Optimum clinical pathway: neurological auto-immune diseases

December 2019

Executive summary

This best care pathway for patients with non-MS neurological immune disease was designed by a working group of neuroimmunology specialist clinicians and a charity representative (see Appendix 4 for group membership) as part of an NHS England Specialised neurology programme of work.

The pathway aims to improve the diagnostic process and ensure patients are managed appropriately, with an integrated service between different levels of specialised and local care both within and outside neurology.

The document emphasises the need for the following to ensure the right care, at the right place, at the right time: 1) optimising management across systems and specialties through timely input delivered within a multidisciplinary clinic setting; 2) reducing variation in patient care and quality; and 3) increasing the rate of patients obtaining an accurate diagnosis and treatment in a timely manner, followed by entry into the correct treatment pathway.

With the recent expansion of immunomodulatory drugs, with specificities for different immune pathogenic mechanisms, the level of knowledge required to ensure an accurate diagnosis for each disease has risen. Patients with neurological auto-immune diseases should have appropriate and rapid access to specialists, in order to get the correct diagnosis and thus appropriate treatment and safe monitoring with as much care delivered locally by good shared care models.

For rare neuro-immunological diseases, concentrating patients into fewer specialised centres and strengthening the networks between centres may strengthen the evidence base of treatments for these patients, make studies more cost effective and robust, and create the potential to compare cheaper generic versions of drugs against expensive licensed drugs. Additionally, there is a role for specialist panels to improve access to new therapies when these are required.

The document outlines the current barriers to the best patient care, and identifies potential opportunities to a system that arise from reducing misdiagnosis rates and suboptimal treatment (see Appendix 2 for some examples).

These guidelines are aimed at achieving the best care in the most patients.

Context

There is a wide spectrum of multisystem neurological auto-immune disorders, with a great deal of immunomodulatory drugs with specificities for different conditions. As such, knowledge required to treat conditions is great and the diagnosis must be exact to deliver the correct care. There is evidence of wide variation in whether this activity is picked up by specialised centres, both across conditions and across CCGs for all conditions. There is also evidence that the service is at capacity. The activity growth and increasing costs may be contributed to by inappropriate management and increasing lengths of stay and complexity and an aging population.

Neuroimmunology patients require support from a wide range of services. In addition to general and specialist neurologists, patients with neurological auto-immune diseases are seen by a range of healthcare professionals, including other specialists such as dermatologists, rheumatologists, nephrologists and chest physicians (in the case of multisystem disorders) and general practitioners (in the case of chronic care) – often with little support and advice on management of rare conditions. This can lead to variation in patient care and quality, including getting an accurate diagnosis in a timely manner and entering the correct treatment pathway.

This information pack is the output of the Neurological Auto-Immune Diseases Clinical Working group's efforts to define an optimum pathway for patients with neurological immune disease. The guidance outlines:

- The "optimum" pathway for patients with neurological auto-immune diseases, from first neurological symptoms to ongoing management.
- The definition of "specialised" neuroimmunology care.
- Efficiencies and improved outcomes.
- Barriers and potential solutions around patient flow and investigation cost, access to new therapies, research and clinical trials and diagnostic tests.

Disease groups

PN

1. Guillain-Barré syndrome
2. Fisher Syndrome
3. Atypical Variants
4. Acute autonomic neuropathy (N P AChR associated and others)
5. Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
6. Multifocal motor neuropathy (MMN)
7. MADSAM (Lewis Sumner syndrome
8. Other CIDP-like disorders
9. Idiopathic Lumbosacral plexopathy
10. Diabetic Lumbosacral plexopathy
11. Brachial neuritis
12. Vasculitis of the peripheral nervous system
    a. SLE/RhA/Sjogren related
    b. Primary vasculitis – WGN, CSS, PAN
    c. Isolated peripheral nerve vasculitis
    d. Cryoglobulinaemic vasculiatis
    e. Post infectious vasculitis
    f. Drug induced vasculitis
13. IgM paraprotein-associated demyelinating neuropathy (2-5 included in a rituximab policy link below)
    a. Anti-MAG
    b. Antiganglioside (including CANOMAD)
    c. WM associated
    d. Cryoglobulinaemic
    e. Cold agglutinin
14. IgG and IgA associated demyelinating neuropathy
15. POEMS syndrome
16. Paraneoplastic neuropathies
17. Small fibre neuropathy
18. Some infectious and parapinfectoous neuropathies (Lyme, virus, Chaga, Leprosy – which may fall under infection or inflammation)

Inflammatory myopathies

1 dermatomyositis
2 polymyositis
3 anti-synthetase syndrome
4 immune-mediated necrotising myopathy
5 overlap myositis
6 sporadic inclusion body myositis

NMJ MG LEMS

CNS Ab

1. Autoimmune encephalitis
   VGKC (LGI1/CASPR2) NMDAR Glycine GABA AMPA ..
1. ADEM/AHEM (overlap w MOG)
2. Relapsing Optic Neuritis
3. GAD associated disease – ataxia and epilepsies (overlap stiff person)
4. Paraneoplastic nervous system disorders
   a. Opsoclonus myoclonus
   b. Cerebellar degeneration
   c. Limbic encephalitis
   d. NM diseases as above
5. Stiff person syndrome (SPS)/Stiff limb syndrome/Jerking stiff person/Progressive Encephalomyelitis with Rigidity
6. PANDAS
7. GFAP syndromes
8 **Transverse myelitis**

CNS non Ab

Vasculitis: PACNS
2ndry vasculitis
Associated with CAA
Large vessel systemic vasculitis (e.g. GCA, Takayasu)
Inflammatory meningoencephalitis
Sarcoid
Behcet
IgG4
Histiocytoses: LCH, ECD, RDD
Susac, Cogan, VKH
Related to systemic inflammmatory disease
(e.g. IBD, Coeliac, CT disease)
complications of immunotherapy
Less clearly classified inflammatory conditions:
SSPE, Erythema nodosum leprosum, Sydenhams chorea,
Rassmussens encephalitis (paediatric),

SUPRA-RGIONAL SERVICE ** LEVEL 3 OP/IP 'OCCASIONALLY'

DIAGNOSIS AND MANAGEMENT (2,3)
- Very rare conditions (e.g. PERM, POEMS, stiff person syndrome resistant auto-immune encephalitis, paraneoplastic conditions)
- Diagnostic challenges
- Patients needing considering experimental treatment (e.g. BMT, clinical trials, other new high cost treatments limited by NHS England)

Specialist team including disease **specialised nurses (6)** & other MDT members
Diagnosis
Management
Education of patients and HCP (4)
Remote advice MDT meetings (4)

Specialist Centre ** eg at regional centre LEVEL 2 OP/IP 'OFTEN'

DIAGNOSIS (3)
- Diagnosis better assessed/ managed by a specialist (see table)
- Diagnosis needing specialised investigations (e.g. nerve or brain biopsy, complex neurophysiology)
- To access specialised health care team for educational/ management
- to access treatment only available at centre

management plan

MANAGEMENT (2,3)
- Disease responds
- Treatment does not requires high cost drugs or high risk drugs? or
- No benefit to patient of ongoing specialised team input (eg physio, OT nurse) or
- Acute illness now resolved

Neurology nurse (6)

No

Yes – shared care while satisfy referral criteria w level 2 and/or level 1 teams

ONGOING SPECIALITY CARE (4)
- Diagnostic or management problems or
- Very rare disorder or
- Suitable for NHS England restricted or experimental treatments or
- Benefit for other services offered in supra-regional services

Remote advice meetings (4)

Yes - discharge back

No - refer to centre

shared care w local neurology (and/or GP)

No - refer to centre

Local Neurology Service LEVEL 1 OP/IP 'ALWAYS'

DIAGNOSIS AND MANAGEMENT
- Definite diagnosis with good response to first line therapy +

AND NOT
- requiring treatment only available specialised centre +
- requiring specialised prescribing) +
- benefit to patient to have input from specialised health care workers (specialist nurses, OT Physio or doctors)
- rare disorder (see Table for examples)
- a condition better assessed by a specialist (see table)

Yes

MANAGEMENT LOCALLY
- Acute condition resolves or
- Chronic condition good response treatment +
- No benefits of specialised service team to patient

Neurology nurse (6)

Acute IP referrals Or A&E access

Yes shared care w GP or discharge

Other crucial service interactions

other neuroscience specialities level 2/3) e.g. neuro: surgery, radiology, physiology direct and remote

Other overlapping specialities all three levels of service for multisystem diseases
e.g. haematology
respiratory
ophthalmology
rheumatology etc.

Neuroreabilitation units (level 2/3) (5)
Local rehabilitation units

Mental health teams
Specialist units (level 2/3) (5)
Local teams

Paediatric transition services (level 2/3)

GP and community team

GP assessment - refer to local neurology service (ensure referral guidelines cover these patients)

GP prescribing for conventional oral immunosuppressive therapies and blood /safety monitoring (1) shared care

Community care for disability

Patient

First neurological symptoms

Pathway

(1) Shared care protocols

The creation and use of shared care protocols will minimise patient travel for blood tests and prescriptions. If developed at a **national level**, it would provide consistency across different GP and hospital practices, and safe movement of patients across practices.

For example, protocols for mycophenolate, azathioprine, cyclophosphamide and ritixumab are currently produced by individual local services leading to unnecessary duplication of work and varied prescribing (some GPs in some areas don't prescribe or don't do blood tests, in other areas or practices they do). Where shared care protocols do exist they are only between a local trust and local GPs.

(2) Data collection

Depending on the drugs prescribed and whether at level 2 or 3, registries and data collection should be included where possible. Data on numbers of patients, numbers prescribed and simple outcomes (either specific and validated for disease, e.g. as advised for IVIG prescribing, or generic, such as Rankin scores or simple quality of life outcomes) will allow predictions for future prescribing, identify centres markedly outside the norm, and allow auditing of effectiveness, severe side effects and cost effectiveness calculations.

(3) Areas of specialist input

The pathway should reduce overall costs and harm to patients by means of:

- accurate and early diagnosis, reducing unnecessary tests;
- early and appropriate treatment – while reducing use of wrong treatments, morbidity and disability;
- access to MDTs to improve QOL and maximise function;
- allow for dissemination of knowledge to local health care workers; and
- spread knowledge to patients and GPs by educational materials to improve adherence and reduce wastage.

Pathway

(4) Services that can be offered locally to reduce need for patients to travel

a) PLEX could be offered locally, such as using mobile blood transfusion services, or renal and haematological services. This would benefit patients and visitors and free up resources and beds, as inpatient beds can be held for up to 24 hours awaiting patient arrival.

b) Telephone/teleconference consultation can be offered for stable patients that don't need examination by a specialist.

c) Consideration for travelling clinics where enough patients exist locally (convenient for patient and spreads knowledge locally).

d) 'MDT advice meetings' from specialised (level 2) and supra-specialised (level 3) levels to local teams to deliver care locally wherever possible and 'educational activity / information/ outreach sessions' for local teams and GPs.

(5) Linked services

Patients with disabilities have complex mental health and rehabilitation needs and those with brain diseases may have cognitive impairment and behavioural changes. Specialist assessments for these needs are required in the level 2/3 services and then linked into local more generic mental health and rehabilitation teams. Currently IP services in some areas will only accept patients with a narrow range of disabilities (eg wont accept patients with only 2-3 disability needs, or wont accept those with complex disabilities). Adequate services at all levels will reduce disability in the community, save social and healthcare usage and improve QOL for patients and carers.

(6) Nurse specialists

Neurology nurses and specialist nurses link into multiple levels of care and people, including patients, relatives, GPs and local and regional hospitals. It is most likely that nurses outside of supra-regional units will be neurology nurses covering a range of similar diseases, or become immune drug specialists organising screening, administration and safe monitoring.

Proposed levels of neurology service

- **Level 3** does not officially exist within the current NHS provider landscape in England, although supra-specialist neurologists (as recognised by their peers and international and national reputations) operate as tertiary referral clinicians currently. However, this often occurs on an ad-hoc and inequitable basis. Designated level 3 services would improve patient care and prevent harm and inefficiencies.

- **Level 2** refers to a neurology service with specialist expertise in the area of the disease (usually in specialised neuroscience centre but not exclusively), that usually will have access to other specialist health care workers, other neuroscience specialities, specialised investigations and non-neuroscience services.

  These will include clinicians running peripheral nerve, or muscle, or myasthenia or Inflammatory CNS clinics (some may be MS experts).

- **Level 1** refers to the local general neurology service, which may be located in a district general hospital or a teaching hospital (the latter may or may not be a designated neuroscience specialised centre, see Appendix 3). This also includes local support services including rehabilitation, disability and psychology.

Levels of service: *Keeping care as local as possible with access to specialist input when required*

Level 1: Local general neurology care

The level of expertise and support in local general neurology services can be varied, for example some district general hospitals have no neurology beds, little access to neurology investigations, and may not have access to daily neurology consultation. This can be addressed in various ways:

- Monophasic conditions that are admitted can often be adequately managed by general medical teams with neurology guidance, for examples GBS, monophasic encephalopathies or antibody negative ADEM.
- Where patients are not admitted as an acute medical admission, all out-patient referrals should be to the local neurologist. However, some conditions may be cared for by other specialities (for example temporal arteritis (TA) may be managed by rheumatology, single attacks of optic neuritis (ON) assessed and investigated by ophthalmology, multi-system disorders may already be under other specialities).
- For longer-term conditions where the general neurologist may not have high levels of expertise across all neurological diseases, patients may best be referred initially to and assessed by the specialist service, and the management pathway outlined.
- MRI or neurophysiology (or access to expertise in interpreting / reporting these investigations in this clinical context) may not be available in the local hospital, and may often need to be performed at a neuroscience centre. Additionally, specialist nurses and the services that they typically offer, including patient education, may only be situated in the specialised centre.
- Some general neurologist may have experience with first line management of neurological inflammatory conditions and can treat some chronic conditions, such as treatment responsive CIDP, ocular MG, late onset antibody positive mild generalised MG managing on pyridostigmine, and neuromyotonia not requiring immunotherapy.
- Good local support services for patients with neurological immune diseases should be available. This applies whether the patient is managed locally or where specialised services at level 2 and 3 are sharing care.

Levels of service – *Keeping care as local as possible with access to specialist input when required*

Level 2: Specialised service

Patients should be referred to the specialised neuroscience centre where:

- there are diagnostic challenges;
- outcome is dependent on the rapid institution of appropriate immunotherapy;
- first line immunosuppression/ immunomodulators have failed; or
- access to specialised support is of benefit to the patient (for example, education and specialist MDT input).

Examples include

- seronegative myasthenia where diagnostic errors occur;
- Musk MG where treatment can be challenging;
- thymectomy for early onset AChR-Ab patients or MG patients with thymoma;
- antibody positive encephalopathies and chronic encephalopathic conditions;
- chronic non-antibody CNS inflammatory conditions;
- CIDP unresponsive to steroids;
- rapidly progressive neuropathies (amyloid, paraneoplastic, vasculitis etc.) that may need nerve biopsy;
- specialised imaging or other specialised investigation;
- neuropathies associated with haematological malignancy; and
- complex CMT requiring orthotic, orthopaedic or other specialist input.

Level 3: Supra-specialised services

Some neuroimmunology conditions are challenging for reasons such as:

- diagnostic difficulties (particularly because many are limited to the CNS with no distinct diagnostic markers);
- poor response to treatments
- requiring access to high risk or high cost immunotherapies or other treatment where there is limited expertise; or
- very rare conditions (which limit the assessment of optimal treatment strategies unless such patients, and thus expertise, are concentrated and data collected in a small number of centres.
- multiple system conditions which are best co-managed across specialities (eg POEMS, neurosarcoidosis,)

In addition, clinical trial recruitment would likely be more feasible within or through such services.

Specialised services will:

- require consultants with expertise in specific diseases above that of a general neurologist (rarer diseases will have fewer experts);
- require a team, especially at supra-regional levels, including specialist nurses, OTs, physiotherapists, psychologists, and non-neurology clinicians such as specialist neuro-radiology and neuropathology experts where appropriate;
- have the expertise to meet the needs of the population for a given geographical footprint; and
- have links into other services (rehab, psychiatry, other neuroscience services).

Referral criteria 'up' and 'down' levels

It was recognised there would be diversity of opinion amongst neurologists as to what should be referred. To maximise patient benefits, the working group designed the pathway assuming the level 1 neuroimmunology service was standard.

Selection for 'referral up' included disorders and situations

a. where access to a more specialist team or drug was advantage to the patient;
b. the diagnosis or management was challenging;
c. where members had experienced examples 'frequently' of misdiagnosis; or
d. thought about best care from a patient and family perspective.

The criteria on the following two slides are meant to provide examples, not a comprehensive list.

Referral criteria 'up' levels

Service level	General	Muscle	Peripheral nerve	NMJ	CNS-Ab disease	CNS non-Ab
Move 1-2	➢ Diagnostic uncertainty ➢ Patient needs specialised investigations ➢ Patient needs to access to specialist health care team for education/management (e.g. specialist nurses, rehab, etc) ➢ Patient needs to access treatments only available in level 2 centres ➢ There is a clinical trial in level 2 service ➢ Local neurology expertise in the disorder is limited	➢ All inflammatory myopathies	➢ Complex GBS requiring specialist ITU support for weaning ➢ CIDP unresponsive to steroids and IVIG ➢ Rapidly progressive neuropathies (amyloid, paraneoplastic, vasculitis, etc.) that may need nerve biopsy ➢ Specialised imaging or other specialised investigation ➢ Neuropathies associated with haematological malignancy ➢ Complex CMT requiring orthotic, orthopaedic or other specialist input ➢ Suspected motor neurone disease/MMNCB requiring second opinion with or without MDT advice ➢ Consideration of sensory nerve biopsies for any cause	➢ Ab-Negative MG for confirmation of diagnosis ➢ MUSK-Ab positive ➢ MG not responding to pyridostigmine and first line IS (IS may be better instituted in level 2) ➢ Thymectomy to be considered ➢ Referral to 'approved' thymectomy surgeon with shared neurology MG care (may not be available in all level 2 units, at which point refer to level 3)	➢ Ab-mediated CNS diseases where diagnosis is unclear ➢ Ab-CNS diseases not responding to first line treatment ➢ NMDRAR-Ab Ab-+ve encephalopathy/brain stem/spinal cord syndrome ➢ Ab-negative encephalopathy/ brainstem/spinal cord not resolving with corticosteroids ➢ NMOSD	➢ Neurobehcet's - refer directly to existing national centres ➢ Any undiagnosed/unconfirmed non monophasic inflammatory CNS disease (e.g neurosarcoidosis, histiocytosis, vasculitis,ateritis, paraneoplastic disorders)
Move 2-3	➢ There is a clinical trial in level 3 service ➢ Patient requires unlicensed new or expensive or high risk therapy (including BMT) ➢ Very rare syndromes ➢ Diagnostic challenges not resolved at level 2 ➢ Access to specialised teams not available at level 2	➢ Refractory to ongoing therapy, for consideration of experimental treatment	➢ POEMS or suspected syndrome (work-up and AHSCT) ➢ Relapsed or progressive Waldenström's macroglobulinaemia needing specialist haematology ➢ Progressive brachial plexopathies for imaging and biopsy ➢ CMT or other hereditary neuropathy patients being considered for genetic Rx trials ➢ Patients suitable for high cost drugs or drugs only available through limited centres	➢ Referral for drugs not available except through limited centres (could operate via an MDT arrangement) ➢ Consideration of thymectomy for non-thymoma cases: ▪ for AChRab negative MG patients ▪ those above age of 50 ▪ all cases via MDT ➢ Patient unresponsive to treatment or diagnosis not secure	➢ 4-5 ➢ Very rare ab-disorders such as glycine receptor ab disease ➢ Ab encephalopathy/brain stem/spinal cord syndromes resistant to treatment ➢ Diagnostic uncertainty of potential Ab related CNS syndrome ➢ NMOSD	➢ 4-5 ; ➢ NeuroBechets ➢ Neurosarcoidosis needing biologics ➢ Complex CNS Vasculitis (any subtype including Susac's syndrome) needing biologics ➢ Takaysau arteritis ➢ Histiocytosis ➢ IgG4 disease ➢ Undiagnosed progressive/treatment refractory CNS inflammatory disease

Referral criteria 'down' levels

Service level	General	Muscle	Peripheral nerve	NMJ	CNS-Ab disease	CNS non-Ab
Move 3-2 or 3-1	➢ Shared care agreements between level 3 and levels 2-1 ➢ Resolution of disease, treatment complete and stable with local expertise resolved ➢ Diagnosis established or gone as far as possible ➢ Treatments initiated, and local expertise is suitable, or supra-specialised centre too far to travel or unnecessary for treatment (consider outreach clinics)	➢ Completion of experimental therapy	➢ Completion of experimental therapy ➢ Diagnosis from level 3 with local management possible and recommended	➢ Thymectomy performed ➢ Successful initiation of rituximab and long-term management now required	➢ Monophasic condition resolved or stable, and condition is chronic, and level 3 team support teams not benefitting patient	
Move 2-1	➢ Resolution of disease ➢ Diagnosis established and treatments initiated, and local expertise is suitable ➢ Specialised centre too far to travel or unnecessary for treatment ➢ Shared care agreements between level 2 and level 1	➢ Disease in remission for at least 12 months and/or no specialist supportive management including AHP support required. Anticipate on-going liaison between level 1 and level 2 until complete remission achieved (no therapy for >12 months) and for sIBM patients as required for worsening bulbar and respiratory function.	➢ Completion of assessment or management at level 2 ➢ Hub and spoke model for ongoing care ➢ ITU step down to local rehabilitation services in GBS	➢ Diagnosis of sero-ve MG confirmed. Mild to moderate disease requiring treatment. ➢ Management plan established in 'IS non-responsive' patients	➢ Monophasic condition now resolved ➢ Shared care when stable, or telemedicine available (where local support services are as beneficial as specialised level 2 MDT care team)	
Stay level 1	➢ Monophasic resolving conditions where no/low risk relapse ➢ Local neurologist has expertise in the disease	➢ Unable to achieve complete remission and patient remains on long-term immunosuppression which can be managed locally. Level 2 support services may still input where required, through shared care or telemedicine ➢ sIBM patients long term monitoring of bulbar and respiratory function	➢ Uncomplicated GBS ➢ CIDP responsive to steroids or in remission – review for relapse	➢ Mild antibody positive ocular MG resolving with pyridostigmine	➢ Disease is responsive to monophasic steroid/PLEX/IVIG (some ab positive conditions with risk or relapse may need referral into level 2 out-patient services) ➢ Neuromyotonia not requiring immunotherapy	➢ Monophasic disease that is steroid/PLEX/IVIG responsive (e.g. seronegative long transverse myelitis) ➢ Multisystem sarcoidosis with mild CNS involvement, e.g. 6th nerve palsy

Barriers

Barriers	
Threats to local neurologists' expertise and autonomy'.	Shared care and respectful approach.
Limited recognition in job plans of the service requirement for such patients	A published concensus best patient pathway would give support to adequate services being resourced
The patchy availability of neuro-immunology expertise	With specialised services can Include in speciality training
Difficulties for patients with disabilities or limited funds to travel to centres.	Implementing telephone consultations, remote MDT skype meetings and remote advice where appropriate. Setting up level 3 services in spaced geographical locations
Confusion by the local teams as to when, where and to whom to refer, and lack of recognition of diagnostic risk/errors.	Allocating responsibility to the regional/specialised service for setting up guidance, education and advice to the local linking services.

Resource requirements

- Current resources focus on local targets, and particularly those that carry financial penalties, such as waiting times for out-patient services.
- Patients with neurological auto-immune diseases require longer consultation, which creates a greater cost.
- Referring into 2nd and 3rd level services for a multi-disciplinary team relies on clinical resources.
- Resources are needed in other good practice parts of the pathway, such as for remote telephone clinics, MDT advice meetings, and educational activities. Additionally IT support to enable remote consultation will be required.

Current out-patient tariffs are similar for complex neuro-immunological problems and benign neurological diseases. For example, tariffs are the same for migraine headache patients requiring no or limited investigations, and a multisystem disease such as probable sarcoidosis with brain involvement, requiring more extensive investigation, lengthy counselling of treatment risks and benefits and long-term safety monitoring

System efficiencies

The best patient care requires prompt accurate diagnosis and optimised treatment to reduce disability in neurological auto-immune diseases.

Impact of diagnostic errors and delays to the patient and system (see appendix 1)

The increasing array of specific and targeted immunotherapies for the different diseases means local services are at increasing risk of selecting inappropriate treatments, which may be associated with unnecessary risk and side effects.

- inappropriate and costly investigations,
- wasted inappropriate treatment, and
- worsened outcomes including disability and death
- potential litigation costs

Examples include the commonly delayed diagnoses of central nervous system vasculitis, neurosarcoidosis, and inappropriate, expensive and harmful immunosuppressive treatment of inclusion body myositis or inherited myopathies.

An audit at the NHNNS showed that 54% of POEMS patients were misdiagnosed as CIDP with median time to diagnosis of 11 months, with a maximum of 77 months. Most have received between 1 and 6 courses of IVIG (£5000 per course) and most have developed some irreversible disability. Lenolidamide and dexamethasone or autologous stem cell transplantation is curative.

Potential solution

By allowing the development of specialised and supra-specialised services

- Reduce diagnostic errors
- Quicker appropriate treatment
- Concentrate patients to increase experience in rare diseases
- Easier to set up set up managed entry agreements with pharmaceutical companies.
- Recruit into RCTs and investigator led studies
- To set up guidelines to then share and improve local knowledge and care
- Could set up neuro-immunology panels to replace IFR for these conditions instead of IFR would give a more informed decision and eliminate inequality across England.

Case study

An example is the managed use of rituximab by the United Kingdom Neuromyelitis Optica service (ABN 2019 Edinburgh). Redosing with Rituximab only when B cell counts rise rather than fixed 6 monthly dosing (without measuring B cells) has led to reduced costs, reduced risks of complications, improved patient convenience and better clinical outcomes.

Access to clinical trials

The neurological auto-immune disease clinical working group suggests the following to address barriers to research and clinical trials:

Barrier	Potential solution
RCT in rare conditions are extremely difficult to recruit for (eg Susacs). Recruiting larger numbers of patients at a few sites is more cost effective for pharma and the site. Funding for investigator led studies eg generic cheap drugs versus expensive licensed drugs difficult to obtain	By concentrating patients into specialised centres, and through networks with local Specialised services may have better support to apply for funding. Consider other funding platforms Setting up observational studies with good prospective outcome data /registries in specialised centres

Diagnostic antibody tests

An important aspect of treating neurological auto-immune diseases is diagnostic antibody tests. The choice of the individual assay is crucial.

Knowledge of sensitivity, specificity and PPV for each test crucial in interpretation. The most accurate tests should be performed and tested in patients with a high test prior probability.

While some assays are quick and easy to do, they may be less accurate than other more time consuming, but accurate assays. The relevance of test results is not understood by non-experts for some assays.

Likewise, the ability to interpret complex immunological profiles with paraproteins and VEGF and peripheral nerve relevant serum antibodies is very specialised. Access to laboratory services and the use of cheaper, low accuracy tests, could lead to misdiagnosis and hence incorrect patients receiving immunosuppressant, treatable conditions being missed and higher rates of morbidity and mortality as a result.

- **Neuroimmunology tests should be conducted in laboratories experienced in neuroimmunology assays with connections to clinicians experienced in their interpretation.**

Appendix 1. Case studies that demonstrate the advantages to patients of having expert neurological inflammatory 'supra-specialist' services

Misdiagnosis and miscommunication A 40-50 year old patient without an initial history typical of myasthenia gravis (MG) developed symptoms of the condition. Patient was seen by a GP, advised that they had the condition and referred to an MG centre. The patient was assumed to have investigation negative (except for mild jitter on neurophysiology testing) MG and had a thymectomy and immunosuppressed over 5 years without improvement. When the patient was assessed there were clear signs of functional hemi facial contraction and variable weakness, a history of onset during a time of severe stress and completely normal investigations. The diagnosis by an MG expert was of functional illness with no evidence of ever having MG.

Misdiagnosis- Primary psychiatric disease mistaken as Autoimmune encephalitis: A young person developed pure psychiatric disease over the course of many months; incidentally, she was found positive for NMDAR antibodies at low levels. This was thought to be pathogenic and she was recommended immunotherapy by an MS neurologist. On review by a specialist centre, this was thought to be unrelated and psychiatric treatment and firm reassurance was given. Follow up at 5 years, she remained well and had completed education and was in a relationship.

Diagnostics - false positives An AChR ab test was not replicated when the sample was retested in another more experienced lab, resulting in a change in diagnosis from chronic fatigue syndrome to MG and the patient also undergoing thymectomy and immunosuppression. The initial response then wore off and neurophysiology remained normal throughout and all subsequent antibody tests were negative. The MG expert again concluded the diagnosis of MG was not likely.

Managing Takayasu disease with the help of a specialist service: A person was diagnosed with Takayasu arteritis in a regional centre. As a rare condition (with neurologic, immunologic and stroke related risks), the local neurologist appreciated the complexities and referred her early to a specialised centre where she was started on biologics. She has remained well for 5 years and is under the joint care of both centres.

Misdiagnosis- Neurosarcoid misdiagnosed as TB: A middle aged person from a developing nation presented to a DGH with seizures and was found to have multiple lung and brain lesions. TB or sarcoidosis was thought to be the two possible diagnoses. All tests for TB were negative. He improved with steroids. But biopsy results showed it was atypical for sarcoid. Hence TB was deemed to be the diagnosis and he received a year of TB treatment. However he continued to have seizures and MRI showed worsening brain lesions. A specialist centre with expertise in this area revised the diagnosis to sarcoidosis and started on sarcoid treatment leading to improvement.

Functional disease v s Opsoclonus myoclonus syndrome: A young person had a 15 year diagnosis of opsoclonus-myoclonus syndrome (diagnosed as a child) without any relevant antibodies. The local team doubted the diagnosis and felt that it was psychologically mediated. However the patient resisted the idea of a psychological diagnosis. She was often treated with steroids and IVIG. She was referred from a tertiary centre to a more specialised centre where following thorough evaluations, a psychological – diagnosis (functional neurologic disease with personality disorder) was upheld. This helped the local team manage her symptoms better and more firmly avoiding harm.

Misdiagnosis- MOG antibody disease misdiagnosed as leukodystrophy: A patient had a demyelinating lesion in the brain as a child. She remained well until early adulthood when she developed a progressive neurologic disease thought to be cryptogenic leukodystrophy. No treatment was deemed possible. She was found to have MOG antibodies, which was thought to be irrelevant as MOG disease did not have a known progressive course. On review in a specialised centre, a consultant with expertise in MOG disease revised the diagnosis to MOG - antibody associated demyelination with a new progressive phenotype. The patient was treated with immunotherapy with improvement and stability.

Access to other therapies A 20-30 year old patient presented with a short psychiatric history, seizures, a movement disorder and subsequently obtundation and was referred to ITU intubated and ventilated. CSF was inflammatory and NMDAR antibodies were positive in the CSF and serum. She was found to have bilateral ovarian teratomas, which were surgically excised. Despite steroids, IVIG, plasma exchange, cyclophosphamide and rituximab she remained *in extremis* on ITU for 8 months. A decision was taken to administer Bortezomib to the patient. After 1 cycle the patient began to respond to command, after 2 she was discharged to the ward, after 3 cycles antibodies became negative and 4 months later she was discharged from hospital to normal life.

Appendix 2. Clinical working group membership

Name	Profession	Organisation
Jacqueline Palace	Workstream clinical lead, Consultant neurologist	Oxford University Hospitals
Anu Jacob	Consultant Neurologist	Walton Centre
Ashwin Pinto	Consultant Neurologist	Southampton
Caroline Morrice	Patient representative	CEO of GAIN
Desmond Kidd	Consultant Neurologist	Royal Free London
James Miller	Consultant Neurologist	Newcastle
Jon Sussman	Consultant Neurologist	Manchester University Hospitals
Michael Lunn	Consultant Neurologist	UCLH