as piloting forms, done independently, in duplicate),	
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3	process		any processes for obtaining and confirming data from	
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5			investigators	
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8	Data items	<a href="#">#12</a>	List and define all variables for which data will be sought	Page 8
9				
10			(such as PICO items, funding sources), any pre-planned	
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12			data assumptions and simplifications	
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15	Outcomes and	<a href="#">#13</a>	List and define all outcomes for which data will be sought,	Page 6,7
16				
17	prioritization		including prioritization of main and additional outcomes,	
18				
19			with rationale	
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22				
23	Risk of bias in	<a href="#">#14</a>	Describe anticipated methods for assessing risk of bias of	Page 8
24				
25	individual studies		individual studies, including whether this will be done at	
26				
27			the outcome or study level, or both; state how this	
28				
29			information will be used in data synthesis	
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33	Data synthesis	<a href="#">#15a</a>	Describe criteria under which study data will be	Page 9
34				
35			quantitatively synthesised	
36				
37				
38	Data synthesis	<a href="#">#15b</a>	If data are appropriate for quantitative synthesis, describe	Page 9
39				
40			planned summary measures, methods of handling data	
41				
42			and methods of combining data from studies, including any	
43				
44			planned exploration of consistency (such as I <sup>2</sup> , Kendall's	
45				
46			τ)	
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49				
50	Data synthesis	<a href="#">#15c</a>	Describe any proposed additional analyses (such as	Page 9,10
51				
52			sensitivity or subgroup analyses, meta-regression)	
53				
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56	Data synthesis	<a href="#">#15d</a>	If quantitative synthesis is not appropriate, describe the	Page 9
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1 type of summary planned

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3  
4 Meta-bias(es) [#16](#) Specify any planned assessment of meta-bias(es) (such Page 8,9,10  
5 as publication bias across studies, selective reporting  
6 within studies)  
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11 Confidence in [#17](#) Describe how the strength of the body of evidence will be Page 9  
12 cumulative assessed (such as GRADE)  
13 evidence  
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18 None The PRISMA-P checklist is distributed under the terms of the Creative Commons Attribution  
19 License CC-BY 4.0. This checklist can be completed online using <https://www.goodreports.org/>, a tool  
20 made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)  
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