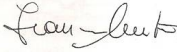


PROTOCOL**Title: Spinal Muscular Atrophy Research and Clinical Hub UK
(SMA REACH UK)**

UK Sponsor	GOSH	
Funder	SMA UK and MDUK	
Chief UK Investigator	Professor Francesco Muntoni Dubowitz Neuromuscular Centre	 (14-11-2019)
Newcastle Principal Investigator	Dr Anna Mayhew Newcastle University	
Co-Investigator	Professor Eugenio Mercuri Rome University	

TITLE:**Improving standards of care and Translational Research in Spinal Muscular Atrophy****Introduction**

Spinal Muscular Atrophy (SMA) is an autosomal recessive genetic disease that affects the motor neurons of the voluntary muscles that are used for activities such as crawling, walking, head and neck control, and swallowing. Approximately 1 in 6000 babies born are affected and about 1 in 40 people are genetic carriers. Childhood SMA can be divided into three subtypes depending on disease onset and severity but all patients suffer from degeneration of motor neurons controlling voluntary muscles with proximal limb and trunk muscle weakness leading to respiratory distress and in the most severe cases, ultimately death. Approximately half SMA children have the severe infant form, named SMA type I that is associated with severe respiratory problems and affected children are never able to sit on their own. The others have SMA type II or type III, defined by the ability to sit or to stand and walk, at some time in the course of development. The clinical course is unusual for a degenerative disease with a prolonged plateau or slowly declining phase after an initial more rapid period of declining function. The disease is caused by the absence of the SMN1 gene resulting in the production of low levels of a protein (SMN) necessary for the survival of motor neurons. Progressive loss of motor neurons in the spinal cord causes muscle atrophy that can lead to fatal respiratory problems, difficulties eating and swallowing and skeletal deformities. Regular pulmonary, nutritional, orthopedic and orthotic assessments and monitoring are necessary for the lifetime of the condition since diagnosis. The impact of this disorder in clinical practice is huge as the management of SMA patients requires a multidisciplinary approach involving specific professions including paediatric neurologists, specialist nurses, physiotherapists, speech and language therapists, dieticians, orthopedic surgeons and orthotics, gastrointestinal surgeons, care advisors. The involvement of the palliative care unit is also required, especially when dealing with SMA type I.

Recent advances into drug development have resulted in specific therapies becoming available for SMA and other compounds are also under investigation via clinical trials. This rapid advances has pushed the development of outcome measures considerably over the last few years and In preparation for the inevitable upcoming clinical trials in SMA there is the ongoing need for a robust clinical and research Network poised for designing and improving upon suitable outcome measures for clinical trials, in non-ambulant and ambulant patients for clinician rated scales and patient reported scales, and identifying possible bottlenecks.

Some important steps have already been taken in capturing data in SMA patients with the development of the SMARtnet and SMA registry databases. SMARtnet is mainly a large collection of clinical and physiotherapy assessment information while the SMA registry is mainly a genetic database; both these databases, despite providing unique information, are incomplete due to the lack of mutual integration. Furthermore, the longitudinal data collected has never been implemented or undergone full validation with RASCH analysis so it has never been reviewed and audited. Now that pharmacological interventions and genetic based approaches are being successfully studied in preclinical models, further implementation of these databases and leading coordination becomes crucial to ensure that patient information and physiotherapy data are integrated in order to put into place the first data management system across the UK and Europe. This will both improve our knowledge of the natural history of SMA, with the clear consequence of implementing improved standards of care, as well as facilitate the preparation of personalized national and international clinical trials.

Aims

The primary aim of this project is to establish the first national clinical and research network named SMA REACH UK (SMA Research And Clinical Hub UK) to establish a national agreement on clinical and physiotherapy assessment and standards of care. We propose designing, piloting and expanding an electronic database created to streamline the collection of data for patients with SMA. This UK SMA database would be a unique infrastructure, originally started at GOSH and Newcastle, which has built up and is becoming accessible to all specialist centres across the UK who treat patients with SMA.

The Dubowitz Neuromuscular Centre at Great Ormond Street Hospital is well suited to lead this project joined by the Newcastle neuromuscular team. The dedicated multidisciplinary team has a history of leadership and experience with the related existing resources, specifically SMARtnet, North Star and SMA Patient registry. The SMA REACH UK project will begin with garnering a clear picture of the available patient pool, which is likely to be over 100 patients at GOSH (0-19 years) and 50-80 in Newcastle (paediatric and adult patients). Information about these patients will be collated from clinical charts and records. Once patients are identified, they will be invited to participate in the collection of harmonized data by enrolling in the SMA REACH UK. This database will be designed, created and run with help from a well-known software engineering company with experience in organizing healthcare systems. The long term aim is to utilize this streamlined assessment tool throughout the SMA community. For this project, we aim to enrol 50% of the available patient population at GOSH within the first year and at least 2/3rds by the end of the project. Enrolment of the majority of patients seen at the 2 larger UK sites will provide enough resource to allow for proper trial and reflection on the functionality of the SMA REACH UK before being expanded to additional sites.

The secondary aim of the project is to utilize the SMA REACH UK database as a longitudinal data house where information can be audited and reviewed. This will

provide clinicians and researchers a rich resource of available information on a large collection of SMA patients, in collaboration with another International centre of excellence in SMA research and treatment located in Rome at the Catholic University, thereby facilitating translational research for this common neuromuscular disease in preparation to design National and International clinical trials. Once the system is finalised, additional national sites that have a history of successful SMA enrolment will be invited to participate and collect high quality longitudinal data. This work will be an invaluable tool for the centres likely to be involved in upcoming SMA multicentre randomised clinical trials in SMA type I, II and III.

Further aims of the project are to ensure the functional scales used are suitable and clinically relevant for future trials.

In addition SMA REACH UK is in the position to be involved in an international initiative called ISMAC (International SMA Consortium) with two prestigious Networks: the PNCRN in the United States (Principal Investigator Richard Finkel) and the Italian SMA Network (Principle Investigator Eugenio Mercuri). The Consortium has been contacted by the Biotechnology Company; Biogen with strong interest in collecting anonymised natural history data on the entire spectrum of SMA severity from routine clinical visits. The main data to be collected, including medical information and physiotherapy assessments, were agreed across the three Networks and will be slightly more extended than the current dataset collected at each Centre. The data collected with the new dataset will be collated on a separate IT platform which will contain anonymised clinical and physiotherapy data from patients who have consented to take part, and will be accessible to Biogen and can be shared with third parties (pharmaceuticals, academic and government institutions) in a strictly anonymised form. The ownership of the data will remain with the PIs at each centre.

Methodology

Location

This project is designed as a large multi-institution study including up to 20 centres in the UK led by GOSH in London in conjunction with Newcastle University. In view to extend this project to an international level, another European centre in Italy (Paediatric Neurology Division at the Policlinco University Hospital in Rome) has been invited to co-operate with designing and piloting the physiotherapy tools.

The large dataset in collaboration with the SMA consortium (ISMAC) will involve only UK centres with a relevant number of SMA patients and we anticipate this will include approximately 5 to 7 centres. In this case, we will be contacting participants at these centres, asking them to re-consent on the new ethically approved consent forms. Furthermore, all other UK national centres open to SMA-REACH will be invited to participate in the ISMAC collaboration, which will involve re-consenting patients to the new ethically approved consent form and completion of a minimal dataset. We anticipate that in total 400-600 eligible patients will be recruited into the study from all neuromuscular UK centres.

If patients choose not to share data as part of this collaboration (or are participating in clinical trials), then they can still be a part of SMA-REACH and data will not be shared with third parties.

Inclusion criteria:

All patients with genetically confirmed SMA type 0, I, II and III aged from neonates to adult age will be recruited (adults can be recruited). The diagnosis of SMA must be documented by the absence of SMN1 on standard genetic tests for the disorder, and the determination of type I, II and III SMA by the ability to maintain a sitting position when placed, and if they are ambulant/non-ambulant. When possible, each patient should also have the determination of the SMN2 copy number.

Exclusion criteria

There are no exclusion criteria if a genetic diagnosis of SMA has been confirmed.

Involvement in clinical trials is not an exclusion criterion nor having had surgical procedures. Patients who are participating in clinical trials with novel treatments will also be included in the database although the data from this subgroup won't be analysed in the natural history study, nor shared with pharmaceutical companies and other third parties as part of the ISMAC collaboration. Patients who have had orthopaedic surgery will also be eligible, as this will further inform the natural history of the condition after surgery. Participants currently or previously taking a treatment intended to effect change in SMA (i.e. salbutamol, hydroxyurea, valproic acid, carnitine, etc) will also be included in the study as no effective treatment has been identified to date. The use of concurrent medications will be recorded at each visit.

Patient selection criteria/Number of patients/Methods for identifying and recruiting patients

Patients will be selected amongst those attending standard follow up clinics in the participating centres according to the mentioned inclusion criteria. We do not foresee many difficulties in recruiting patients as the project does not require any extra appointments for the patients and their families and the assessment does not require any extra invasive procedure on top of the standard clinical procedures. It does, however, include an extended physiotherapy assessment.

We anticipate that we will be able to enrol the vast majority of the patients regularly followed in the routine clinical care. .

Medical Assessment/Physical Examination

Standard clinical procedures for all patients will include the recording of the following parameters at each visit (every 7 months +/- 4 weeks) (Consensus Statement for Standard of Care in Spinal Muscular Atrophy, Ching H. Wang, et al, Journal of Child Neurology Volume 22 Number 8 August 2007 1027-1049), in addition to the procedures outlined in appendix 3

Height (standing or arm-span), weight and blood pressure

Physical examination as noted in appendix 3

Pulmonary function test (Spirometry) will be also performed at each visit (forced expiratory vital capacity, FVC as percent predicted). No additional tests are required.

In young children (<5 years) or when there is no compliance, or following clinical indication (daytime hypercapnia or FVC<60% at the spirometry), regular overnight sleep studies might be indicated as part of the current standard of care. No additional tests are required.

ECGs are usually performed at the first appointment and repeated every few years as follow-up or more often if there is a clinical indication.

Additional ECG will be performed prior commencing Salbutamol therapy and after three months of being on therapy. Follow-up ECGs are performed once a year in all patients receiving salbutamol therapy.

Bloods are taken on average once a year to monitor the Vitamin D level and electrolytes in patients on Salbutamol. No additional bloods are required.

Whole spine X-ray will be performed following the clinical indication (i.e. presence of spinal curve, back pain) and repeated follow-up will depend on the scoliosis progression. No further tests other than what is required for clinical care will be requested.

Lumbar spine or total body DEXA scan are not regularly performed and are requested following a clinical indication (bones fractures following minimal trauma, back pain, low vitamin D level, pre-op for spinal surgery). No additional DEXA scans other than those required as part of routine clinical care are required as part of this project.

Speech and language therapy and dietician review will be recorded when requested following a clinical indication.

Please refer to appendix 3 for additional standards of care parameters

Furthermore, we will record any patient's cause of death, and number of chest infections within the last 6 months.

Physiotherapy Assessment

All patients regardless of SMA type or ambulation status will receive a physiotherapy assessment in keeping with standard clinical practice for children and young people with SMA. This will involve gathering a thorough physiotherapy subjective history (current concerns/changes regarding mobility, falls, fatigability, endurance/exercise tolerance, equipment and orthotics evaluation, discussion of orthopaedic concerns, pain, activities of daily living, environmental concerns and home modifications); and an objective assessment of motor development, muscle length/contractures, joint range of movement, muscle strength (myometry or manual muscle testing if appropriate) and posture involving spine, head, lower and upper limbs. For the ambulant population further assessment of higher level motor functions such as gait, standing posture, stairs, 10 metres run/walk test etc. will be part of the assessment.

In addition to the standard physiotherapy assessment, several functional measures will be used to assess current level of physical functioning. Due to the nature of this project and the current work being done in developing more sensitive SMA specific scales it is

likely that that the protocol will be drawn from but not exclusively involve the scales mentioned below. Novel outcome measures may also be trialled and form part of the protocol.

Functional Scales for Non-Ambulant Patients

SMA Type 1

Due to the nature of this form of SMA and the young age of the child usually one of the below assessments will be completed, only in exceptional circumstances both will be completed. Length of time to complete these assessments will vary, but can be estimated to take 30 minutes.

CHOP INTEND (The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders) – this is a scale used for the assessment of movement and function of very weak infants with SMA type 1 or weak SMA 2. It consists of 16 items of motor function graded 0-4 with a maximum achievable score of 64 (Glanzman et al, 2010). We estimate this will take 30-40 mins per patient.

WHO DEVELOPMENTAL MILESTONES- For SMA Type 2/3 non-ambulant (all SMA patients). – either conducted as a stand-alone assessment or part of the RHS scale – see below)

Hammersmith Functional Motor Scale Expanded (HFMSSE) (O'Hagen et al, 2007) – this scale assesses motor function in patients with SMA, the original 20 item HFMS (Main et al, 2003) was expanded to include 13 additional adapted items from the Gross Motor Function Measure to enable the scale to be more sensitive to the higher functioning ambulant population. It is an ordinal scale with 33 items, with a 3 point scoring system (2 unaided, 1 with assistance, 0 unable); the items are ordered to become progressively more difficult. The maximum score achievable is 66, the minimum 0. It includes items in supine, prone, sitting, four point kneeling, standing, walking and stepping in addition to transitional movements such as rolling and transferring from the floor/chair to standing. All items are to be tested without use of orthotics (spinal and lower limb). We estimate this will take 30 - 40 minutes for all children who can sit. It can be conducted in association with the RHS (noted below). For weak children, it will take much less time as significant number of items are for higher functioning children. This assessment will require a set of standard 4 stairs, plinth/ mat and stopwatch

Revised Hammersmith Scale (RHS): (Ramsey D et al, 2017) The final RHS consisted of 36 items for very weak SMA 2 through to very strong SMA 3. With regards scoring, 33 items were graded on an ordinal scale of 0, 1, 2 where 0 denotes the least level of ability/function progressing to the highest level of ability to achieve a score of 2, the remaining 3 items were scored 0, 1 where 0 is unable and 1 was able to achieve. The maximum achievable score is 69. The scale is ordered to limit position change with items grouped according to position tested for example sitting, supine, prone, standing etc., items within that position progress from easier to more difficult i.e. items in supine move from crook/hook lying to lie to sit. To avoid a ceiling effect, the RHS contains revised items from the NSAA including two timed tests, and for the weaker end of the spectrum it also contains a revised item from the CHOP INTEND. Two RHS items incorporated the equivalent WHO motor milestone as their top score, item 16 cruising and item 18

walking. The RHS will be performed together with the HFMSE using a single adapted proforma and takes approximately an additional 5 minutes to be completed. All WHO items can be scored withing the scale.

Revised Upper Limb Module for SMA (ULM for SMA) – this tests items which reflect the functional limitations observed in the arm function of patients with SMA (Mazzone et al, 2011). The 2013 version contains 9 core items and 7 extra items (see appendix for current working manual) testing upper limb function. It is recommended for use in children greater than 30 months. It involves items which test both proximal and distal motor function of the arm. We estimate this will take 10-15 mins per patient.

Functional Scales for Ambulant Patients

In addition to the HFMSE / RHS WHO and RULM ambulant patients may be tested on two further assessments -

6 Minute Walk Test (6MWT) – this is a measure of functional exercise capacity and in SMA it used as a measure of endurance/fatigue. It is able to identify a functional deterioration in the ambulant population and identify differences between type 3a and 3b SMA (Montes et al, 2011; Mazzone et al, 2013). It involves walking up and down a 25 metre track without aids or orthotics for as fast as possible for 6 minutes. Lap splits, minute splits and total distance are recorded, in addition to any rests and falls. The protocol is a modified version of the American Thoracic Society guidelines. It takes approximately 15-20 minutes to complete. It is conducted if the centre has the necessary space / time to do this test.

Parent Reported/Patient Reported Outcome Measures (PROM)- (OPTIONAL):

In addition to the functional outcome measures and clinical assessments described we will be requesting the parents and children/young people themselves to comment on their abilities through use of PROM scales, these are likely to also comment on aspects of wellbeing and quality of life. There are not currently any SMA specific PROM scales and therefore we will be looking at a variety of scales to determine their suitability of use and these may be adapted into a more specific scale, it is likely that the protocol is drawn from but not exclusive to measures described below. We also hope to involve patients in the redesign of SMA specific patient reported questionnaires in order to gain an accurate representation of items which are meaningful for children/young people with SMA and their families.

Egan Klassification Scale (EK2) – This will be used for older non-ambulant patients and consist of a series of 17 questions reporting on physical function including ability to transfer, cough, swallowing, fatigue and arm function. The EK measure has been determined to be valid for use in non-ambulatory individuals with SMA (<http://rcfm.dk/english/ek-scale/#english-versions-and-manual>)

It will take approximately 5 minutes to complete the EK2. Additional PROMs will need to be reviewed for length of time they take to be completed.

Additional physiotherapy assessments (as required):

HINE Section 2 (non-sitter infants) – includes 8 items scored on a 5-point scale with 0 as the absence of activity, and a maximum score of 4 points

WHO Motor Milestones (all patients)- includes 6 gross motor milestones as defined by WHO. These milestones are included within the RHS assessment and will be conducted in addition to the CHOP-INTEND where applicable.

Vignos scale (all patients)- to assess lower extremity function. Grading ranges from 1-10; 1 means that the subject can walk and climb stairs without assistance and grade 10 refers to the subject being confined to a bed

Brooke scale (all patients)- to assess the upper extremity function. Grading ranges from 1-6; 1 means that the subject can elevate their arms full range to the head with the arms straight and while grade 6 refers to no useful function of hands. This is the entry item on the RULM.

Impact of Range of Motion (ROM) on Function and manual strength testing

ROM and strength testing will be recorded according to clinical relevance. Grading should be assigned as follows:

- None = no contracture
- Minimal = no influence on function
- Moderate = Some impact on function but still able
- Severe = Significant impact / makes function difficult or impossible

Please refer to appendix 1 for detailed procedures.**Collection of retrospective data and ethnicity**

As part of the study, we will collect retrospective data going back over 10 years (collected on the SMARTNET database) in order to ensure all clinical data is captured. Furthermore, we will collect information on each patient's ethnicity.

Patient Interviews (OPTIONAL):

In addition to these questionnaires, individual interviews with selected patients will be done with the specific purpose of understanding patient's perception about the condition, interventions performed and Standards of Care. The patients will be selected depending on availability and willingness to participate.

The interviews will be recorded for the purpose of being transcribed. Once transcribed, they will be destroyed only keeping the written transcription as part of the SMA Reach data for further analysis.

The interviews will be performed at the most convenient time for the patient. They will be done either face to face, through a phone call or videoconference.

Approximate length of assessment (physiotherapy subjective, objective & functional assessments)

Infant (type 1) – 40 minutes, assessments of infants may take more or less time than that stated. This will include CHOP, HINE and WHO plus joint range

Non ambulant (type 2 & 3) – 1 - 1 hour 30 minutes, including HFMSE with RHS, RULM, joint range, FVC, height, EK2 – for older individuals or where the RHS and HFMSE are unsuitable.

Ambulant (type 3) – 1- 2 hours. HFMSE / RHS, 6MWT

Informed consent

The study does not require any invasive techniques. However, patients and their families will be informed of this study verbally and with a patient information sheet, and they will be asked to sign an informed consent/assent form before entering the study to allow the entry of their data into the new database including the extended physiotherapy assessment. They will be registered on the new database using an anonymous code number. The code number will be maintained as it was in patients previously consented for SmartNet. New consented patients will have a progressive number according with the current SmartNet database. This will be transferred to a SMA REACH UK registration number once the new database is operational.

Sub-study: Strength and function tests in ambulant and non-ambulant SMA 2/3 (OPTIONAL):

We would like to collect information on upper limb strength and function tests in a Sub study of 5-10 patients with SMA II and III, aged 6-15 years to relate to data collected using the above mentioned functional scales. This optional assessment will take place on the same day as routine clinics every 6 months. Data collected as part of this sub study will be anonymised and sent to France for analysis. The analysis will be conducted by The Institute of Myology and the equipment developers' Sysnav navigation technologies using their high-tech software which is necessary to interpret the data. Further to analysis, data collected from these tools will be shared and correlated with data stored on the SMA REACH UK database.

Moviplate, Handgrip and Pinchgrip (Appendix II) - 30 min. (OPTIONAL):

These are three non-invasive new tools recently developed at the Institut de Myologie (Paris) specifically designed for the quantified measurement of the upper limb motor abilities. The Moviplate test is performed with the patient sitting at a table on which the Moviplate apparatus has been placed or if the patient is unstable on a chair, the device is placed on the table of their wheelchair. This machine consists of a plate with two small elevated platforms, which the patient must touch alternately. The patient performs the test sitting down with the forearm placed on a table that has been adjusted to the patient's height. The aim of the test is to tap alternately the two platforms a maximum number of times in 30 seconds, using a co-ordinated extension movement of the wrist and fingers.

The hand-grip and pinch tests are dynamometric measurements of maximum palmar grip and thumb index pinch strength. These are obtained using the handgrip and pinch dynamometers, with the forearm placed on the table and the dynamometer held by the evaluator.

All strength and function tests will be repeated twice per upper limb and during each evaluation session. If the lowest measurement does not fall within the [90% highest

measurement-110% highest measurement] interval, patients are allowed to repeat the tests a third time. The highest value achieved in the two or three tests is recorded.

Accelerometry - ActiMyo (Appendix II) (OPTIONAL):

ActiMyo was developed by Sysnav and the Institute of myology

Actimyo is a wireless system. It consists of two 28g watches that contain three axis accelerometers, three axis gyroscopes and one magnetometer. The two watches continuously record linear accelerations and angular velocity. They have an 18 hour autonomy. The patients are provided with the system and a written patient-directed instruction sheet. Physiotherapists who provide the patient with the actimyo also receive a health care provider-directed instruction sheet.

The system continuously records data during the day time. Watches must be replaced on the docking station every evening, for two purposes: power supply filling, and data uploading. Data are stored on a USB stick which is not accessible to the patient. Then, if the patient has access to a wireless internet connection point, data may be transferred by internet to the central center for analysis, namely the Institute of Myology. It must be noted that the data are a non-understandable anonymous list of points, and that nothing allows the patient to be identified, which guarantees patient privacy. Data are recognized as issued from a specific Actimyo (every actimyo is labelled and sends its label with the data) during a certain period of time. If the patient has no internet connection, data can be collected by the investigation center and upload by the center.

Additional information for those enrolling onto the nusinersen (SPINRAZA®) Managed Access Agreement (MAA)

We will request consent to collect pseudo-anonymised data from the SMA REACH database to be shared with the following institutions:

- NHS England- To monitor patients treatment start and stop criteria as per the terms of the managed access agreement. To monitor case ascertainment in the SMA REACH database.
- The National Institute of Health and Care Excellence- To ensure compliance with the data collection terms of the managed access agreement i.e. to monitor data completeness of mandatory data fields. To monitor case ascertainment in the SMA REACH database.
- University of Strathclyde- To allow matching of clinical and PROMS data.
- Biogen (the company that makes SPINRAZA®)- To enable the company to analyse the clinical and cost effectiveness of the technology and present a submission of the evidence to NICE for a health technology appraisal.

This is as part of the nusinersen (SPINRAZA®) Managed Access Agreement (MAA) set-up in 2019. The consulting doctor will request patients to sign up to the MAA as a separate consent form. Patients with SMA 1, 2 and 3 and meet the criteria set by NICE will be eligible for nusinersen treatment. Further information can be found under NICE guidelines <https://www.nice.org.uk/guidance/TA588>

Study design

We propose to deliver this project over a phased time period of two years:

Phase 1 (First year).

Objectives:

- a. Identify and describe SMA patients population seen at all neuromuscular centres seeing SMA patients
- b. Establish a merged database with clinical and genetic data
- c. Piloting standardized assessment database for SMA patients
- d. Continue recruitment of patients at GOSH, Newcastle and opening up new sites across the UK. Pilot new and adapted physiotherapy assessment tools
- e. Organize a patient/parent focus group with clinicians aimed to update on standards of care.

The early implementation of the SMA REACH UK database initiated in a small number of Centres in UK, will continue at these centres and newly opened centres which have significant number of patients. The Dubowitz Neuromuscular Centre at GOSH is well suited to lead this project, as being already provided the clinical and academic leadership for the UK North Star Network and SMARtnet, in conjunction with Newcastle University.

a. Clinical information of patients with SMA seen at GOSH is recorded in patient charts. A means of easily collating this data does not exist, therefore the first aim of this project will be to identify and describe the SMA population seen at GOSH and Newcastle thereafter.

b. Establish a merged database with clinical and genetic data collating the existing registries (SMARTnet and SMA registry) and grow the collaboration within the National Neuromuscular Database (NaND). The data collected would be jointly administered by the Dubowitz Neuromuscular Centre and MRC Neuromuscular Centres in London and Newcastle. Designing the database will be done with the assistance of Certus, database engineers who have considerable experience designing, building and supporting adaptable software and services, to assist healthcare organizations in the management of complex data and processes.

c. Piloting standardized assessment database for SMA patients to characterize the course of SMA patients and to report data on clinical and biological outcomes for use in trial planning. We will make use of the SMARtnet and SMA Registry infrastructure to create a data house where these measures can be assessed, housed and added to.

d. Patients with genetically confirmed SMA followed at all neuromuscular centres seeing SMA patients, will be consented to be recruited into a longitudinal natural history study and sample size will be based on the figures determined from the point a. (identify and describe SMA patients population seen at GOSH and Newcastle). The recruitment period will be ongoing with the planned full assessment (clinical and physiotherapy) will be performed at baseline, 6 months and 12 months (for most of the patients these latter assessment will fall in to the second year). In parallel to these first UK sites, other international centres with high expertise in SMA care and clinical trials will run parallel projects also recruiting SMA patients to piloting the new tools during their physiotherapy assessment. The principal sites, including the international sites running parallel projects, will meet before the recruitment begins at each site to discuss practical issues and to perform training sessions and inter-observer reliability studies among all the examiners involved. Before starting the recruitment, a designed External Advisory Board will be consulted on the aims of the project and will be invited to attend the Focus group. e. As described above in the physiotherapy assessment section, various physiotherapy assessment tools will be will be piloted during an extended physiotherapy assessment. The SMA REACH UK study will run alongside parallel projects in Italy and USA which will use the same outcome measures, giving a larger dataset which will allow for more rigorous Rasch and psychometric analysis in order to develop robust outcome measures to assess the physical abilities of patients with SMA, thus ensuring the UK is clinical trial ready and aligned to the international agenda.

f. The first focus group will be hosted by GOSH and UCL Institute of Child Health and will occur with the funding and organizational assistance of the well-known UK SMA charities, As discussed in past SMA conferences, the patient population is eagerly awaiting clinical trials. There is a need to identify what study parameters the patient population find feasible and acceptable. This focus group will be focused to identify the degree to which each outcome measure is tolerated, the acceptable frequency of visits, the duration of each visit and length of the study, as well as the general feelings towards study design (i.e. is a traditional 1:1 placebo: active study design acceptable or should alternative study methodology be considered). This information will be collected and analysed after the focus group and will serve as advice for clinical trials, with the attempt to tailor study design to meet patient/family needs and expectations.

Phase 2 Objectives:

- a. longitudinal data analysis collected as required to monitor standard of care and change if needed
- b. organise workshops and training in preparation to expand the Network to the remaining UK Centres

The first longitudinal data analyses will be performed once all recruited patients will have completed at least six months in the study. We will establish the distribution of scores and variability observed over the period from the started recruitment. At this stage the final database amendments will be completed before the network is expanded to national level and remaining centres will be invited to participate to the standardized collection of data. The sites involved will meet before the recruitment is expanded to discuss practical issues and to perform training sessions and inter-observer reliability studies among all the examiners involved.

This second phase will include the provisions of national network workshop and training, equipment and consumables.

This project is expected to be extended further to allow the following objectives:

- a. Initiation and maintenance of the broader network
- b. Periodic longitudinal data analysis collected
- c. Organize patient/parent focus groups with clinicians aimed to discuss implications of potential upcoming therapies; dissemination of results.
- d. Allow the stabilization of the ISMAC collaboration
- e. Allow the prospective long-term follow up of patients with SMA to obtain information about both the natural history of the disease and the effect of different SMA specific drug treatments

This third and last phase shall focus on the maintenance of the broader network after each site have begun recruitment to ensure that individual Clinical Network Centres provide longitudinal data collection for at least 18 months. As there is no pharmacology involved, there is no need to limit the recruitment period. As such, patients will be recruited and enrolled up until the end of the study, allowing us to add as many data points as possible. This will strengthen the adherence of each centre to recognized standards of care, will allow national and international audits and will monitor the impact of evolving standards of care on the natural history of the condition but will also facilitate SMA patient recruitment into clinical trials. In the third year a second patient/parent focus group with clinicians aimed to discuss implications of potential upcoming therapies will be organized and hosted in one of the main UK Centres, with the participation of relevant international clinicians and researchers in order to lay the groundwork to expand the UK Network to other International Centres of excellence in management and research in SMA.

Application of the outcome measures.

In each centre the physiotherapy assessments will be completed by designated physiotherapist(s) who will be fully trained in the specific clinical outcome measures used. The medical assessment will be completed by designated doctor(s) trained in the specific assessment required for children and young people with SMA.

Where informed consent has been acquired the physiotherapy assessments may be videoed in order to determine inter and intra-rater reliability, and to give the possibility of second evaluations of the scores by another investigator. In addition to videoing, where informed consent has been acquired photographs will be taken during the physical assessment in order to construct manuals for the physical assessments/outcome measures.

The videos will be stored in keeping with the strict UK data protection laws and kept on a secure UCL IDHS (data safe haven) server which conforms to the NHS information governance toolkit. As inter- and intrarater reliability testing will involve NHS Staff as subjects, a detailed application for these assessments has been made to the UCL Research Ethics Committee, The inter- and intrarater reliability testing of the RHS in a UK cohort of neuromuscular physiotherapists will form part of an Advanced Physiotherapy MSc project conducted by the SMA REACH physiotherapist.

There will be specific forms for medical practitioners and physiotherapists. Recording of the information will involve use of the SMAREACH scannable key medical information and medical assessment forms for the medical assessment/physical examination. Regarding the physiotherapy assessment a newly created SMA REACH UK worksheet has been created.

Information from both assessments will be uploaded to the anonymised SMA REACH UK database. Patients will be identified by an anonymised SMA REACH UK code, the master key information will be available to specific members of the research team and the clinic administrator. In the initial stages this will involve the use of the previous SMArtnet system and where the SMArtnet system does not allow for the recording of new outcome measures a separate database for novel outcomes will be kept. Following the initial pilot of outcomes the SMA REACH UK database will then be created and all anonymised assessment information will be stored here.

Figure 2. Current Schedule of events for SMA REACH UK

Anticipated Milestones	Anticipated target date
Open SMA sites across the UK and recruit eligible patients to SMA-REACH	Ongoing
National SMA-REACH meeting	Annually
Piloting standardised physio assessment database for SMA patients	Ongoing
Continue recruitment at GOSH (expected to recruit 2-4 patients per month) and Newcastle (expected to recruit 1 patient per month)	Ongoing
Establish a merged database with clinical and genetic data	
Organize a patient/parent focus group with clinicians aimed to update on standards of care and implications of potential upcoming therapies; dissemination of results.	Annually or as required
Workshop and training for other UK centres in preparation for expansion of the Network to other UK centres	Annually
Recruit Adult SMA patients by opening adult centres to SMA-REACH	Start 2019
Allow the stabilization of the ISMAC collaboration with Biogen. Collect and send data to Biogen upon patient consent Allow the prospective long-term follow up of patients with SMA to obtain information about both the natural history of the disease and the effect of different SMA specific drug treatments	Ongoing
Continue with recruitment/data collection and publication of data	Ongoing

Visits to sites

There will be regular sponsor led monitoring visits to sites open to SMA-REACH, as part of audits and reviews.

Discussion of the Results.

The participating centres will meet before starting recruitment and one year after the recruitment has started to discuss the state of recruitment and to plan further steps. A final meeting will be held after the results of the statistical analysis will be available.

Further Statistical Design/Analysis.

The distribution of each of the outcome variables will be assessed. Appropriate descriptive statistics (means and standard deviations for normally distributed data, medians and ranges for data not normally distributed) of each of the measures at each time point will be compared. Also, the mean and standard deviation of change from baseline to 6 months and 1 year will be calculated for each measure. The sample size should provide sufficient precision in the estimates of the means and standard deviations.

Descriptive analysis will be carried out by computing means and medians of continuous variables (as appropriate according to the type of distribution, i.e. whether approximately normal or not), together with ranges, standard deviation and standard errors. Proportions and 95% confidence intervals will be computed for categorical variables.

The Cronbach's alpha will be used to assess the internal consistency of each test. The inter- and intra-rater reliability will be evaluated through the Intraclass Correlation Coefficient (ICC).

Appropriate statistics for repeated measures study design (ANOVA and multivariable mixed effects regression modelling) will be used to assess changes of scores in each scale over time (baseline, 6 and 12 months).

More in-depth examination of scale robustness will be performed via RASCH analysis.

The data elicited from the patient interview will be analysed with qualitative methods according with the specific purpose of the set of interviews.

Confidentiality of Personal Data

Personal data which will be stored for routine clinical purposes will only be accessible to authorized individuals in this study. Personal data will not be entered into the database as part of this research. The clinical data collected will only be linked to the patient by a study code number and will contain no personal identifiers. Informed consent/assent will be obtained from participants to collect and retain this data. The data that will be used for analysis and dissemination for research purposes will be completely anonymised. All staff in UK NHS Trusts are obliged to adhere to their Duty of Confidentiality, GDPR and Caldicott Principles.

Potential Risks to Participants and Researchers

There are no extra invasive procedures involved in this research protocol. Assessments will be designed to minimize fatigue for individuals and hospital attendance. Additional assessments as part of the ISMAC collaboration are not expected to impact on patients' and family's clinical commitment as these will coincide with their clinical appointments.

Potential Benefits for Participants

The information collected in the database will lead to a better monitoring of current standards of care and improving where needed. Furthermore this may facilitate future patient recruitment in clinical trials.

Participants will not receive any payments specifically for taking part in this study. We expect to conduct the assessment in coincidence with the clinical appointment (every 7 months +/- 1 month), however due to the slightly extended time needed for the assessment, refreshments for patients will be provided. It is unlikely the assessments will fall outside the clinical appointment but whenever this will occur, travel costs or reimbursements will be available for families.

Ethical Issues

No specific issues have been identified to arise from this study. Informed consent/assent will be documented using the information sheet and consent/assent form, and GDPR will be adhered to as per routine clinical care. All data held and disseminated for research purposes will be anonymised, containing no personal identifiers.

The study protocol and associated documents for use in the study will be reviewed and approved by the Research Ethics Committee. The commencement of the study at each UK site will be subject to NHS R&D management approval.

Safety Monitoring plan

The study does not foresee any safety issues as the patients will undergo assessments that are similar to those used in routine clinical practice.

Medical audits/reviews and research into SMA

Key personnel upon patient consent will undertake reviews and produce reports that will improve our knowledge of the natural history of SMA and improve standard of care for patients, from data gathered in both the SMARTNET and SMA-REACH database.

Dissemination of Results:

Approximately 3 months will be left to allow for the end of study analysis, data synthesis and publication preparation. The results of the study will be published in peer-reviewed scientific journal(s) and reported as part of submissions to regulatory bodies (NHS R&D offices and Research Ethics Committee). The results of the study are likely to be published in peer-reviewed scientific journal(s) and reported at relevant scientific and patient conferences. Although there may be no direct benefit to those enrolled, this work will result in a clearer picture of long term natural history of SMA in preparation for the inevitable and rapidly approaching clinical trials.

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APPENDIX I

For the functional outcome measure manuals please see the additional folder titled protocol appendix with the manuals/proformas for the scales mentioned in the physiotherapy assessment section.

Also please see accompanying functional scale worksheets v5.3, 16/09/2019

APPENDIX II

Myotools and ActiMyo

Figure 1: Moviplate

This is called a Moviplate and looks at how fast your child can move their fingers up and down.

Figure 2: Handgrip

This is called the Handgrip. Your child will be asked to pull the handle as hard as they can to show us the strength of their grip.

Figure 3: Pinch Grip

This is called the pinch grip: your child will be asked to pinch the silver plate as hard as possible and the machine will measure how strong their fingers are.

Figure 4: ActiMyo

This equipment is called ActiMyo; it looks like a watch and measures level of activity over time.

APPENDIX 3

Please follow the standards of care guidelines as noted within the following link

<https://www.medicalhomeportal.org/diagnoses-and-conditions/spinal-muscular-atrophy>

<http://www.smasupportuk.org.uk/international-standards-of-care-for-sma>