Rare Neuromuscular Disorders Group

Congenital Myasthenic Syndromes:
Oxford University Hospitals NHS Foundation Trust

Annual Report October 2017

The Congenital Myasthenic Syndrome (CMS) service at The John Radcliffe Hospital combines a specialist genetic analysis laboratory with a dedicated inpatient (funded locally) and outpatient clinical service to offer a multidisciplinary service for patients across the country.

The core CMS team comprises of:

Clinical team

Dr Jackie Palace	Consultant Neurologist (Service Lead)
Dr Sandeep Jayawant	Consultant Paediatric Neurologist
Dr Sithara Ramdas	Consultant Paediatric Neurologist
Dr Stephanie Robb	Consultant Paediatric Neurologist (GOSH)
Dr Pinki Munot	Consultant Paediatric Neurologist (GOSH)
Dr Ravi Knight	Consultant Neurophysiologist
Dr Manon Lee	CMS Clinical Fellow
Birute Saul	CMS Service Co-Ordinator
Hayley Ramjattan	Neuromuscular Physiotherapist
Mary Quirke	Myasthenia Specialist Nurse
Julia Goodgame	Neurological Clinical Services Manager

Laboratory team

Weatherall Institute of Molecular Medicine

Prof David Beeson	Lead Molecular Geneticist
Dr Wei-Wei Liu	Molecular Geneticist
Dr Judy Cossins	Molecular Biologist
Dr Richard Webster	Post-Doc Electrophysiologist Medical Researcher
Ms Susan Maxwell	Research Assistant

Oxford University Hospitals Team

Dr Carolyn Campbell	Director of Genetics Laboratories
Dr Tracy Lester	Principal Clinical Scientist
Dr Mike Oldridge	Clinical Scientist

Service Overview

The service sees about 235 patients each year as outpatients and offers remote advice to Doctors, patients and their carers around the country regarding the diagnosis and management of CMS patients. The clinical team review patients primarily in an outpatient setting, often performing additional investigations, such as

QMG scores (Quantitative Myasthenia Gravis Score), pulmonary function testing (spirometry) and EMGs (Electromyogram).

Clinical Team:

Consultants: There are five Consultants in the service (four Paediatric Neurologists and one Adult Neurologist).

The Consultants share the clinical workload. This includes outpatient clinics, email/telephone advice, genetic reviews and inpatient reviews when necessary.

Clinical Training Fellow:
The Clinical Fellow's post is split between the NHS clinical service and the University laboratory service. During the three year post, the Clinical Fellow aims to obtain a higher degree aimed at furthering CMS diagnosis or treatment.

Molecular Genetics:
Professor Beeson in his role as the lead for the CMS genetics service provides valuable input into directing appropriate testing and treatment. This includes determining the disease mechanism on all newly identified mutations in known CMS-associated genes looking for novel genetic causes of CMS where mutations are not identified in the standard CMS-associated genes.

Consultant Neurophysiologist:
Dr Knight performs all EMGs and Single fibre EMGs.

Neuromuscular Physiotherapist:
The CMS service has a dedicated 0.2 WTE Neuromuscular Physiotherapist, who attends both the adult and paediatric clinics. The role of the Neuromuscular Physiotherapist is to support the assessment and management of patients in clinics; using standardised assessment tools, specialist physiotherapy assessment and treatment skills, and offer guidance on exercise, activity levels and participation. This support is particularly important in the adult population where access to specialist physiotherapy in the community can be patchy. The role extends to care outside of clinics, with links to community therapists and supporting coordinated medical input during hospital admissions.

Specialist Nurse:
The role of the Myasthenia Nurse is wide ranging, either providing direct or remote care, or practical advice to patients, families and the MDT. In clinic they are available to provide education and support to patients and families recently diagnosed or dealing with the long term psychological, physical and practical issues of chronic illness. They are a readily accessible point of contact for patients and families via email or telephone contact, either providing advice or signposting. If patients and families are receiving input from the MDT, they are a reference point for

specific condition related information to support care delivery and management to enable patients to live well. Patient education is also a large part of the role.

CMS Service Co-Ordinator:
The Co-Ordinator oversees the administration of the service, the Patient Day, liaises regarding the CQUIN meetings, and has contact with other hospitals on a daily basis, and is the first point of contact for the patients and professionals. They are responsible for co-ordinating information from referring physicians prior to review by the Clinical Team. They liaise with the laboratory and multi-agency professionals who may be involved in the care locally.

Clinical Service
The clinics are half day adult/paediatric clinics led by the Oxford clinical team, and twelve full day joint clinics with the GOSH team, which alternates between Oxford and London. This allows good practice to be shared between the centres.

In addition, we held a joint Paediatric clinic at St Thomas' hospital on the 13 July 2017 with Dr Heinz Jungbluth. We are also holding an adult joint clinic at King's College Hospital with Dr Fiona Norwood on the 29 September 2017.

We are in the process of liaising with Dr Maria Farrugia regarding a peripheral clinic in Glasgow. We are waiting for their Trust to give the approval for the clinic to go ahead

Both the clinical and laboratory teams offer an advice service to Healthcare Professionals around the country and overseas. This involves e-mail, telephone and letter correspondence regarding numerous patients, including those seen in clinic who are under local follow-up and patients who are unable to be seen at the centre due to geographical access issues or severity of illness.

This year we were awarded, in collaboration with the Newcastle Muscle Group, European Network (ERN) status for rare neuromuscular disorders. The European Commission (EC) is supporting Member States in the development of European Reference Networks (ERNs) to link existing highly specialised healthcare providers across Europe, such as the CMS service and other neuromuscular services in Oxford. The development of ERNs will facilitate timely access to care, both diagnosis and treatment, by centralising knowledge and experience, medical research and training, and resources for these diseases and conditions. However, due to the political uncertainty of "Brexit", terms and conditions of ERNs might need to be revised in the future for UK centres participating in these networks.

The CMS Service has Telemed appointments available within our clinics, where we contact patients who are unable to attend clinic due to travel difficulties or they are feeling well in themselves and just want to chat to the team over the phone, and will defer their appointments until later in the year can request these appointments with the Consultants approval. This has been welcomed by patients. In addition, we are thinking about the possibility that some patients could do their own assessment,

using a “self-assessment QMG form”. This would allow us to monitor patients evolution remotely more accurately.

The clinical and genetic research teams offer an advisory service to the diagnostic genetic laboratory on specific genes that need testing usually after consultation with the referring clinicians. This part of the service reduces the gene screening activity and keeps the costs down. These are referred to as “genetic reviews”.

Genetic service

The Diagnostic Genetics Laboratory at the Churchill Hospital, Oxford provides specialised genetic screening for patients with suspected CMS or related rare neuromuscular conditions. There are currently a number of genes screened for that are associated with CMS: *CHRNA1, CHRNB1, CHRND*, *CHRNE, CHRNG, RAPSN, COLQ, CHAT*, *DOK7, GFPT1* and *DPAGT1*. Each of these genes encodes proteins involved in maintaining the function of the neuromuscular junction.

In addition to these, further screening for *MuSK, AGRN, ALG2, ALG14, COL13A1,GMPPB, SLC5A7, LRP4, TOR1AIP1 and SLC18A3* genes is available within Professor Beeson’s research group, based at the Weatherall Institute of Molecular Medicine.

If a mutation in the genetic code is identified, additional tests can also be undertaken in Professor Beeson’s laboratory to determine the pathogenicity. These include:

- Electrophysiology to assess *AChR* channel kinetics for fast or slow channel syndromes or reduced conductance syndrome.
- *AChR* cell surface expression to test for *AChR* deficiency syndromes
- *AChR* clustering assays to test pathogenicity of *RAPSN*, *DOK7, MuSK* and *AGRN* variants
- Exon trapping to test splice site mutations and synonomous intronic variants
- Reporter assays to test for promoter variants
- Expression assays to test *CHAT*, *GFPT1*, *DPAGT1*, *MUSK*, *AGRN*, *ALG2*, *ALG14,* and *GMPPB.*

Once the screening has been performed, the patients are either reviewed in outpatient clinic, or alternatively, the details of the case are reviewed by the clinical team and remote advice offered to the referring clinician.

In addition, whole screen Exome and whole screen genome screening is performed via Professor Beeson’s group in selected cases of CMS, where the genetic cause remains unidentified and the diagnosis of CMS is undoubted. This technology helps the identification of novel variants in genes originally not CMS-related. In these cases, further studies to determine pathogenicity need to be undertaken.

As our understanding of these conditions increases, it has become apparent that treatment choice is determined by the underlying pathogenic mechanism of the CMS subtype the patient has. Some of the treatments used routinely in some CMS subtypes cause deterioration in other subtypes. Accumulated experience allowed us to develop a treatment algorithm, which is routinely used in our clinics [**Appendix 1]**.

Service Objectives and Outcomes

The purposes and goals of the service

- Make a definitive CMS diagnosis (including prenatal diagnosis where requested) **[Appendix 4a]**
- Treat effectively
- Deliver high-quality health care to patients with CMS
- Provide special neuromuscular physiotherapy advice
- Provide information for patients, families and their schools and other health care professions about CMS. (See later - Page 8: Service Engagement and Communication)

Outcomes

Activity Levels

In addition to seeing about 220 patients in the outpatient clinics, the clinical team also reviewed the genetic results of 290 patients in April 2016 - Mar 2017 period, offering advice on diagnosis and management to the referring Clinician. We also had 2 CMS inpatients (21 occupied bed days) who were admitted electively to the ward in order to optimise their treatment regime.

DNA samples: the number of DNA samples received by the diagnostic laboratory was 121, compared to 123 last year. This suggest sample numbers remaining stable after the addition of new glycosylation genes, *DPAGT1* and *GFPT1,* to our screening panel two years ago. At the moment we screen a total of 11 genes, but we regularly expand this to include any new CMS related genes discovered.

Activity Levels Recorded **[Appendices]**:

- Number of new and follow-up outpatient visits and geographical information. **(Appendix 4b,4c, 4d and 4e)**
- DNA sample activity – number of patients **(Appendix 4f),** DNA sample geographical data **(Appendix 4g).** Number of exons analysed **(Appendix 4h).**
- Day cases and inpatient activity is also reported, although this is actually outside of the Highly Specialised Funding

- Number of remote genetic reviews from April 2016 to 2017was 290(steering specific genetic tests performed dependent on clinical information). **(Appendix 4i)**
- Number of remote consultations from September 2016 – August 2017 was over 121 phone calls and 408 emails. This represents our effort in communication with patients and other medical professionals from the UK and abroad.
- Number of Telemed appointments from September 2015 to August 2016 was 7.

Performance Indicators

- Turnaround time for DNA reporting: The turnaround time for DNA reporting is approximately two months per gene. However, if it is urgent, then the turnaround is approximately two weeks.
- Clinic Waiting Times: Patients are offered an appointment within 8 weeks.
- Patient Satisfaction (see later – page 6)

Geographical Distribution

- Geographical data of outpatient activity (**Appendix 4c**) genetic tests (**Appendix 4g**) and remote reviews (**Appendix 4j**) are shown - We are reporting Country of residence

As a National Referral Centre for CMS, Oxford aims to offer equal access to patients from across the whole of England and Scotland. Some patients cite transport costs as a limiting factor. For patients living far from Oxford, we try to offer them the flexibility to schedule their appointments to fit in with leisure travel plans. In cases where the patients are physically unable to attend outpatient clinic, remote advice is offered to their local Clinician regarding their diagnosis and management.

As well as offering a national service, the team also offer advice on international patients. In the period April 2016 – March 2017, 9.65% of our genetic reviews came from overseas patients, compared to 6.67% last year. This confirms our efforts in establishing us as a centre of international expertise in CMS. We are receiving more enquiries regarding from EU countries using the S2 EU Cross-border Healthcare Directive referral process. We currently have 4 patients coming through this process successfully.

Patient Satisfaction

Feedback from patients, relatives and carers offers important insight into the quality of service provided. These views are collected in the form of a questionnaire that is

given to the patients and their carers when they attend an outpatient clinic appointment. We give our patients a feedback questionnaire in order to capture more information about the performance of the CMS Service measured against the quality indicators and to identify any gaps in service provision. We have been using this questionnaire since April 2013 in all our outpatient clinics. This information is collated on to our database and any negative feedback is disseminated to the CMS team for positive action and steps (**Appendix 5)**.

We receive positive comments, as well as negative feedback. The negative feedback on our questionnaires mainly relates to the parking issues that the Trust experiences.
The Trust's new parking policy came into action this April and it was hoped that this released extra parking for both patients and staff. The Trust are also liaising with the County Council to try and negotiate further parking places for our patients.
Some of the positive comments received this year:

Very appreciative from clinicians involved.

All staff really helpful as usual.

Always good to come to the JR. Always looked after really well.

Great hospital facilities.

We have updated our patient pre-clinic information booklet in March 2017, to include new staff members **[Appendix 8]**.

Financial Update

To be presented by the OUH Financial team lead by Carol Ann Gourlay, Neurosciences Finance Manager.

Service Developments

Development of new quality-health care measures and indicators

We are developing a set of new indicators to better measure the quality of the healthcare provided by our service. They will be added to our previous ones, and incorporated into our questionnaires and databases. They will be collected prospectively from this year. The new indicators include the following:

- Percentage of genetic reviews within 8 weeks
- Detection rate for genetic test
- Overall percentage of patients with a final diagnosis
- Overall percentage of patients with a final diagnosis reached on new patients without prior diagnosis

- Concordance with the diagnosis centres of origin (in cases of second opinion)
- Percentage of patients involved in research (patients enrolled in existing registries and natural history studies, biological samples donated to biobank)
- Safety incidents, mortality and morbidity outcomes.
- Quality of Life Measures

Telemed clinics and remote monitoring of patients

The Telemed clinics were set up in March 2015 as some patients were finding it difficult to attend clinic due to geographical access issues. The CMS Co-Ordinator liaises with the patient to arrange a convenient time for the team to call the patient from the CMS clinic. After the telephone consultation, a letter is dictated and sent to their doctor. We have used this method in eleven patients so far and this has proven successful. Therefore, this is a way to monitor patients more easily and for them to save in travel expenses, as some patients have difficulty affording the cost of travel. This also stops patients from being lost to follow-up. In addition, we have developed a simplified QMG form (appendix) so that patients can do a self-assessment at home, and we can monitor their evolution even if they are not seen in clinic.

New patient Liaison and Project Nurse

The CMS Service appointed a new nurse in combination with our NMO service to work on projects, such as, keeping our website up to date, producing patient information literature, and analysing performance outcome questionnaires from the clinics. This person will lead on analysis of patient services and implement improvement projects where needed and in association with our Myasthenia & NMO Nurses. This was funded from income from the two services.

Pregnancy Packs

We are producing for all patients with child bearing potential, an information pack for Health Care Professionals & patients regarding the safety of the most commonly used drugs in pregnancy & breastfeeding.

Clinical and translational research

Newly identified CMS-associated genes and next generation sequencing

The CMS Service continues to incorporate a number of CMS patients without a current genetic diagnosis into next generation sequencing techniques. This is part of a preliminary trial into the use of next generation sequencing (as part of the Biomedical Research Centre funding) for the routine screening of genes in rare Mendelian genetic disorders. We have found mutations in a new gene not previously known to be related to CMS (TOR1PA1) and further studies are currently

being undertaken. Previously, using the same methodology, we were able to identify DPAGT1, *ALG2* and *ALG14, GMPPB,* and *COL13A1* as causative genes for CMS.

Given the number of new CMS-associated genes that are being identified Drs Michael Oldridge and Tracy Lester are actively exploring generating a Next Generation Sequencing CMS panel to be used in the screening. This would be designed to detect the more common CMS, variants in the genes described above, the less common CMS forms caused by mutations in large genes such as *AGRN* and *MUSK* that are currently screened for in the research laboratory, and the many new CMS-associated genes currently being identified by next generation sequencing (total approximately 30 genes).

Current translational research projects

As reported, several forms of CMS show a marked beneficial response to Salbutamol or ephedrine. At the moment we are studying the molecular mechanism of Salbutamol at the neuromuscular junction. We believe that this drug provides a compensatory mechanism to stabilise the motor endplate structures, improving neuromuscular transmission. A better understanding of it will help us to provide more efficient treatments

Future translational research projects

As stated above, an understanding of the underlying molecular mechanism of disease due to the different mutations is fed back to the clinical team to direct appropriate therapy. Next generation sequencing is revealing a series of new CMS-associated genes and projects are underway to determine how the different mutations affect signal transmission at the neuromuscular junction. Further projects are being undertaken to study the beneficial effects of salbutamol. At present the precise mechanism through which Salbutamol improves neuromuscular transmission is not known, but research into the mechanism may provide a scientific pointer to similar compounds that have greater efficacy. We are exploring with Novartis the potential use of a more potent β2-adrenergic receptor agonist which, in preliminary work, has been found to be muscle-specific and to have markedly reduced side effects.

We have recently been awarded the Myaware prize studentship starting on October 1st 2016 aimed at identifying small molecules that can increase expression levels of the *DOK7* protein and thus could be used as an alternative therapeutic strategy.

Service Engagement and Communication

Website

A webpage for the service is hosted on the OUH website and includes: patient CMS booklet, referral information and pre-referral form, as well as points of contact for Clinicians. The website has recently been updated with the contact information for

the CMS Team. Patients can also access our annual reports on the website, as well as information from the Patient Day we hold, including the presentations, which patients have asked for. We endeavour to continually update the website, so the information is as up to date as possible. Our CMS booklets have been updated with the latest relevant information regarding recently identified CMS and therapy (**Appendix)**.

Pre-attendance Clinic Information Pack

The content has been approved by the Trust Media and Communications Department. The information pack is placed on the CMS service webpage. The information pack is sent to all new patients attending the service prior to their appointment. This has been updated this year to include new staff members.

Information in clinic

Newly diagnosed patients are given in clinic a CMS booklet, puplished by 'Myaware' **(Appendix 2)** with the latest information about the diagnosis, treatment and management of this condition. In addition, there are given a CMS-DVD with testimonies of several CMS patients, so that patients and families can understand their condition better. We also send these documents to school when requested by the parents of patients with CMS

Patient Day

The CMS Patient Day took place on the 22 April 2017 in Oxford. A total of 28 patients and their family members attended (68 in total). The agenda consisted of overviews, presentations, and breakout sessions where patients interacted with each other and the CMS team **(Appendix 6)**. This year the patients had made suggestions about the subjects they wished us to cover and with that in mind, we arranged for 'Myaware' to attend to discuss benefits and income support related topics. We also had a teaching session on pilates, which our patients found thoroughly enjoyable. In addition to educational objectives patients find this meeting socially and psychologically helpful because they meet with individuals who are in a similar situation as themselves and many make long-lasting contacts.
Patients completed a questionnaire feedback with a positive outcome **(Appendix 7)**. The next National Congenital Myasthenia Patient Day is due to take place in the spring of 2018 in Oxford. 'Myaware' have been informed and representatives will be attending. We uploaded the presentations onto our CMS website, via the Trusts website, so the patients can refresh themselves and other patients are able to view them.

CQUIN

The CQUIN requirement is designed to encourage collaborative learning and Quality Service Development is based on long standing precedent in the highly specialised services (HSS).

The meeting includes discussions of clinical outcomes, comparison of centres' outcomes, and identification of where providers need to adopt new ways of delivering consistent outcomes across all clinical teams. The meeting to discuss the 2015-2016 report took place on 23January 2017 in Newcastle. The 2017-2018 HSS Rare Neuromuscular Disease Service Audit Meeting is anticipated to take place in early 2018.

Service Problems

3,4-DAP supply.

Although Biomarin has up to now tolerated the prescribing of the cheaper generic 3,4-DAP, in the UK we have some concerns this may change in the future. They are currently trying to obtain a licence for Firdapse in CMS in the USA.

Of concern: We and neurologists in the US have been made aware that a commercial company were able to gain access to a CMS patient Facebook Group and offered free Firdapse to US patients while awaiting the license. This has been of concern to the myasthenia charities and the neurologists here, and in the US.

Provision of Salbutamol

The problem with the manufacturing of Salbutamol modified release capsules (Ventmax®) persists. The product was discontinued in 2015 and is no longer available. There has been no replacement modified-release preparation. There are no current issues with the supply of normal formulation Salbutamol tablets or liquid formulation, which are manufactured by GSK. All our patients are doing well on the tablet or liquid formulations. However the relatively higher costs of the salbutamol tablets compared to the previous MR version and the liquid versions has meant some GPs insisting on prescribing the liquid formulation which has a short half-life and is bulky to transport. The following information was obtained from our hospital pharmacy regarding the cost and half-life of the tablet and liquid formulations of salbutamol.

"Salbutamol s/f syrup is significantly cheaper compared to immediate release tablets (approx. 95% cheaper) but due to contract agreements and confidentiality reasons the hospital was unable to verify the precise figures.

Salbutamol 2mg/4mg tablets (Activis): The manufacturer states 50% of the drug is excreted within 4 hours, and fully excreted in 24 hours. Other brands of immediate-release salbutamol tablets have been quoted to have different half lives in the range of 5 to 7.2 hours.

Salbutamol s/f syrup (Ventolin): The manufacturer does not state a half life for its preparation. However other sources suggest is it 5 hours. For oral preparations, tablet and syrup, the bioavailability is about 50%. Here at the OUH we only keep 4mg (x28) tablets and the s/f 2mg in 5mL syrup (150mL)."

Meetings, Presentations and Publications

Meetings

Dr J Palace, Professor D Beeson, Dr Stephanie Robb, Dr P Rodriquez Cruz, Birute Saul, Hayley Ramjattan, Julia Goodgame, Dr. Tracy Lester, Dr Mike Oldridge

Highly Specialised Services Clinical Outcome Collaborative Audit Workshop Newcastle upon Tyne 23 January 2017

Collaboration with Newcastle and GOSH physiotherapists on outcome measures used in clinic. Newcastle upon Tyne. October 2016

Oral Presentations

The 38th Edinburgh Neurology course, 4th October 2016, "The Congenital Myasthenic Disorders," Dr Jackie Palace.

CMS Patient Day, Oxford. 22 April 2017, Dr Jackie Palace

13th International Conference on Myasthenia Gravis and Related Disorders, New York Academy of Sciences, NYAS, 7 World Trade Center, New York. May 15th -17th 2017. Talk: "Therapeutic Strategies for Congenital Myasthenic Syndromes, Dr Jackie Palace.

13th International Conference on Myasthenia Gravis and Related Disorders, New York Academy of Sciences, NYAS, 7 World Trade Center, New York. May 15th-17th 2017. Talk: "Myasthenic syndromes due to defects in COL13A1 and the N-linked Glycosylation pathway, Professor David Beeson

Danish Paediatric Neurology Conference November 14th-15th 2016. Hereditary Myasthenic Syndromes: new genes and better treatment,

CMS Patient Day, Oxford. April 22nd 2017. Genetics of inherited myasthenia.

Nuffield Department of Medicine Grand Round, Oxford. April 28th 2017. Genetic disorders of the neuromuscular synapse – Can we treat them?

13th International Conference on Myasthenia Gravis and Related Disorders May 15-17 2017 Myasthenic Syndromes Due to Defects in COL13A1 and in the N-Linked Glycosylation Pathway

Chinese Neuromuscular Disorders Symposium. Shanghai, May 25-29th 2017. 27th - The neuromuscular Junction: genetic disorders and 28th – How to treat congenital myasthenic syndromes.

Sophion ion channel modulation symposium, Clare College, Cambridge. June 14-15th 2017. Treatment for genetic disorders of the neuromuscular junction.

"Congenital Myasthenia Syndromes", British Paediatric Neurology, Birmingham, 2016, Dr Sandeep Jayawant

Congenital Myasthenic Syndromes PEDICON New Delhi February 2017 Dr Sandeep Jayawant

Congenital Myasthenia International Neuromuscular Symposium February 2017 Pune, India, Dr.Sandeep Jawant.

CMS Patient Day, Oxford. April 22nd 2017, "Congenital Myasthenia:An overview." Dr.Manon Lee

Physiotherapy Management of Congenital Myasthenic Syndrome – MDUK Care Conference, Nottingham. (June 2017) Hayley Ramjattan, NM Physiotherapist

Publications

Brady S, Healy EG, Gang Q, Parton M, Quinlivan R, Jacob S, Curtis E, Al-Sarraj S, Sewry CA, Hanna MG, Houlden H, **Beeson D**, Holton JL. Tubular Aggregates and Cylindrical Spirals Have Distinct Immunohistochemical Signatures.J Neuropathol Exp Neurol. 2016 Dec;75(12):1171-1178

Luo S, Cai S, Maxwell S, Yue D, Zhu W, Qiao K, Zhu Z, Zhou L, Xi J, Lu J, **Beeson D**, Zhao C. Novel mutations in the C-terminal region of GMPPB causing limb-girdle muscular dystrophy overlapping with congenital myasthenic syndrome. Neuromuscul Disord. 2017 Jun;27(6):557-564.

Ross JA, Webster RG, Lechertier T, Reynolds LE, Turmaine M, Bencze M, Jamshidi Y, Cetin H, Muntoni F, **Beeson D**, Hodilvala-Dilke K, Conti FJ. Multiple roles of integrin-α3 at the neuromuscular junction. J Cell Sci. 2017 May 15;130(10):1772-1784.

Chang T, Cossins J, **Beeson D**. A rare c.183_187dupCTCAC mutation of the acetylcholine receptor CHRNE gene in a South Asian female with congenital myasthenic syndrome: a case report. BMC Neurol. 2016 Oct 7;16(1):195.

Gomez AM, Stevens JA, Mané-Damas M, Molenaar P, Duimel H, Verheyen F, Cossins J, **Beeson D**, De Baets MH, Losen M, Martinez-Martinez P. Silencing of Dok-7 in Adult Rat Muscle Increases Susceptibility to Passive Transfer Myasthenia Gravis. Am J Pathol. 2016 Oct;186(10):2559-68.

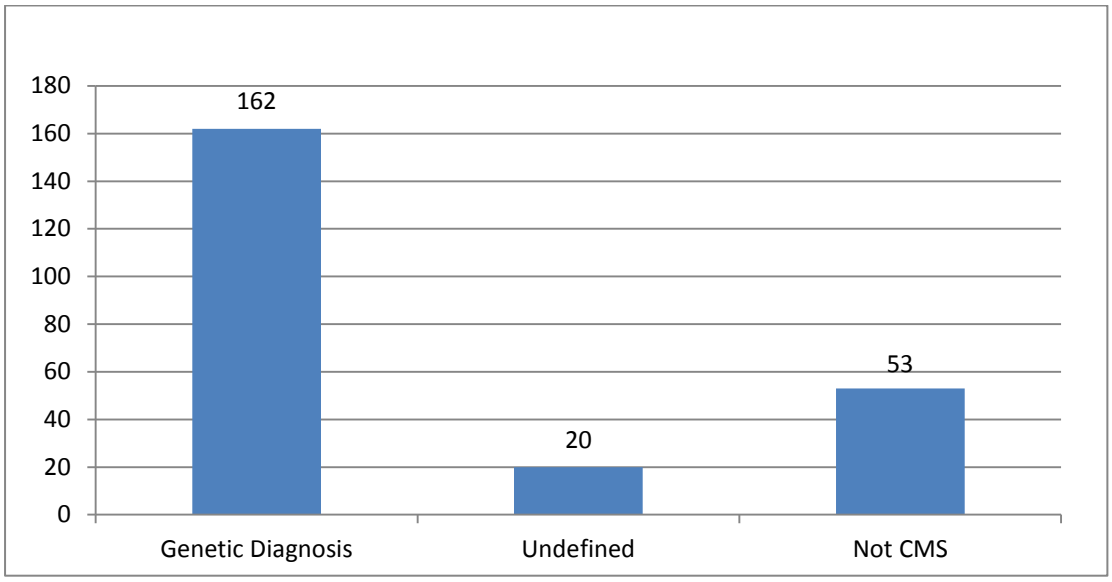
Beeson D. Congenital myasthenic syndromes: recent advances. Curr Opin Neurol. 2016 Oct;29(5):565-71.

Myasthenia in Children Ed **Dr Sandeep Jayawant**.Commissioned by MacKeith Press London .

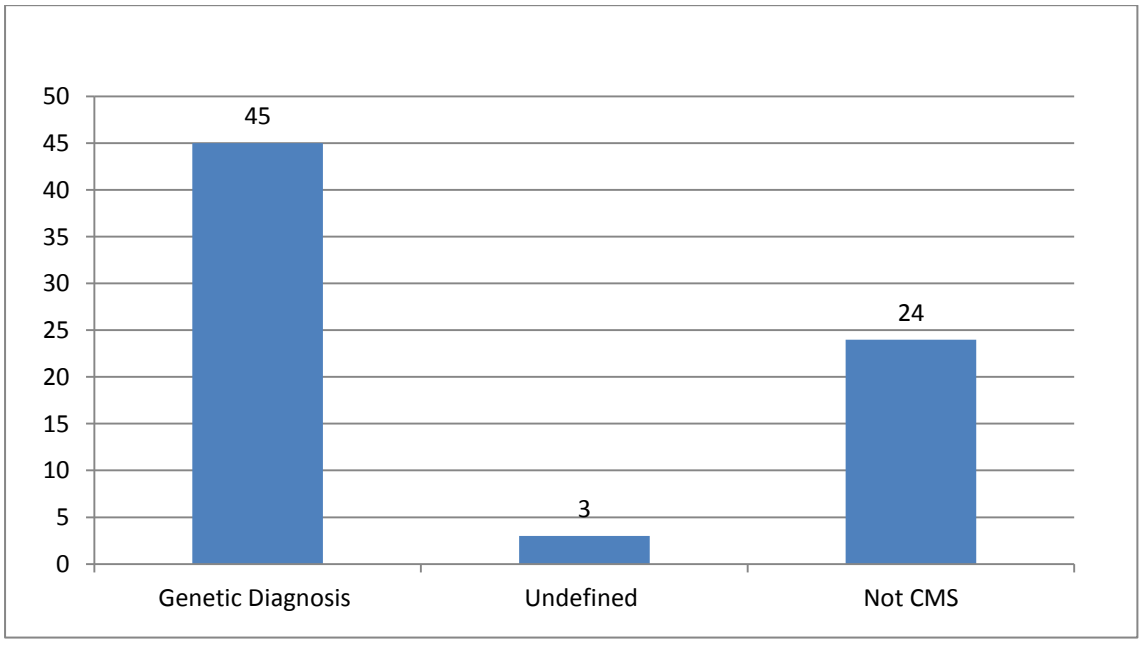
Hayley Ramjattan. Congenital Myasthenic Syndrome (CMS) and Myasthenia Gravis (MG): Guidance for Paediatric Physiotherapists Managing Neuromuscular Disorders, Association of Paediatric Chartered Physiotherapists (APCP). Written in collaboration with APCP Neuromuscular Committee. May 2017.

Appendix 4a

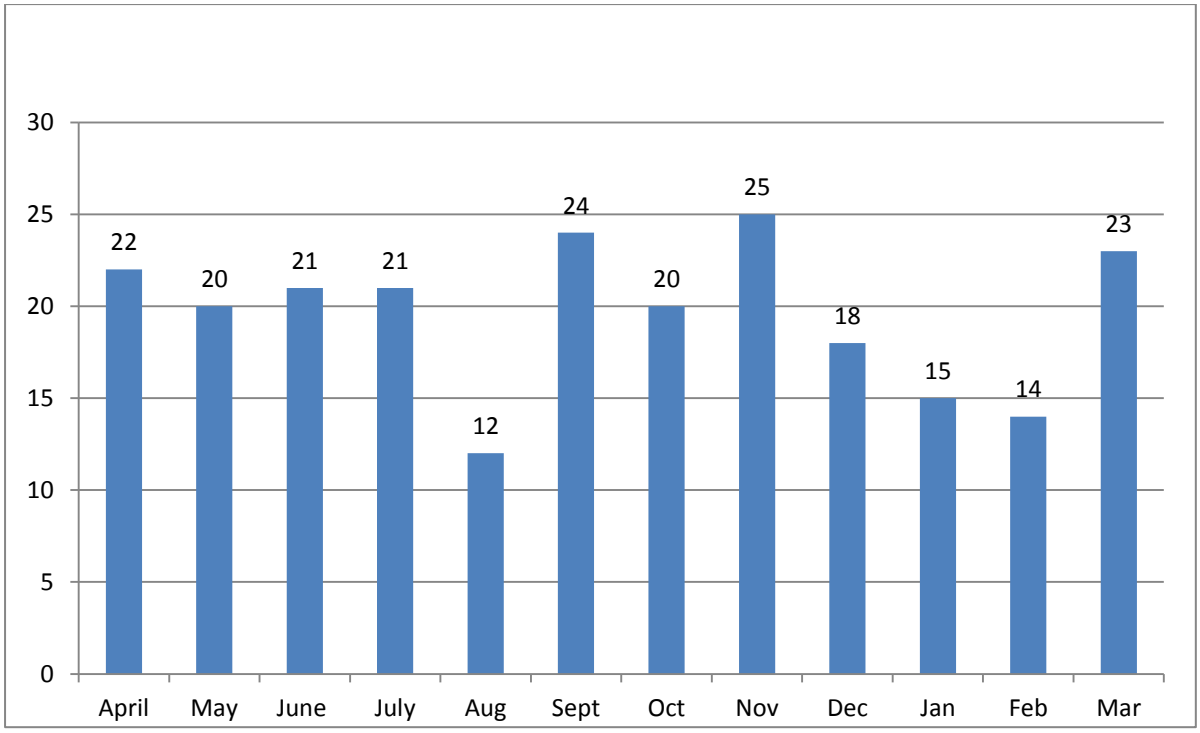
Number of patients with confirmed diagnosis Apr 2016 – Mar 2017



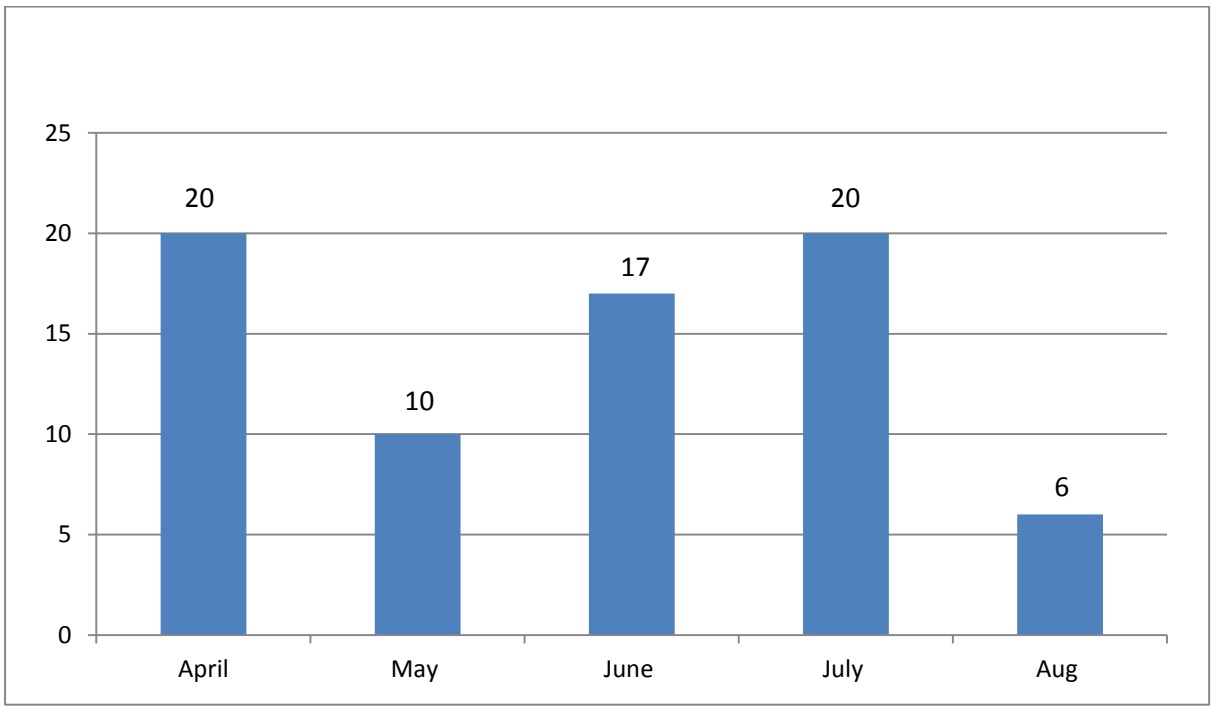
Number of patients with confirmed diagnosis Apr 2017 – Aug 2017



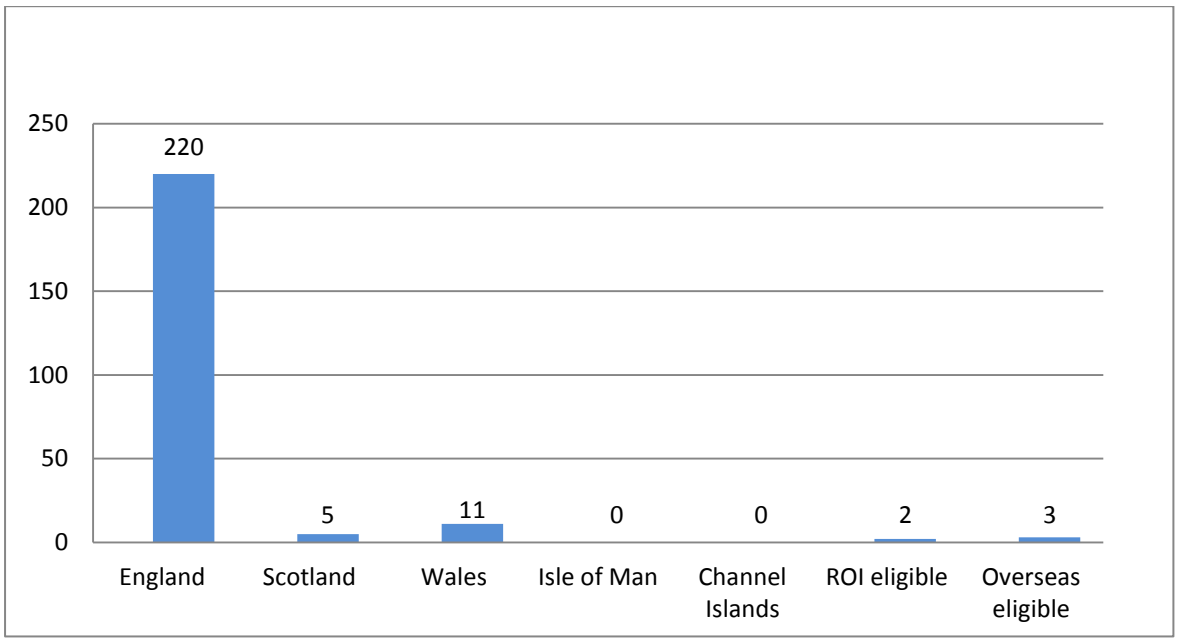
Appendix 4b
Outpatient attendances April 2016- March 2017 (12 months)



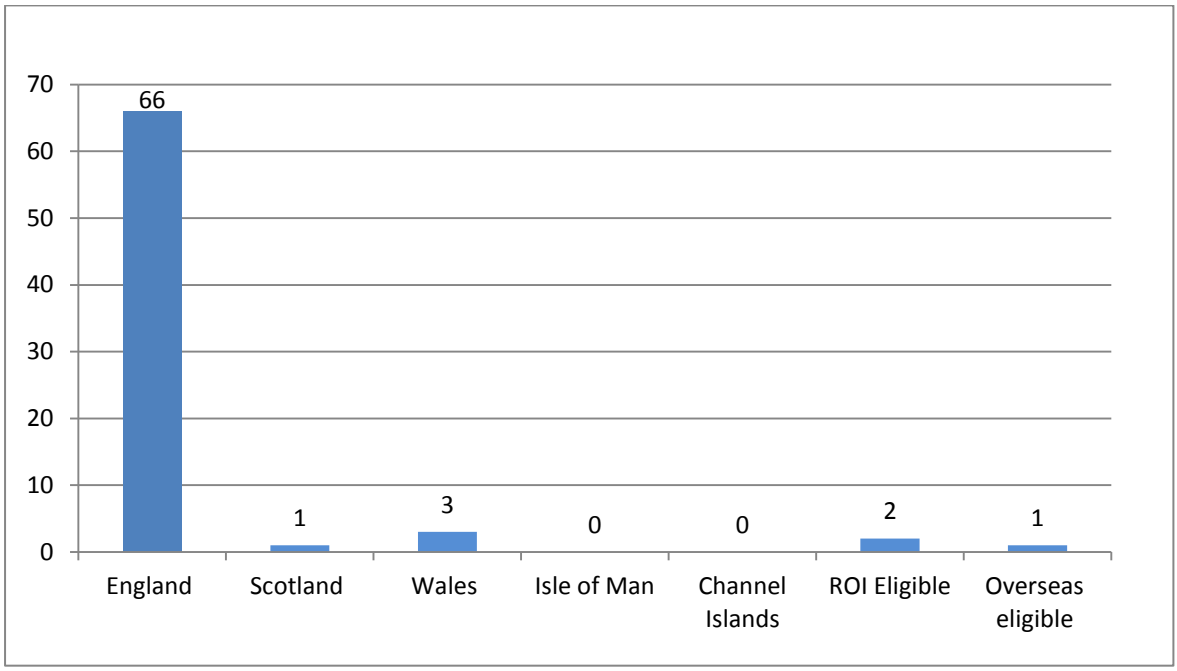
Outpatient attendances April 2017 – Aug 2017 (5 months)



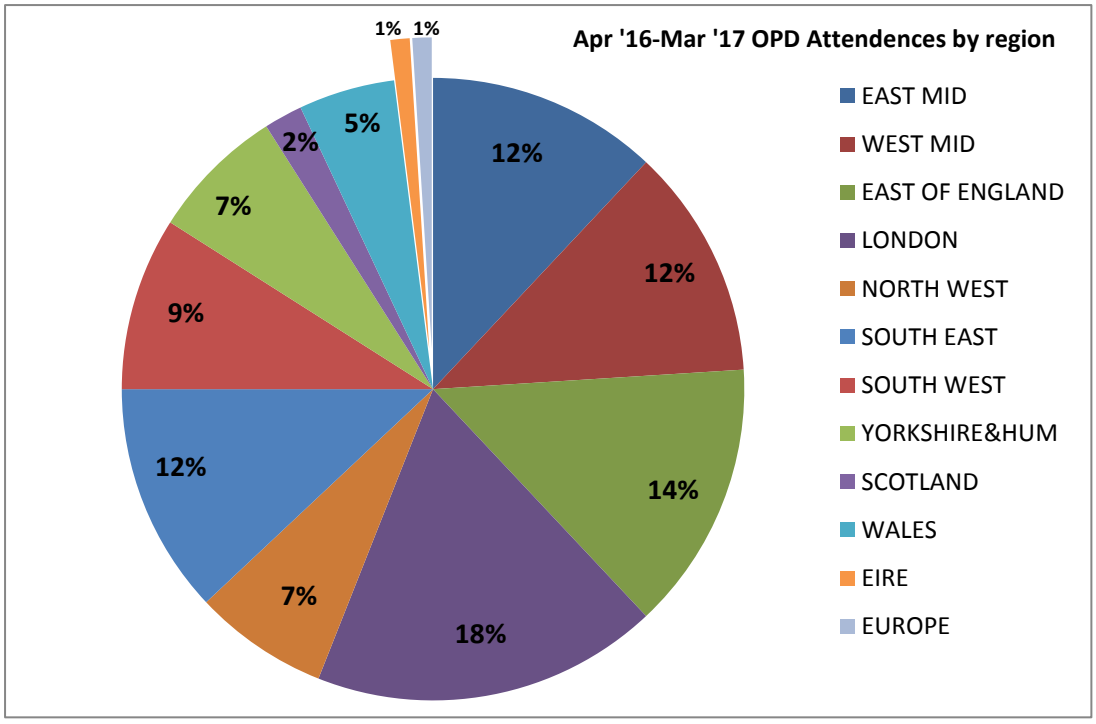
Appendix 4c: Regional outpatient geographical data April 2016 – March 2017 (12 months)



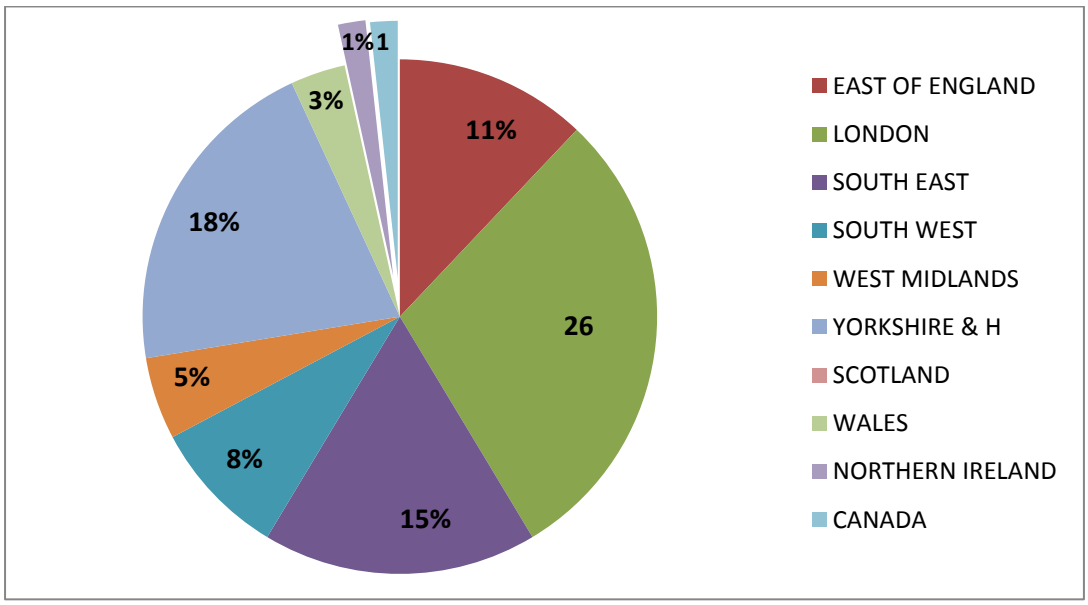
Regional outpatient geographical data April 2017 – Aug 2017 (5 months)



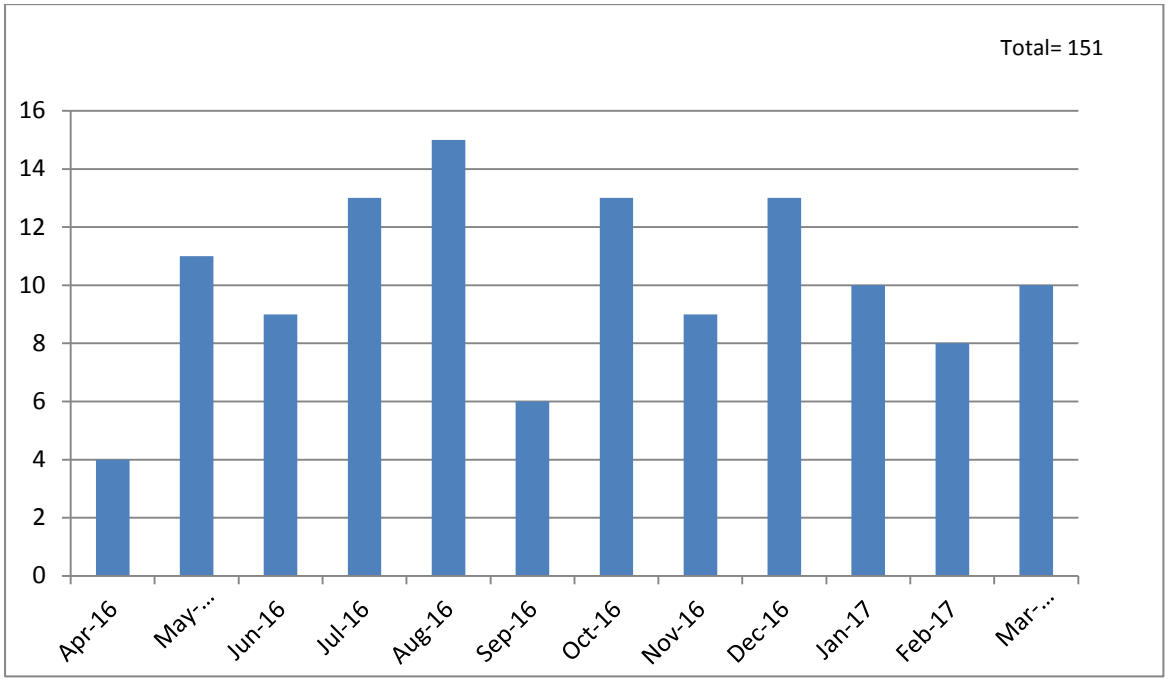
Appendix 4d:
Regional outpatient geographical data April 2016 – March 2017 (12 months)



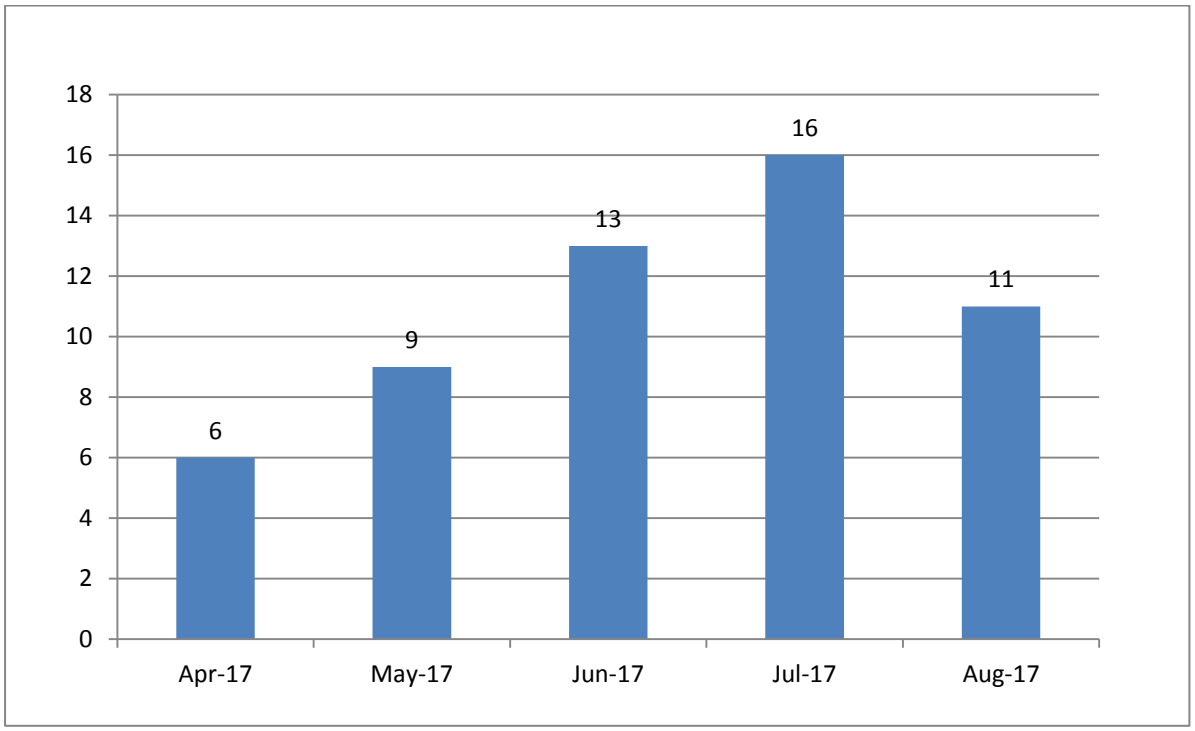
Appendix 4e: Regional outpatient geographical data April 2017 – Aug 2017 (5 months)



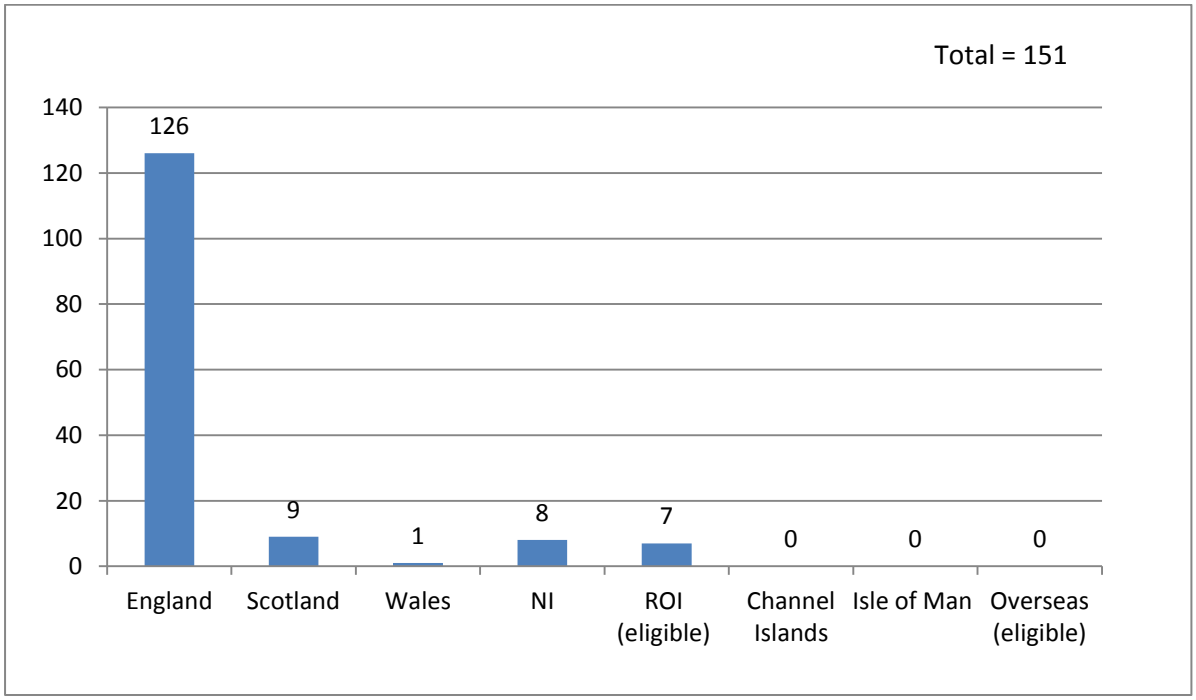
Appendix 4f
DNA samples received April 2016 – March 2017 (12 months)



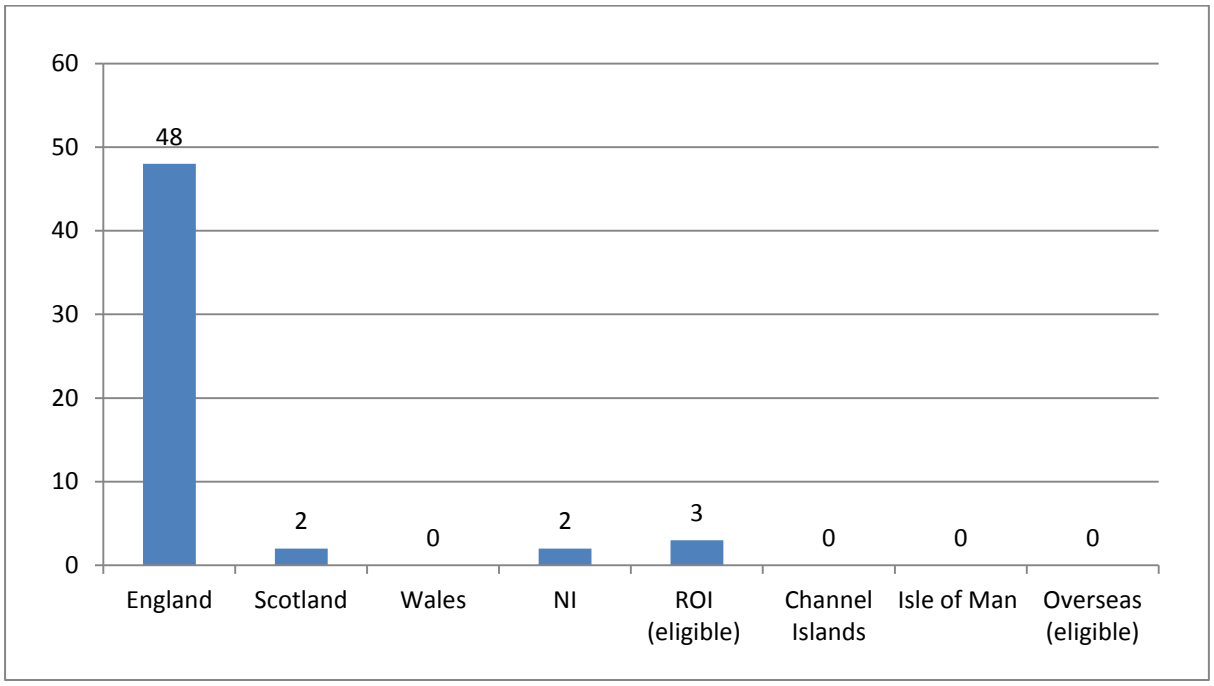
DNA samples received April 2017 – August 2017 (5 months)



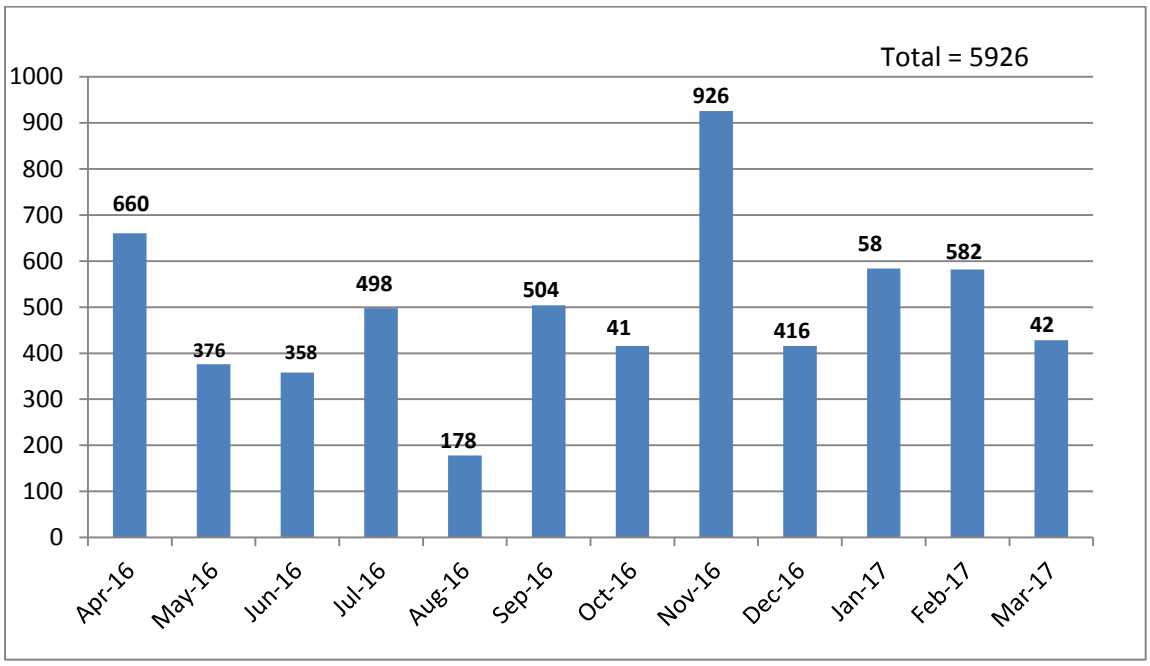
Appendix 4g:
DNA samples received geographical data April 2016 – March 2017 (12 months)



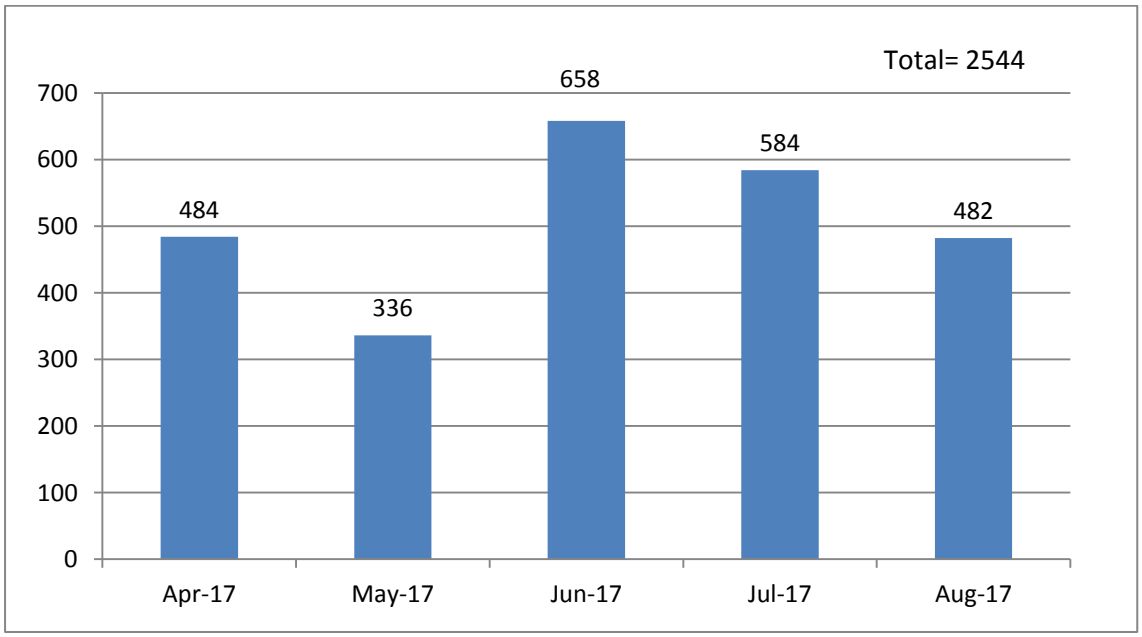
DNA samples received geographical data Apr 2017 – Aug 2017 (5 months)



Appendix h:
DNA (exons analysed) April 2016 – March 2017 (12 months)



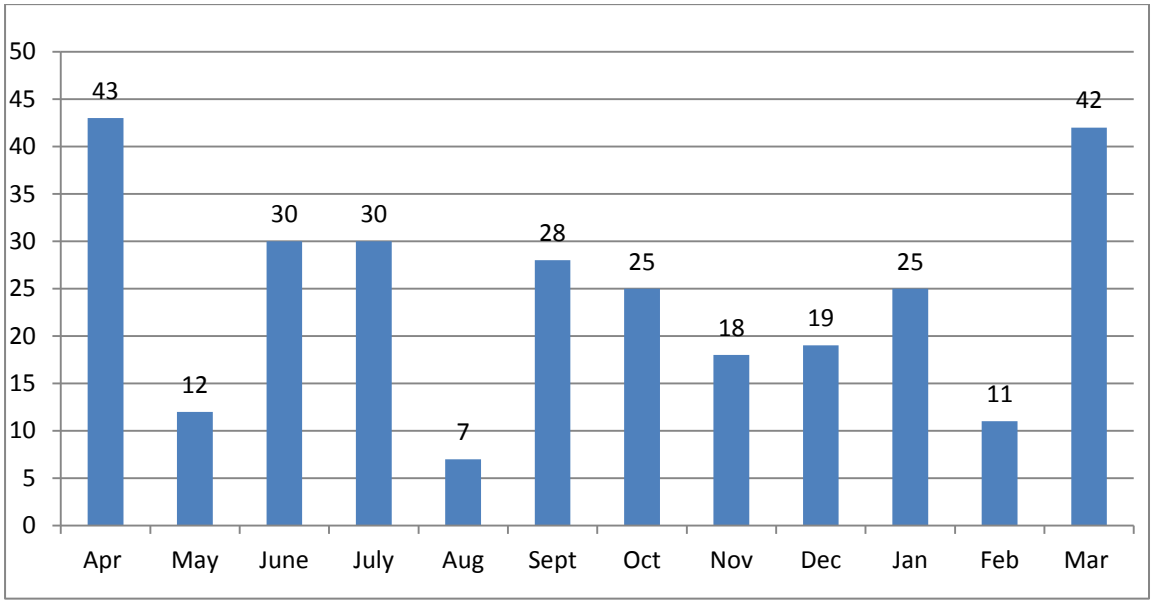
DNA (exons analysed) April 2017– Aug 2017 (5 months)



Appendix 4i

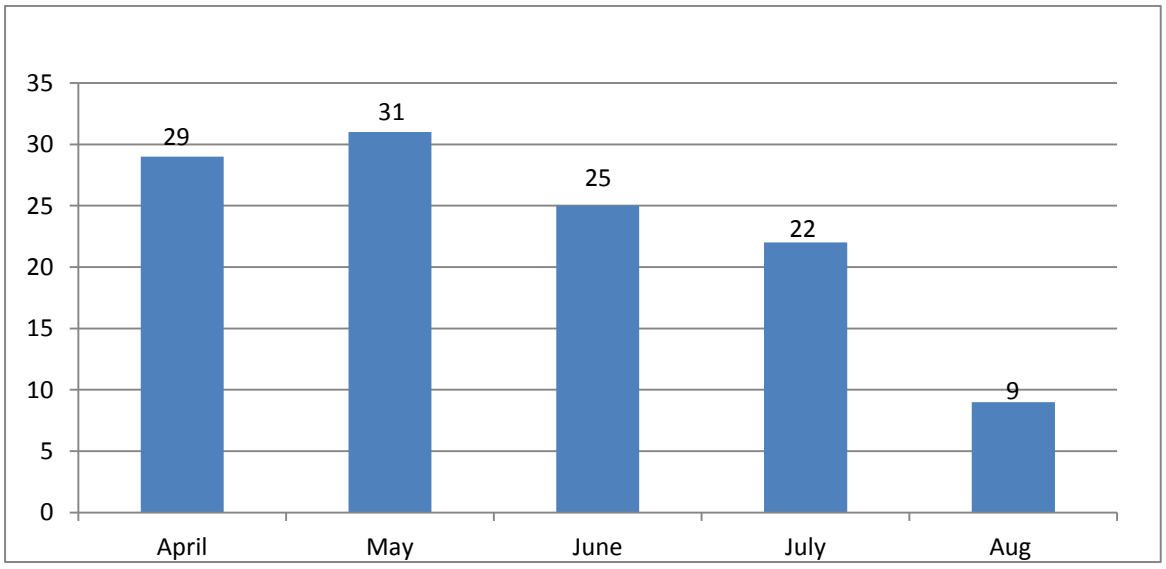
Remote Genetic Reviews by Clinical Team

April 2016 – March 2017 (12 months)



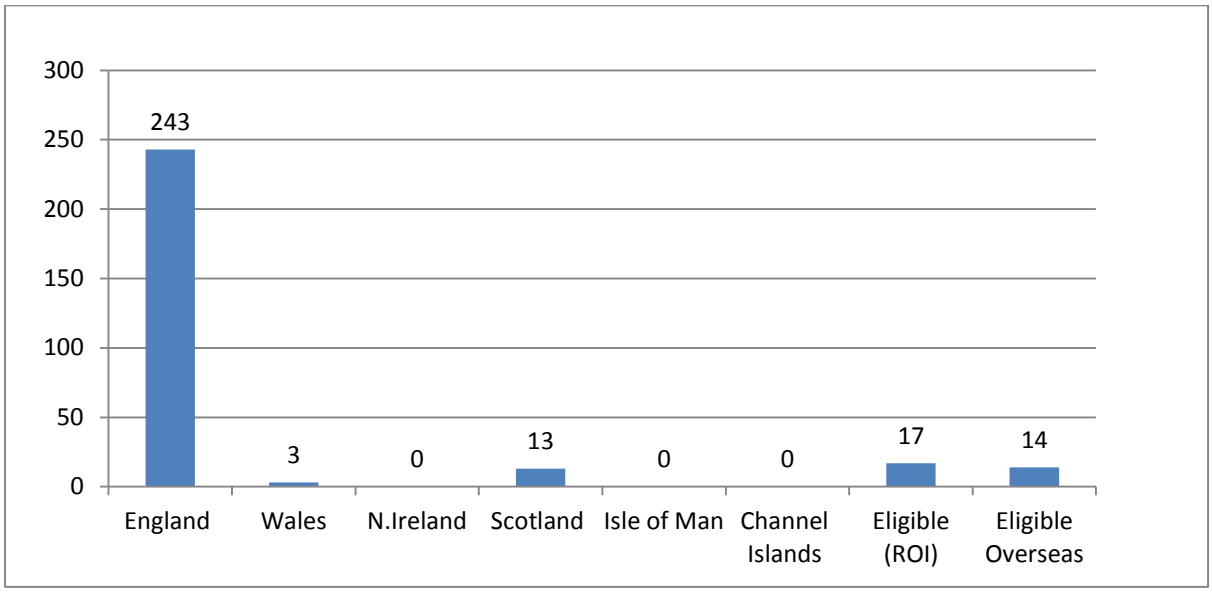
Remote Genetic Review by Clinical Team

April 2017 – August 2017 (5 months)

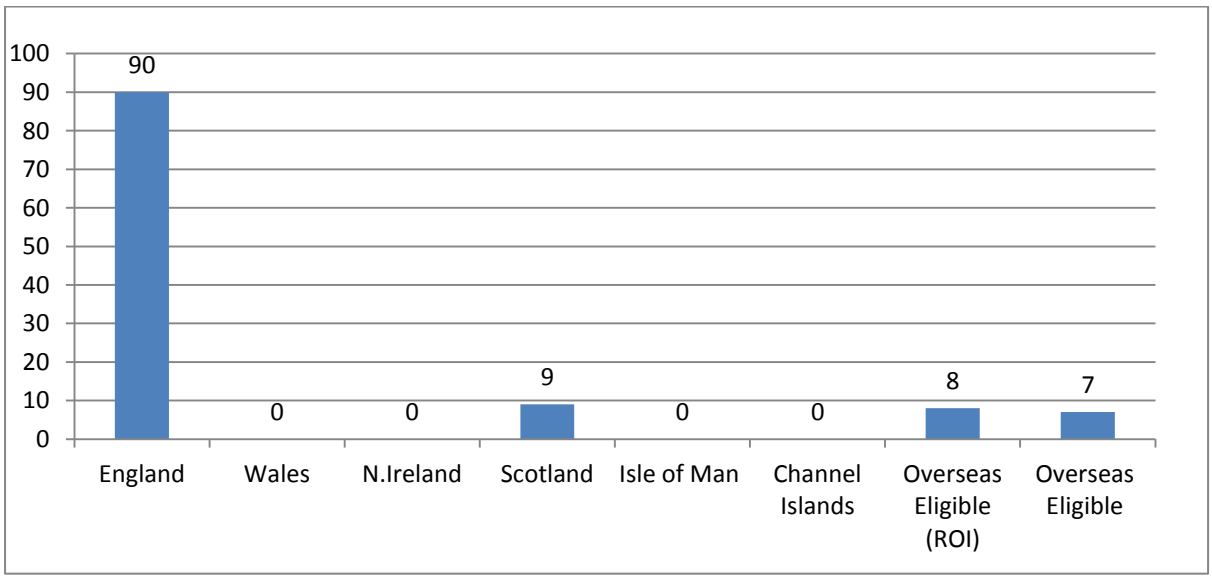


Appendix 4j

Remote Genetic Review by Clinical Team:
Geographical data April 2016 – March 2017 (12 months)



Remote Genetic Review by Clinical Team:
Geographical data April 2017 – August 2017 (5 months)



Patient day 2017

Please rate the Day	#	%
Excellent:	9	69%
Very Good	4	31%
Good	0	0%
Fair	0	0%
Poor	0	0%

Which part of the day did you enjoy most?	#	%
Research/Genetics talk	5	38%
Exercise sessions	2	15%
All of it	2	15%
Nirvana's talk	1	15%
Q&A Discussions	1	8%
Lunch	1	8%
Breakout sessions	1	8%

Suitable Venue	#	%
YES	13	100%
NO	0	0%

Please rate the Venue	#	%
Excellent	8	62%
Very Good	5	32%
Good	0	0%
Fair	0	0%
Poor	0	0%

Did you enjoy lunch & refreshments	#	%
Yes	13	100%
No	0	0%

Please rate lunch/refreshments	#	%
Excellent	4	31%
Very Good	6	46%
Good	2	15%

Fair	1	8%
poor	0	0%

Would you like to attend a similar day in the future?	#	%
Yes	11	85%
No	2	15%

On future days what activities would you like?
Balance of research/workshops/questions was near perfect. Maybe something on medication.
More information – university etc.
More research - enjoy hearing about other people's experiences. How to stay well.
Much of the same please
Similar
Specific Q&A for children in break out group (like last year)
The balance is right. I'm satisfied.
Would like to exchange numbers or create a group with other families with CMS

Comments/suggestions
Fabulous day - thanks :-)
No
Thank you so much. These days are v v beneficial.
Very good hotel. Stayed overnight. Comfortable and excellent food in resturant. Nice to meet other CMS sufferers and their families.
Very heart warming/emotional talk by Nirvana