Introduction

The SMA Trust is the only charity in the UK solely dedicated to funding research into Spinal Muscular Atrophy (SMA).

The objective of the SMA Trust is to be active and progressive in the search for a cure for Spinal Muscular Atrophy (SMA). Methods to halt or alleviate the disease are also sought in order to treat both children and adults with SMA to make their lives and the lives of their families more fulfilling.

To realize this vision means investing more funds in research, developing strategic partnerships with the research community, research funding bodies and pharmaceutical companies and ensuring that advances in understanding and treating SMA are communicated as quickly and effectively as possible.

This Research Strategy identifies the opportunities we must grab in pursuit of our objective and highlights the mechanisms through which we will develop our research funding over the next 3 years, to continue to deliver significant and measurable advances in understanding and treating the disease.

We believe that there has never been a better opportunity to translate the significant new knowledge of SMA that has accumulated across the world over the last decade, into potential treatments. We believe that in the coming years any person in this country diagnosed with SMA should have the opportunity to participate in clinical and therapeutic research studies.

To develop on our core objective, we have developed a strong scientific team:

The SMA Trust Team:

Our trustees include two scientific experts in their fields and renowned academics:

- **Professor Angela Vincent, MBBS (Hon PhD Bergen) FRCPath FMedSci, FRS** is Emeritus Professor of Neuroimmunology at Oxford University, and an Emeritus Fellow of Somerville College. She still heads the Neuroimmunology Group working on the role of autoimmunity in neurological diseases.
• **Professor Kevin Talbot, MBBS, BSc, DPhil, FRCP**, is the Professor of Motor Neuron Biology at the Oxford University Nuffield Department of Clinical Neurosciences, and a Consultant Neurologist.

**These trustees are supported by our Scientific and Clinical Advisory Group (SCAG), which is made up of:**

• **Professor Kevin Talbot, MBBS, BSc, DPhil, FRCP**, (Chair – none voting) is the Professor of Motor Neuron Biology at the Oxford University Nuffield Department of Clinical Neurosciences, and a Consultant Neurologist.

• **Michael Sendtner**, Full Professor and Chairman of the Institute of Clinical Neurobiology, University of Wurzburg, Wurzburg, Germany. His primary research interests are on studies of the mechanisms of neuronal cell death, the establishment and analysis of animal models for motoneuron diseases, and development of therapeutic strategies for the treatment of amyotrophic laterals sclerosis (ALS) and SMA.

• **Thomas Gillingwater, BSc, MBA, PhD, MIoD, MCMI, FRMS**, Professor of Neuroanatomy at the University of Edinburgh, Editor-in-Chief at the Journal of Anatomy and Founder Director, CEO & CTO at NeuroORG Business Consulting Ltd.

• **Richard Finkel, BA, MD**, is a paediatric neurologist and director of the neuromuscular programme at the Children’s hospital of Philadelphia, which he established as a world class centre. His research interests are concerned with the development of outcome measures and with the design and execution of clinical trials in SMA, Duchenne muscular dystrophy, Fabry and Pompe diseases. Richard Finkel is also a manuscript reviewer for Paediatric Neurology and serves on many prominent committees.

• **Kate Bushby, MBChB, MSc, MD, FRCP**, Professor of Neuromuscular Genetics at Newcastle University. Kate has been a leader of the European Commission funded TREAT-NMD programme, which has been instrumental in driving international co-operation in SMA therapy.

The SCAG is supported by Vanessa Christie-Brown, Research Co-ordinator. Vanessa was appointed as a result of the SMA Trust Research Strategy. She was a research scientist for many years, working in the field of Immunology, initially at the Royal Postgraduate Medical School, Hammersmith Hospital and later at Imperial College.
The Trustees are supported by the SMA Trust management team:

- Joanna Mitchell, *Executive Director.*
- Casimir Knight, *Trustee.*

### Overview of Current Themes in SMA Research:

1) **The cause of SMA** has been established as a genetic defect which leads to low levels of a critical protein called SMN. How this protein normally functions in the development and maintenance of motor neurons is still debated. Although, increasing levels of SMN using drugs or gene therapy is the most obvious way of treating SMA, a full understanding of why low levels of SMN lead to motor neuron loss may allow other approaches to promoting muscle strength and improving function in people with SMA.

2) **Models of SMA** are an important tool for understanding the basic mechanisms of the disease and for testing potential therapies. Although there are some very good models in existence, as technology advances, new and improved models may provide ways of accelerating basic and translational research.

3) **Gene therapy and DNA based therapies** provide the most obvious way of correcting the basic defect in SMA and either preventing the disease developing if given early, or maintaining and improving function when the disease is already established. Research using animal models of SMA has demonstrated the feasibility of this approach. Several research groups around the world are now actively engaged in moving into clinical trials in humans. This involves considerable work in demonstrating safety, overcoming the technical challenges of delivery of therapy to the nervous system and in developing methods of clinical assessment to determine efficacy.

4) **Other therapies for SMA** are likely to be required in addition to SMN replacement. A full understanding of how muscle and nerve interact with the SMN protein and how other pathways may promote the health of motor neurons may lead to the identification drugs which will be useful as therapies.
5) **Research into management and care** is critical to enhancing the well being of those living with SMA. Furthermore, the successful conduct of clinical trials depends critically on appropriate ways of assessing the disease progress using clinical examination or laboratory tests (biomarkers of disease activity).

### Strategic Priorities:

To achieve this we will fund research in the following way:

a) **Yearly project grants** (Operating grants & Fellowships circa €100 – 200k), via SMA Europe, which address these specific priorities:

   1. Understanding and Function of the SMN Complex as it relates to the Natural History of the Disease;
   2. Innovative Approaches for Therapy of SMA;
   3. Projects addressing bottlenecks impairing rapid transition from basic research to clinical trials: outcome measures and biomarker validation (physiological markers, pulmonary function, muscle mass quantification, CNS imaging etc), administration route of potential therapeutics including studies in the inter-species differences in crossing the Blood Brain Barrier;
   4. Natural History of the early phase in SMA, especially describing the shift from the pre-symptomatic to the symptomatic phase.

b) **Response-mode programme of activity for**, (in order of strategic priority):

   1. Pre-clinical development of treatments to prevent or to slow the progression of SMA;
   2. Training & maintenance of the SMA research community;
   3. The mechanism of the disease and the function of the SMN protein;
   4. *Clinical trials (funding wholly or partly; infrastructure – (e.g. databases);*
   5. SMA biomarkers;
6. Influence scientific community to engage with SMA;

7. Restorative treatments e.g. Stem cell therapy;

*NB: It is thought that clinical trials will move further up the list of priorities in due course.

c) **Large programme grants** (this is in very early discussions, nothing tabled yet, most probably collaborative).

d) Small travel grants to PhD students and post-doctoral workers specifically to attend international research meetings or to visit collaborative laboratories to learn new skills.

In pursuit of these aims, we will seek out and support those who can assist in their successful delivery: collaboration is absolutely fundamental to success. We will, however, continue to maintain rigorous governance and reporting standards in order to ensure that we support scientific and medical research of the highest quality and relevance to SMA. We must remain sufficiently flexible to respond to advances in technology and scientific understanding of SMA, whilst bearing in mind the need to prioritise activities, should opportunity exceed resource.