Northern Treatment Advisory Group

Minutes of meeting held on the 28th February 2017, 9-12am,

Meeting Room 4, The Durham Centre

Present:

- Ian Davidson (ID) Director of Quality and Safety, North Durham CCG & Chair of NTAG.
- Matthew Grove (MG) Consultant Rheumatologist and Head of Service, Northumbria Healthcare NHS Foundation Trust.
- Bhavana Reddy (BR) Head of Prescribing Support, RDTC (professional secretary)
- Matthey Lowery (ML) Formulary Pharmacist, Newcastle upon Tyne NHS Foundation Trust
- Janette Stephenson (JS) Head of Medicines Optimisation, North East Commissioning Support Unit.
- Ali Wilson (AW) Chief Officer, Hartlepool & Stockton-on-Tees CCG.

Apologies were received in advance from: Tom Hall (Public Health), Andrea Laudon, Simon Thomas, Graeme Kirkpatrick and Chris Gray and Sunderland CCG.

RW's post remained vacant and it was noted that Toks had now semi-retired so would no longer be attending NTAG and that his position would be filled by Tom Hall or Tanja Braun.

The group noted that as apologies from public health had been received the meeting wouldn't be quorate however BR stated that she would run all decisions by TH prior to issuing them. BR was due to meet TH next Wednesday.

No declarations were received prior to the meeting on receipt of the agenda and when the Chair invited any declarations of interest to be made, none were made.

1) Draft Minutes September Meeting

The group approved the November minutes with no changes.

ACTION: Secretary to publish November minutes on the NTAG website.

2) Matters Arising

a) Lycra Suits.

The group re-looked at the information received regarding Lycra suits. It was noted that the data received from the IFR team showed that Lycra is being prescribed across the region and not just in the south of the patch. It was noted that use is increasing compared to previous years. The group noted the following points:

- There is limited evidence on which to base the clinical effectiveness of Lycra garments in the management of cerebral palsy and other neurological or musculoskeletal conditions. Available studies which have mostly been in children with cerebral palsy tend to be lacking in quality and have many limitations (e.g. small patient numbers, mostly case studies/series, non-standardised and/or subjective

outcome measures and short duration). Only one published small randomised controlled trial (n=16) was identified.

- There is also a lack of consistent, agreed outcome measures. Study withdrawal is common, due to practical or comfort issues in wearing the suits.
- Studies to date have shown variable results. While some studies showed a beneficial effect from the use of Lycra suits, others have shown a negative or detrimental effect. Clinical effectiveness is unclear; long-term studies are lacking.
- No published cost effectiveness studies were identified. Cost varies depending on the type of garment required and the manufacturer. Standard prices of more commonly used garments range from about £90 to £3000.
- Specialists have indicated that current use has not been audited. The clinical data is sparse so an audit of current patients that have received these garments would be beneficial to aid decision making.

The group therefore agreed that there is limited evidence of efficacy for Lycra garments and therefore they would not be approved. It was agreed that it is likely that IFR applications will likely continue therefore the following criteria may aid IFR panels. Approval could be considered for those patients who are likely to gain significantly more benefit from the intervention than might be expected and if the following criteria are met:

- Children between 3 and 16 with a diagnosis of cerebral palsy.
- Following a multidisciplinary assessment by the occupational therapist and physiotherapist and support from a consultant paediatrician that the child is likely to achieve an improvement in (or maintain) functional abilities regarding balance or movement control.
- The application is filled in by a specialist. GP applications should not be accepted.
- Where the child and family/carers are motivated to support the introduction and maintenance of use of the intervention.
- Regular monitoring at appropriate intervals by the multidisciplinary team to assess progress. Use of the Lycra suit should be discontinued if benefits cease to be achieved or maintained.

The group also agreed that further data on current patient use was required and specialists should be encouraged to audit use, to aid in identifying criteria for use and potential savings from a reduction in use of other treatments. This should be fed back to applicants when IFR applications are received.

ACTION: Secretary to draft recommendation as above.

3) Appraisal: Dimethyl fumarate for moderate to severe chronic plaque psoriasis.

The appraisal report was introduced by the secretary.

Dimethyl fumarate is an oral fumaric acid ester (FAE) thought to improve psoriasis through immunomodulatory, anti-inflammatory, antioxidant and antiangiogenic effects. A marketing authorisation application is currently under evaluation for treatment of adults with moderate to severe chronic plaque psoriasis requiring systemic therapy.

The following points relating to this agenda item were noted and discussed by the group:

- An oral compound FAE preparation containing dimethyl fumarate (main active component) and monoethyl fumarate salts (Fumaderm®) is licensed for moderate to severe psoriasis in Germany. Although unlicensed in the UK, Fumaderm® is imported for use by specialist dermatology centres particularly in patients who fail or are intolerant to other non-biological systemic therapy.
- A pivotal phase III RCT compared dimethyl fumarate to placebo and Fumaderm® in 671 adults with moderate to severe plaque psoriasis, aiming to demonstrate superiority of dimethyl fumarate to placebo, and non-inferiority to Fumaderm®. At week 16, dimethyl fumarate was superior to placebo for the co-primary outcomes of Psoriasis Area Severity Index (PASI) 75 (37.5% vs 15.3%) and Physician Global Assessment response of 0 “clear” /1 “almost clear” (33.0% vs 13.0%); and non-inferior to Fumaderm® for PASI 75 (37.5% vs 40.3%, non-inferiority margin ±15%)
- Previous studies on compound FAE therapy also suggest that they are superior to placebo and possibly similar in efficacy to methotrexate but the overall quality of the evidence is low due to limitations such as small patient numbers and use of non-validated outcome measures.
- The rates and types of treatment emergent adverse events (TEAEs) in the pivotal study were similar between the dimethyl fumarate and Fumaderm® groups and consistent with the known safety profile of FAE. TEAEs were mostly considered to be mild but led to discontinuation in nearly a quarter of patients receiving active treatment. The most common adverse effects were GI symptoms (nausea, vomiting, abdominal pain, flatulence, diarrhoea) occurring in about two thirds of patients followed by flushing.
- Lymphopenia occurred in about 10% of patients receiving active treatment. The MHRA and EMA have issued warnings regarding cases of PML reported in patients on FAE with severe prolonged lymphopenia. Regular monitoring of full blood count is required during treatment.
- The cost of dimethyl fumarate is not yet available. The manufacturer is currently conducting an economic analysis to determine the most cost-effective price in the UK. Assuming it may be 10% less expensive, this corresponds to an estimated annual maintenance cost of £1,655.64 to £4,966.92 depending on dose.
- Specialists with experience in using FAE based at The Newcastle upon Tyne Hospitals NHS Foundation Trust have said that the reports of PML in patients on FAE with lymphopenia combined with the availability of better drugs in their experience have led to a reduction in their prescribing of FAE. They still use FAE in patients who have failed standard treatment but who do not qualify for biologics due to a PASI or DLQI score <10.

The group discussed the above points and agreed that dimethyl fumarate may be an option where unlicensed Fumaderm® is currently being used in patients who do not qualify for biologics. It is likely that dimethyl fumarate will be cheaper than imported Fumaderm® however a price is not yet available. As a licensed product dimethyl fumarate should be used over Fumaderm® as per MHRA guidance.

ACTION Secretary to draft recommendation as above.

4) Appraisal: Transcutaneous vagus nerve stimulation for treatment of cluster headache and migraine.

This item was referred to NTAG via IFR panel as an increasing number of requests had been received. The secretary introduced the evaluation report.

The vagus nerve is a complex cranial nerve with a variety of functions. Experience with implanted electrical stimulation devices for the treatment of epilepsy suggested that vagus nerve stimulation may be helpful for people with cluster headache and migraine.

Non-invasive transcutaneous stimulation of the vagus nerve (nVNS) is a newer treatment modality which aims to treat headache disorders while avoiding the need for an implanted device. The mechanism by which nVNS treats headache is poorly understood, but may be due at least in part to inhibition of pain signalling by the neurotransmitter gamma amino butyric acid (GABA).

Gamma Core (electroCore LLC) is a handheld device, the size of a mobile phone, which provides non-invasive transcutaneous vagus nerve stimulation (nVNS). It is intended for treatment of adults with primary headache, including migraine and cluster headache, and medication overuse headache.

Cluster Headache: Cluster headaches are characterised by recurrent attacks of unilateral pain, often in or around the eye or temple. Attacks usually last between 15 minutes and 3 hours, and are almost invariably described by patients as the worst pain they have ever experienced. Attacks may be episodic (occur in clusters of 1 week to 1 year, separated by remission lasting at least 1 month) or chronic (remission is absent or lasts less than 1 month). The prevalence of cluster headache is roughly 0.2%, and it is at least 2.5 times more common in men than in women.

The Prevention and Acute Treatment of Chronic Cluster Headache (PREVA) trial was an open-label RCT which compared the gammaCore device plus individualised standard care to standard care alone. The nVNS group had greater reductions in cluster headache frequency than standard care alone (-5.9 vs. -2.1 attacks/week) and were more likely to reduce attack frequency by at least half (40% vs. 8.3%). Quality of life and headache impact scores were significantly improved. However the trial is limited by its open-label design and short duration. Sham devices, as used in other trials, had not yet been developed when this trial was conducted.

Another RCT for acute treatment of cluster headache found no difference in cluster headache pain intensity when nVNS was compared to sham nVNS. A subgroup analysis suggested there may be a significant benefit in patients with episodic, but not chronic, cluster headache. Some limitations of the trial were that the sham nVNS device did not cause localised muscle contraction at the application site in the same way as the active device. This may have led to accidental unblinding, and in fact the authors noted that “a considerable proportion of patients correctly guessed their treatment allocation” after one treatment. This may have introduced bias. In addition the trial may have been underpowered as treatment effects were overestimated.

Migraine: Migraine is a primary headache disorder characterised by episodic headaches accompanied by other symptoms such as photophobia, phonophobia, nausea and vomiting. Migraine is often accompanied by aura, which commonly features positive or negative visual phenomena. Migraine is much more common than cluster headache, with a prevalence of around 18% in women and 6% in men.

One double-blind sham-controlled RCT assessed nVNS for treatment and prophylaxis of migraine. The trial found no difference between groups in the mean number of monthly headache days. Several smaller, non-randomised studies have been conducted for both indications, but add little to the available evidence on effectiveness. Limitations of the randomised trials, such as incomplete blinding and short duration, mean that their results should be interpreted with caution.

NICE published interventional procedure guidance on the use if non-invasive vagus nerve stimulation in March 2016. The guidance does not name any specific products but does state that it applies to handheld devices applied to the neck. In the UK, this definition currently applies only to gammaCore.

NICE found that there was no evidence of substantial safety concerns, but that the evidence for efficacy was limited. They therefore recommended use of nVNS only with special arrangements for clinical governance, consent, and audit or research. Further research is encouraged. The guidance has no information on cost or cost-effectiveness. NICE also highlighted that cluster headache is an uncommon disorder with limited treatment options while migraine is substantially more common. NICE considered therefore, that good evidence of efficacy for migraine is therefore particularly important.

Treatment with nVNS appears safe and well-tolerated. The longest-term safety data come from a very small (n=19) 52-week cohort study in patients with cluster headache. There are theoretical safety concerns due to the diverse functions of the vagus nerve, but experience with implanted devices suggests no excess of adverse events.

Treatment with gammaCore costs £225 per patient per month. A German cost-effectiveness analysis suggests that this is cost-effective in cluster headache patients but no UK analyses are available. Drug costs are lower in the UK than those quoted in the analysis, which may alter the cost-effectiveness.

The group agreed that there was insufficient evidence of efficacy and cost effectiveness at this stage to recommend use of this treatment for cluster headache or migraine.

ACTION Secretary to draft recommendation as above.

5) Appraisal: Home Iontophoresis for Hyperhidrosis

This item was also referred to NTAG via the IFR panel.

Hyperhidrosis is a common disorder characterised by sweating in excess of that needed for normal thermoregulation. Primary hyperhidrosis occurs in otherwise healthy people and is typically focal affecting the, palms, soles and axillae. It is a socially distressing condition, which can have a significant impact on a patient's quality of life.

Iontophoresis is a non-invasive process in which a low intensity electrical current is applied to the affected area of skin through water baths or wet contact pads. It is widely used in the UK, and most dermatology departments treat palmar and plantar hyperhidrosis, but not all provide a service for those suffering in the axillae. Patients typically receive one course of iontophoresis consisting of 7 to 12 sessions over a four week period in the hospital setting. If a course of treatment is successful, it will need to be repeated at one to four weekly intervals, and for this patients are encouraged to purchase their own iontophoresis device for home-use.

Tap water iontophoresis has a long history of safe and well tolerated use when administered correctly. Although some side effects such as a burning or tingling sensation, tingling, erythema and small vesicle formation may be experienced during treatment, these are usually mild and rarely necessitate discontinuation of treatment. Iontophoresis using a home device is not expected to result in any additional side effects to those typically experienced in a hospital setting.

Tap water iontophoresis has a long history of use for the treatment of hyperhidrosis in a clinical setting, but the evidence supporting its use is based largely on clinical opinion and several small studies. Only one small study has assessed the efficacy of home iontophoresis using a device readily available in the UK. In this study patients with primary palmoplantar hyperhidrosis received a course of iontophoresis in a hospital setting. If treatment was successful, patients were provided with information on purchasing an Idrostar unit for home use. Most patients (72%) found that hospital iontophoresis was an effective and well-tolerated therapy. However, home iontophoresis was less effective with 62% reporting it was 'much less effective' than hospital treatment. Patients applied lower currents at home compared with those administered by nursing staff in the hospital, which may explain the reduced efficacy.

Iontophoresis for hyperhidrosis is a nurse led service, and costs are expected to be limited to activity costs for the initial treatment schedule. Based on 2017/18 National Tariff prices a typically course of iontophoresis in an outpatient setting cost £528 to £808. However, the costs would be significantly higher if patients not purchasing a home device were to receive ongoing maintenance therapy at one to four weekly intervals in an outpatient setting. A range of iontophoresis devices suitable for home-use are available in the UK, costing from £360 to £1,300 (inc VAT). If the NHS were to provide a device for patients to administer their own treatment at home instead of in a hospital setting there may be some scope for cost savings to be made. However, the margin would depend upon the acquisition cost of the device, and ultimately the number of outpatient sessions replaced. With a combined cost of £552 for the first outpatient attendance and the cheapest device, home use would need to replace at least seven further outpatient attendances to be a cost-effective option.

There are no national guidelines on the use of iontophoresis in the management of hyperhidrosis, and treatment is conducted according to local protocols. Patients typically receive one course of iontophoresis consisting of seven treatments given over a period of four weeks (Day 1, 2, 4, 7, 10, 15 and day 22) in the hospital setting. Each treatment session varies from 20-30 minutes depending on the areas being treated.

If the initial course of treatment is successful, it is recommended that a single maintenance session should be carried out as soon as the sweating starts to return. The frequency of the maintenance treatment varies with the individual, but is normally required at one to four

weekly intervals. Most dermatology departments encourage patients purchase their own iontophoresis unit for home-use in order to administer their own maintenance treatment.

The group agreed that there is insufficient evidence to approve the use of a hand held device for home iontophoresis for treatment of hyperhidrosis. There was also some discussion around the funding of iontophoresis in a hospital setting as there was limited evidence of efficacy for this practice; it was also noted that excessive sweating is not a disease and could in some cases be classed as cosmetic. This would be discussed further by the value based clinical commissioning group.

ACTION Secretary to draft decision summary as above

6) Work Plan and Topics for next year.

The group discussed the work plan. It was noted that there were a few items for discussion for the June meeting:

- Sodium Oxybate for adult patients with narcolepsy and cataplexy; this had been approved by NHS England for use in children.
- Rituximab for treatment of chronic graft versus host disease.
- Ozurdex treatment pathway (updated)

The following new drugs had also been added to the work plan:

I. Bezlotoxumab for Clostridium difficile infection and for the prevention of recurrence after second-plus episodes. It is a monoclonal antibody that targets Toxin B produced by C. difficile. Given as a one-off infusion.
II. Pitolisant for Narcolepsy with or without cataplexy in adults.

7) AOB

Regional Medicines Optimisation Committees:

The group discussed the RMOC's and the engagement events that a few members had attended. It was noted that RMOC's would be set up to start in April; however they will currently concentrate on medicines optimisation. Members agreed it was therefore important for NTAG to continue meeting as agreed previously. Dates for 2017 had already been circulated and these would go ahead.

It was agreed that another GP was needed following Roger's resignation. AW agreed to discuss this within Hartlepool CCG as a representative from the South of the patch was required. BR agreed to contact JC as a finance representative had not been able to attend for the last few meetings.

No other business was raised and the meeting concluded.

The date of the next meeting was noted to be 6th June 2017

Minutes produced by B Reddy, Professional Secretary to NTAG, 10th March 2017.