**Introduction:** Spinal Muscular Atrophy (SMA) is a genetic condition affecting muscle strength. It is caused by a gene alteration in both copies of the SMN1 gene leading to disruption of normal survival motor neurone (SMN) protein formation. Individuals affected by SMA have no SMN1 protein. This means the motor neurones in the spinal cord (anterior horn cells) cannot replicate and will either not be formed or die off (atrophy). It is a serious and progressive condition. It does not affect intellectual ability. There are different clinical subtypes based on maximum function achieved and age of onset:

- **SMA 0** - this is the most serious form of the disease and is associated with decreased foetal movement, joint contractures, dysphagia and respiratory failure. Typically, these babies only live a few weeks or months.
- **SMA 1** - accounts for 60% of cases and 90% of those affected are dead by 1 year – these children never achieve independent sitting and are usually diagnosed in the first six months of life.
- **SMA 2** - these children present in early childhood unable to walk — they all develop scoliosis and often require respiratory support as children or adults.
- **SMA 3** – individuals who achieved standing and walking; they present typically in later childhood and able to walk for a period of their life. A further sub classification speaks of SMA3a, with patients becoming wheelchair-dependent in childhood and SMA3b where patients lose ambulation in adulthood.
- **SMA 4** – symptoms start in adolescence or early adult life after a normal childhood; they experience mild disability.

Although these categories represent a description of the patient’s functional potential, the demarcations are not necessarily as rigid and the relation with the level of SMN2 protein expression is not tight either.

Nusinersen is the first and only approved treatment for SMA and is manufactured by Biogen. It is delivered via the intrathecal route. The initial license and SMC approval was for SMA 1. This indication has now been widened to SMA 2 and 3, although the evidence in these individuals is limited and has largely been extrapolated from the SMA 1 group. As SMA 4 affects adults mildly and SMA 0 is so severe, it is felt that neither of these groups would gain clinical benefit from Nusinersen.

**Administration:** Nusinersen is administered via an intrathecal injection. For infants this can be done under local anaesthesia, however for some older children and adults, this may require light sedation or a general anaesthetic. The recommended dose of Nusinersen is 12mg (5ml). The drug requires a loading phase which constitutes the first 4 doses. The first 3 loading doses are given at 14 day intervals, +/- 1 day. The 4\textsuperscript{th} loading dose is given 30 days after the 3\textsuperscript{rd} dose +/- 1 day. Thereafter, a maintenance dose is given every 4 months indefinitely.

For more challenging spines with severe scoliosis, introduction of the drug will often require access via the interlaminar or transforaminal space using radiological guidance. In patients with SMA 2, who have not had scoliosis surgery, the degree of scoliosis is usually significant. They are also likely to have severe osteopenia (due to immobility) and visualisation of the interlaminar space may be challenging even using CT. Hence the
risks of delivery are increased, including puncture of retroperitoneal structures. There is also the cumulative risk of radiation when using CT guidance to deliver this drug with concerns for developing neoplastic disease. The risk is not only to the individual but also to their future children should they wish to have a family, due to radiation exposure to their gonads. Cervical/cisternal punctures have been described in the literature but this will require the specific expertise of an interventional radiologist and also have potential risks. Likewise, small numbers of patients have been treated using an Ommaya reservoir but this option has not been widely explored.

In people who have undergone scoliosis surgery, siting of an injectable implantable infusion port anchored onto the patient’s back or abdomen is a practical approach. Access through the fused bony work will be made through a small bony window (fashioned by a spinal surgeon) under general anaesthesia. This procedure will take about 30 minutes. The intrathecal catheter is then passed through this window, and is connected to an outside port allowing administration of the drug. In patients who have not had spinal fusion, the insertion of the catheter and port system will also be undertaken under general anaesthesia (except that a bony window will not be required) with the first dose of Nusinersen being given at the time of surgery or shortly thereafter. The port will allow subsequent administration of the drug to be undertaken, without concerns around access to the intrathecal space or concerns around involving various professionals including anaesthetists, radiologists, angio suites (if considering fluoroscopic guidance) or theatre space and bed availability. It is anticipated that subsequent treatments will then be carried out according to schedule in a clean environment such as a designated clinic or ward.

However, the insertion of an intrathecal catheter – port system is a procedure that will carry some risk, particularly in patients receiving general anaesthesia who may also have respiratory muscle weakness. Patients need to be able to lie flat (prone) during the procedure and post-operatively will require close monitoring. Longer term potential risks include catheter blockage and infection; this concern is heightened by the fact these patients already have in-situ metal work. The extent and effects of these risks are currently unknown thus open discussions with patients will be important before proceeding. For patients who feel the catheter and port system is unacceptable, the alternative of intrathecal injections will not be possible at this juncture due to clinicians being unable to ensure elective theatre time is guaranteed i.e. in the event of emergency and unplanned procedures, elective surgeries will be rescheduled and this would include treatment with Nusinersen.

It should also be noted that using Nusinersen delivery through an intrathecal catheter–port system will imply that the drug is being used off-license. In this case permission from the Health Board will be sought to ensure potential risks have been explored, a risk / benefit analysis has been considered and approved and that all local governance issues have been addressed.

The Scottish Nusinersen Pathway

The Scottish Muscle Network have developed a pathway for the treatment of SMA in Scotland to ensure that all children and adults have equitable access. This pathway has been divided into two sections.

- SMA 1 Pathway (Paediatric pathway)
- SMA 2 and 3 Pathway (Children and Adults)

All children and adults expressing an interest in Nusinersen who meet the inclusion criteria will be assessed on an individual basis. The decision to treat any patient will be discussed within an experienced
multidisciplinary team (MDT) setting that includes pharmacists, neurologists and paediatricians that treat and manage SMA patients, anaesthesiologists, cardiologists, respiratory clinicians, nurses and physiotherapists who are specialists in neuromuscular disorders or who have a special interest in muscle wasting conditions. Access to this MDT will be initiated by the Consulting Physician who will present the case in full. In difficult cases where the MDT is not in agreement, a further opinion will be sought from the National MDT Steering Committee for SMA in England. If an agreement is reached to treat a patient with Nusinersen, then the responsible physician will submit an application via the ultra-orphan drug process (PACS 2).

SMA 1

Inclusion Criteria
Children with SMA 1 who are not invasively ventilated.

Exclusion Criteria
Children who are currently on invasive ventilation with tracheostomy; these children can be reconsidered if they improve and are able to be weaned from their ventilation.

Other considerations
- As this is still a treatment in the early stages of administration, children and their families will require to participate in assessment protocols and procedures which may be time consuming and require frequent hospital visits. This is to ensure we are monitoring the effects of the drug in alignment with the Scottish Medicines Consortium’s requests. Information on the child’s progress will be entered into the national SMA REACH database in order for results to be compared throughout the U.K. This also enables longitudinal data collection to monitor patients throughout their treatment. It should be noted that these assessments are time consuming and although there are specialist NM paediatric physiotherapy services in Scotland, as more children are treated, capacity will be limited, and clinical time potentially drawn from other NM conditions.
- Children and their families will be expected to participate in therapy programmes.

SMA 2 and 3

Clinicians recognize that not all children and adults who wish to access this drug will be suitable candidates and that the supporting evidence for this category of patients is simply based on extrapolation of data from treatment of SMA1 patients. In order to protect those adults who are more vulnerable in terms of health and wellbeing, screening procedures will be necessary and the following criteria must be satisfied. In adolescents transitioning to the adult service and in adults, we envisage that the implementation of the intrathecal catheter-port system would be the most practical approach that will allow uninterrupted schedules of treatment with Nusinersen when compared to the alternative approaches.

Whilst clinicians are aware that there is no infrastructure in place in any of the 4 main centres in Scotland (or the smaller district general hospitals) that would allow treatment of adults with SMA 2 and 3, we are currently working with the various Health Boards to establish a service that would allow provision of treatment in a reliable fashion. If the proposed intrathecal catheter-port system is not applied then different services will need to be in place to fund access to elective theatre space and time, anaesthetists, neurologists, respiratory intervention, pharmacy and physiotherapy. The Scottish Muscle Network, in partnership with the National
Services Division is in the process of collecting information on the current levels of service provision available to this group to better understand Health Board readiness to commence treatment in adults.

The SMC have also advised that outcome measures need to be collected on this population to assess the functional benefit of Nusinersen after three years of treatment.

**Inclusion Criteria**

- All patients with SMA 2 and 3 where functional gain with Nusinersen is anticipated and who have some residual motor reserve will be considered under the pathway. **This will include ambulant and non-ambulant patients with SMA 3. The functional gain would include upper limb/distal hand function, neck strength or posture, preservation of ambulation where relevant, improvement in bulbar function and respiratory muscle strength.**
- Patients with spinal rods / metalwork will be assessed on an individual basis and after discussion with the spinal surgeons. Whilst these patients pose a higher risk, the Scottish Muscle Network is aware that some of these patients may have started treatment prior to spinal fusion. This will be discussed prior to any such surgery. For young people with spinal fusion, a phased approach, where experience is gained with the catheter-port system, will be introduced as there is no experience in Scotland of treatment with this group. The Scottish Muscle Network have made contact with colleagues in other parts of the world to learn from their experience with this group and to ensure that clinicians have fully researched the procedure prior to its introduction in Scotland.

**Exclusion Criteria**

Whilst it is not possible to list all criteria, all appropriate patients with SMA 2 and 3 will be assessed on an individual basis.

- Patients on 24 hour ventilation / tracheostomy ventilation.
- Patients where access to the lumbar spine is prevented by spinal scoliosis / anatomical obstruction.
- Patients who have trismus that would preclude intubation and general anaesthesia.
- Patients with raised intra-cranial pressure
- Patient with anorexia / nutritional deficiency
- Patients with significant mental health problems or who have difficulties attending hospital appointments.
- Patients on long-term anticoagulation therapy which would pose problems when performing surgery/accessing the intrathecal space, and potential bleeding long term, secondary to movement of the intrathecal catheter.
- Patients with significant life limiting co-morbidities

**Pre-operative assessments**

Given the intrathecal catheter–port system will require to be carried out under general anaesthesia, and where required a bony window in patients who have had previous spinal fusion, patients will require the following pre-operative assessments:

1. **Anaesthetic assessment** – The anaesthetist will assess the spinal space and access to this. They will assess the anaesthetic risks. They will assess problems around intubation (especially in patients with mouth opening limitations).
2. **Cardiac assessment** to assess suitability of patient for General Anaesthesia and if treatment is required to optimize pre-operative state.

3. **Respiratory assessment** to assess if respiratory muscle status can be optimized further pre-operatively.

4. **Orthopaedic assessment** including radiological tests with CT of the spine pre-operatively.

**Monitoring and Assessment of Efficacy**

1. **Functional Assessment**: All adults will require to undergo a screening assessment by an experienced physiotherapist and regular assessments (minimum of every six months) to assess change. This will include all or some of the following: the Egen Klassificateion (EK) Scale, Revised Upper Limb Module (RULM), Revised Hammersmith, Functional outcome Measure assessment (SMA Reach) and the 6MWT. This is not exhaustive as further validated scales are being developed within the national SMA Reach group. **It should be noted that these assessments which are very time-consuming, may prove challenging as there is currently no adult neuromuscular physiotherapy service in the East and North of Scotland and a limited service in the West of Scotland.**

2. **Respiratory Assessment**, and **sleep study** by a respiratory / critical care consultant experienced with neuromuscular disorders: Forced Vital Capacity (FVC), Peak cough Flow (PCF) and ToSCA on a regular basis dependent upon the baseline pulmonary function tests.

3. **Neurophysiological assessment** to assess baseline compound muscle action potentials and changes over time. In the majority this would be an upper limb CMAP. In SMA 3 patients, a lower limb CMAP could also be studied. Baseline measurements will be obtained and then reassessed on an annual basis.

**Long term treatment with Nusinersen in SMA 2 and 3**

Initially the drug will be administered for a period of 3 years. Physiotherapy assessments will be carried out throughout the 3 year period on a 4-6 monthly basis and there must be evidence of stabilization, improvement in function and no evidence of significant side effects or complications to justify continuation of treatment.

There will be an MDT discussion regarding continuation of treatment and if deemed suitable, then the case would be put forward to the Chief Medical Officer to apply for continuation of Nusinersen administration.

**Stopping Strategy**

1. If at any point during the pathway, the patient wishes to terminate their treatment with Nusinersen, they will be supported by their treating consultant and the MDT team. They will continue to receive appointments for their ongoing care in the same way as those patients not being treated by Nusinersen.

2. If during assessment the patient is showing deterioration in their outcome measures, discussion around termination of treatment will be initiated.

3. If the patient develops a life limiting co-morbidity.
Nusinersen (Spinraza®) Pathway for Spinal Muscular Atrophy

**SMA Type 1**
Not invasively ventilated

- **No**
  - Pathway ends
- **Yes**
  - Pre-op assessments
    - Anaesthetic
    - Cardiac
    - Respiratory
    - Orthopaedic

  - Deliver treatment
    - Favourable opinion
    - Not favourable
      - Pathway ends

**Ongoing assessments**
- Functional (by experienced physiotherapist, at least every 4-6 months)
- Respiratory
- Neurophysiological

**SMA Type 2 or 3**
Functional gain anticipated
Has residual motor reserve

- **Yes**
  - Pathway ends
- **No**
  - Pre-op assessments
    - Anaesthetic
    - Cardiac
    - Respiratory
    - Orthopaedic

  - Deliver treatment
    - Favourable opinion
    - Not favourable
      - Pathway ends

- Evidence of stabilisation
- Improvement in function
- No significant side effects or complications

- **Yes**
  - Continue treatment
- **No**
  - Stop treatment
**SMA Type 2 or 3 ADULT REFERRAL PATHWAY**

Patient happy to be considered for Nusinersen to be delivered via intra-thecal catheter port system → **No → Pathway ends**

Yes → Discuss with MDT → opinion not favourable → **Pathway ends** → discuss outcome with patient

↓

Favourable opinion

↓

Does patient have spinal rod or previous fusion? → **Yes** →

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**Pathway 2**

1. Refer to Anaesthetists for opinion as to whether fit for GA
2. Refer to Respiratory and Cardiology: what is prognosis and how can we optimise Rx pre-surgery?

↓

Favourable

↓

Not fit → **Pathway ends**

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Discuss case with spinal surgeons

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Bony window possible

↓

Bony window not possible

↓

Favourable opinion

↓

Pathway ends

↓

Put forward for treatment

↓

Pathway ends

↓

Put forward for treatment

↓

**Pathway 1**

1. Refer to Anaesthetists for opinion.
2. Refer to Respiratory and Cardiology: what is prognosis and how can we optimise Rx pre-surgery?
3. Ask Respiratory if lateral decubitus positioning safe for respiratory muscle status during procedure?

↓

Favourable opinion

↓

Not favourable

↓

Put forward for treatment

↓

Pathway ends
NOTE
This pathway is not intended to be construed or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to pathway recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national pathway or any local pathways derived from it should be fully documented in the patient’s case notes at the time the relevant decision is taken.

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