BPNA
British Paediatric Neurology Association

James Lind Alliance
Priority Setting Partnerships

The Top Ten UK research priorities for interventions in childhood neurological disorders

A British Paediatric Neurology Association and JLA Priority Setting Partnership

"Shaping future research on childhood neurological disorders by bringing together patients, their parents and carers and health care professionals to identify and prioritise unanswered questions around treatments, therapies or procedures to advise researchers and funders."

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TABLE OF CONTENTS

INTRODUCTION

The BPNA

Children with neurological conditions develop significant, often severe, disability and pose huge health challenges. Epilepsy, the most common neurological disorder in childhood, affects 112,000 children & young people in the UK. Approximately 27,000 children in England and Wales are affected by motor disorders and there are at least 70,000 children and adults living in England with one of the 60 muscle-wasting conditions. Hence, the estimated prevalence of all childhood neurological conditions may be in excess of 15:1000.

Whilst huge progress is being made in novel therapies, there remains a need also to address interventions that may improve quality of life in parallel.

Involvement from patients, carers and the public as partners in research improves the utility and conduct of research, with further positive impacts on the people involved. A priority setting partnership was therefore developed to set the research priorities with regard to interventions in children and young people with neurological conditions.

The British Paediatric Neurology Association would like to thank the members of the Steering Group, Expert Panel and the James Lind Alliance (JLA) adviser, Suzannah Kinsella, for overseeing and guiding this process. We would not have succeeded without their leadership, expertise, and dedication.

Image from the final priority setting workshop in March 2022

The PSP Co-Leads

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Dr Ming Lim

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It has been a privilege to be part of the first Priority Setting Partnership undertaken for childhood neurological disorders. At least 200,000 children in the UK live with a range of disability resulting from neurological disorders. As advances are made in our understanding of neurological disease, we need to work in partnership with those most affected to determine the important unanswered questions, and priorities for research moving forward.

We reached out to parents, caregivers, patients and health care providers across the United Kingdom to ask what matters most to them. This two-year process has culminated in priorities that reflect the unanswered questions that are most pressing to those living and/or caring for children with neurological conditions.

As neurologists we see the impact of neurological conditions on the children we care for and now understand what is most important to them. These priorities, if addressed, will help children with neurological disorders to achieve the best possible quality of life, with researchers continuing to search for more effective treatments and interventional strategies.

The Childhood Neurological Disorders Priority Setting Partnership would not have been possible without the individuals, families, care partners, charities and professionals who participated in the surveys and final workshop. We thank them for lending their time and voices.

ACKNOWLEDGEMENTS

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***Information team members involved in full data analysis**
#Information team lead in full data analysis

ACKNOWLEDGEMENTS

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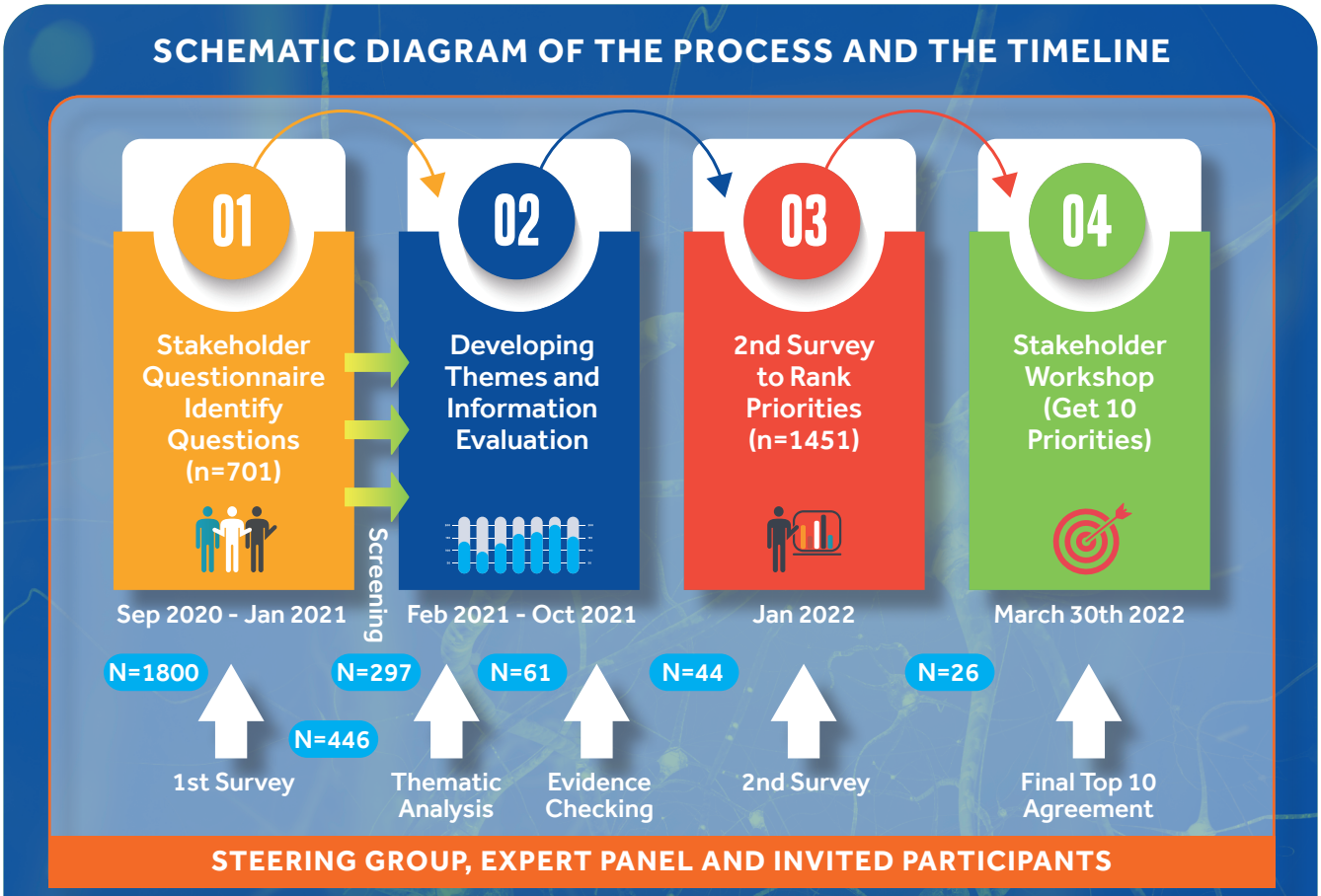
***Information team members involved in full data analysis**

OUTLINE OF THE PROCESS



Childhood neurological disorders (CNDs) are a wide and varied group of conditions affecting a child's central (brain and spine) and peripheral (nerves and muscles) nervous system and include many rare (e.g. neurofibromatosis type 1) and common diseases (e.g. headaches, epilepsy and cerebral palsy).

The James Lind Alliance has a well-established process to research priority setting.

Patients, Carers and Health and Care Professionals were invited to complete an online survey to identify any questions that they may have regarding interventions (treatments, therapies etc.) for children and young people aged 0-25 years with CNDs.

Once all the uncertainties were gathered (701 people submitted 1800 uncertainties) duplicate questions and those that are out of scope (i.e. may be about causes rather than interventions for childhood neurological disorders) were removed. 297 remaining uncertainties were themed, and 61 research questions were generated. The available scientific literature was searched to assess if the questions were already answered.

44 unanswered research questions were then taken forward to a second survey where participants were asked to choose their personal top ten questions. The results of the second survey resulted in a ranking of these 44 questions.

A final "long list" of 26 unanswered research questions was taken to a face to face workshop for the participants to discuss and agree on a "Top Ten."

THE TOP TEN PRIORITIES

01 Can early therapy interventions improve functional and developmental outcomes in babies experiencing brain injury during pregnancy or infancy?

02 What are the most effective interventions to support sleep in children and young people with neurological conditions?

03 How should we best manage emotional well-being in children and young people with neurological conditions?

04 What are the most effective strategies to support communication in children and young people with neurological conditions? (e.g. use of high and low technology augmentative alternative communication (AAC) and to improve speech intelligibility.)

05 What are the most effective medicinal and non-medicinal treatments to manage distressing symptoms (e.g. pain, irritability) in children and young people suffering life limiting neurological conditions?

06 What are the safest and most effective anti-seizure medications for seizures in new-born babies less than 28 days old?

07 Which medications should be used, and in what sequence, in the management of muscle stiffness (hypertonia) in children and young people?

08 Are medications (e.g. antibiotics and/or immune treatments) effective in the management of PANS/PANDAS? (Paediatric Acute-onset Neuropsychiatric Syndrome/Paediatric Acute-onset Neuropsychiatric Disorders Associated with Streptococcal infection)

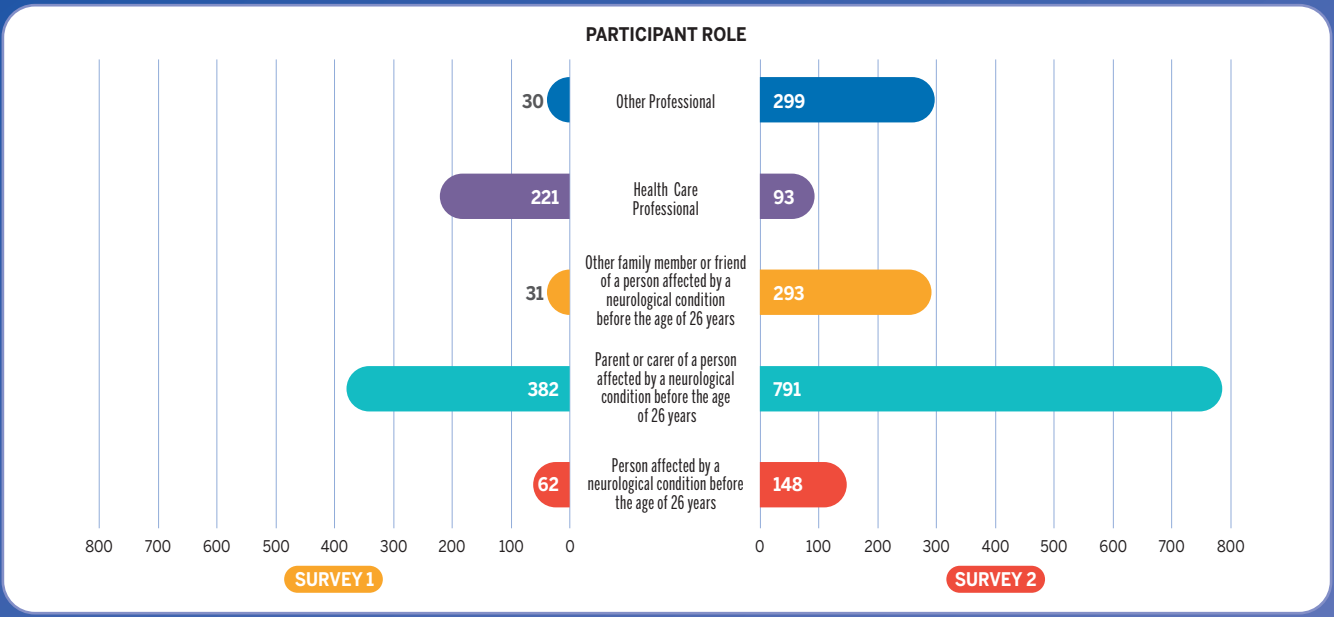
09 Which psychological interventions are most effective in children and young people who have functional neurological disorders?

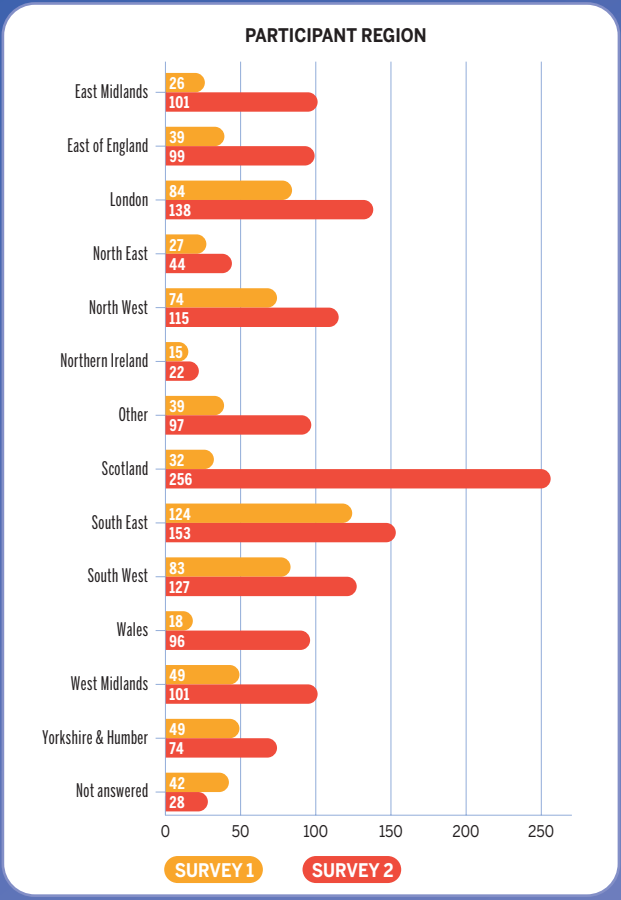
10 What are the best non-medicinal interventions (including therapies, orthotics e.g. splints, high and low technology supports) for children and young people with motor disorders?

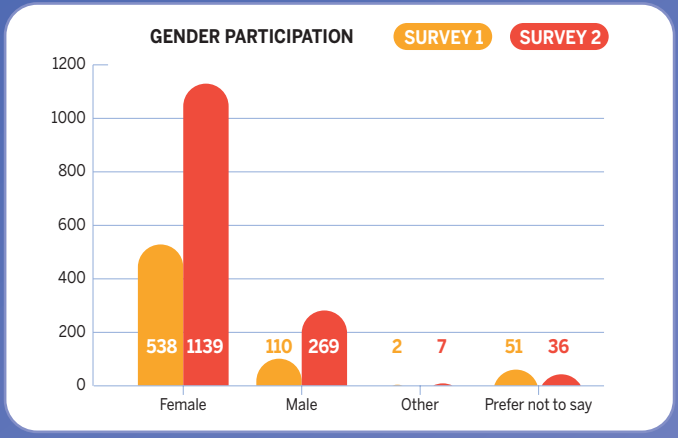
WHO PARTICIPATED?

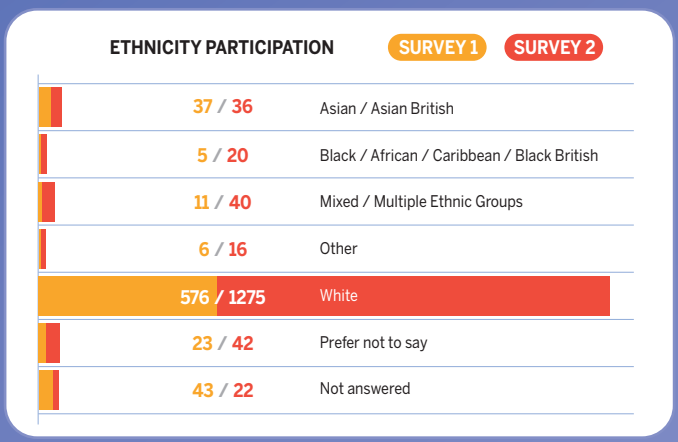
The Surveys

There was fabulous engagement from parents, young people and health care professionals across the UK. The tables below demonstrate engagement in survey 1 and survey 2.









THE FINAL WORKSHOP

27 people attended the final workshop. They included 14 health care professionals, 11 parent-carers and 2 young adult representatives. Due to COVID-19, 3 participants attended virtually, 1 per small group.

Facilitation of the three small groups led to lively discussions and the day was expertly facilitated to keep to time and rank all the 26 questions to produce the final top ten questions. Feedback received from workshop participants on the Top 10 was largely positive.

Participants came to the workshop having considered and individually ranked the 26 questions. During the course of the day, participants adjusted their priorities as they listened to others in their small groups and their views evolved.

"I felt the discussions were balanced and informed, after listening to other participants' personal experiences I slightly changed the order of my top 3."

There was a high level of consistency between groups on the top three and bottom five, from the first small group ranking session, but the middle ranking priorities generated greater discussion.

"A number of those questions (Q11-20) moved a lot in and out of the top 10 list (12-16, 19). They deserved to be in top 10 as well but apparently a selection had to be done."

There was evidence of negotiation and "bartering" (e.g. if a priority went into the top ten, which could it replace?).

"There were a number of questions here (Q21-26) which I felt were very important, and should have been prioritised more, but it felt greedy to push these higher up when my main priority was already in the top 10."

There was one suggestion to change the wording on the question for final publication of the top ten with respect to the question regarding newborn seizures, to clarify that this was for infants less than 28 days. No other wording changes were agreed in the plenary session, despite some suggestions.

There was some disappointment expressed by some participants where their top priorities did not reach the top ten.

"Again I felt that some of these questions should have been ranked higher like ones associated with NF1 and respiratory symptoms should have been higher than emotional wellbeing as once you tackle these issues emotional wellbeing will improve..... I understand we all bring our own bias to the table however I do feel some of the priorities were not given the right consideration to burden on life"

Pitfalls of the process were fed back in a constructive way:

"I think these (the ranked questions) generally reflect the groups views well. The multiple group sessions worked generally to smooth out very strongly held views, perhaps with the exception of one priority which was influenced by two individuals representing a specific patient group. Given the diversity of childhood neurological disorders, and the structure of the JLA process, it might have been appropriate not to include more than one person from each group of attendees (young person, parent, HCP) representing a specific group of patients."

The ability for some participants to attend virtually was well received, but there was comment regarding equity of their voices.

"I think those who were attending virtually were at a disadvantage as they did not have the benefit of discussion with other delegates over lunch or break times"

QUESTIONS 11-26 from the Final Workshop

Question	Final Rank
How safe and effective are cannabis based medications in childhood onset epilepsies?	11
In children and young people with epilepsy, how effective are psychological, communication, and environmental interventions to support their associated difficulties (e.g. anxiety, low mood and behaviour that challenges?)	12
Can restorative interventions aimed at directly repairing damaged brain tissue, e.g. stem cells, improve outcomes following injury to the brain occurring during pregnancy or in infancy?	13
What are the most effective interventions to support feeding and nutrition in children and young people with neurological conditions?	14
What are the most effective interventions for children and young people with gut problems (dysfunction) in association with neurological conditions?	15
What are the most effective treatments to manage tic disorders in children and young people?	16
What interventions are effective in managing respiratory symptoms for children and young people with neurological conditions?	17
What are the most effective treatments for the management of the skin lesions of neurofibromatosis type 1 (NF1)?	18
What are the most effective treatments for migraine in children and young people?	19
What are the most effective rehabilitation approaches in children and young people with acquired brain injury?	20
Does psychological input at diagnosis improve outcomes in children and young people with immune mediated neurological disorders?	21
What are the most effective treatments for the management of neurofibromas in neurofibromatosis type 1 (NF1)?	22
What impact does nutrition have on outcomes in childhood neurological inflammatory conditions?	23
What are the benefits of DBS (Deep Brain Stimulation) in children and young people with abnormal muscle tone (dystonia)?	24
What are the safest and most effective treatments for malignant brain tumours in children and young people?	25
How safe and effective is the ketogenic diet as an early second line treatment compared to anti-seizure medications for epilepsies in children and young people?	26

In this section, we tell the stories of each of the Top 10 Priorities.

We include the original questions that inspired them, some information on the question and lack of evidence. Finally, people with an interest in research tell us why each priority matters to them.

PRIORITY NUMBER 01

Can early therapy interventions improve functional and developmental outcomes in babies experiencing brain injury during pregnancy or infancy?

Examples of Original Uncertainties

"What are the core ingredients including modality, intensity, dosage of early intervention to support ongoing developmental skill acquisition in babies/ infants at high risk of CP" - **Therapist**

"What effect does feeding therapy have on feeding outcomes for babies with brain injuries (e.g. HIE, stroke) when it is introduced very early and consistently in their first weeks/ months of life?" - **Therapist**

"Can we improve outcomes in cerebral palsy with more targeted early intervention?" - **Doctor**

Commentary on the question by Dr Tomoki Arichi & Dr Anne Gordon

Injuries to the developing brain during the perinatal period (around the time of birth) can have a profound effect on brain structure and function, leading to lifelong neurodisability such as the motor difficulties seen in cerebral palsy. Advances in investigative tools such as neuroimaging have vastly improved our ability to identify brain injuries, and thus recognise which children are at high risk of later difficulties and/or to make early diagnoses. This is crucial, as it has long been known that the brain has an increased capacity for neuroplasticity (i.e. the ability to change through growth and reorganisation) during early infancy. There is now increasing evidence that by harnessing and taking advantage of this neuroplasticity, brain development or neural reorganisation after injury can potentially be optimised, leading to lasting improvements in function and neurological outcomes. This can be achieved through multi-disciplinary targeted early interventions focusing on skill development, prevention of complications, and parent support.

However, consensus is still lacking about how best to deliver these interventions and outcomes have been highly variable across different patient groups. This may be due to the clinical heterogeneity inherent to this population who may have different underlying aetiologies, symptom

PRIORITY NUMBER 01

severities and ages at the time of intervention. This is further compounded by unavoidable variance in environmental, sociodemographic and family factors. To resolve this, we need to improve our mechanistic understanding of precisely how injuries lead to neurological difficulties and what neurobiological processes are taking place during recovery. This will allow us to cut through the heterogeneity by guiding personalised targeted interventions. Finally, large-scale systematic studies are needed including randomised control trials and of holistic approaches which factor in the family and home environment.

Dr Tomoki Arichi

Senior Lecturer, King's College London & Consultant in Paediatric Neurodisability, Evelina London Children's Hospital

I am a Consultant in Paediatric Neurodisability in London where I manage the care of children who have chronic neurological difficulties as a result of an injury to their brain before or around the time of birth. I am also a Neuroscience researcher and use computational methods, MRI scanning and engineering to study how the brain develops at the start of our lives and how this can be affected by injury.

A key overarching goal for both aspects of my work is therefore to gain a mechanistic understanding of how injuries lead to neurodisability and how we can harness key processes like neuroplasticity to improve outcomes.

Whilst there is an increasing body of evidence from basic science and clinical studies that early intervention can have very positive effects on neural recovery and development, systematic research is clearly needed to establish the "what, when, and how" of such interventions.

Dr Anne Gordon

Chief Therapist, Evelina London Children's Hospital & Allied Health Professions lead for children and young people, NHS England; Honorary Senior Lecturer, King's College London

I am a consultant occupational therapist in paediatric neurosciences in London, where I lead a rehabilitation service for children with hemiparesis or at high risk of cerebral palsy. This service delivers evidence-informed protocolised intensive intervention programmes in partnership with parents/carers, community and hospital-based therapists.

I am also a post-doctoral researcher with an interest in evaluating the benefits of re/habilitation for children with neurodisability from both a mechanistic as well as activity and participation perspective. My PhD study was a prospective longitudinal study of stroke outcome in infants, children and young people.

In my strategic, operational and wider work roles I am particularly motivated to reduce inequity of access of children to effective evidenced interventions, to support clinicians in making informed decisions about how they use resources and prescribe re/habilitation services, and ultimately giving children and young people the best possible start in life'.

What are the most effective interventions to support sleep in children and young people with neurological conditions?

Examples of Original Uncertainties

"What is the best management strategy for sleep maintenance difficulty?" - **Doctor**

"How can sleep quality be improved when tics are preventing a restful night?" - **Parent**

"Do sleep systems have a beneficial impact on sleep quality in children with neurologic conditions?" - **Therapist**

Commentary on the question by Professor Paul Gringras

Sleep disorders are common in many children with neurological conditions. Sleep can be disrupted in almost every conceivable manner. A combination of intrinsic and extrinsic factors often come together in a perfect storm to disturb sleep rhythms and fragment sleep throughout the night. Importantly sleep is often the easiest modifiable factor and improving sleep often improves overall outcomes.

Intrinsic factors include the presence of nocturnal seizures, intellectual disability, pain, motor and visual impairments. Sleep-related breathing problems are common in children with neuromuscular disorders but also any condition with abnormal upper airway tone or central events secondary to poor brainstem control, aspiration, and gastro-oesophageal reflux.

Extrinsic factors include caregiver variables around employment, single parents, and co-sleeping. Children with neurological conditions are frequently prescribed many medications, including anticonvulsants and medications to reduce muscle tone. These can all, singly or in combination, alter sleep maintenance, increase risk of sleep-related breathing difficulties, and reduce levels of daytime alertness.

Apart from melatonin there are no RCTs of any medication to improve insomnia and sleep fragmentation - yet medications such as clonidine are often used in this role. Children with primary 'neurological' sleep disorders are often therapeutic orphans - in contrast to adults for whom new sleep disorder drugs come on to the market rapidly there are no licenced drugs for children in the UK with Restless leg syndrome (RLS) or Narcolepsy (Sodium oxybate only under clinical commissioning criteria). Studies of such medications would need national registries and multi-centre studies, trials where the BPSA, BPNA and NHS should be world leaders. All such studies need to fully involve parents and young people in choices of outcome measures and study design in the knowledge that results, recruitment, and retention will also improve.

Professor Paul Gringras

Consultant in Sleep Medicine, Evelina London Children's Hospital

I lead a busy paediatric clinical and academic sleep unit. We rely on multidisciplinary team work to allow optimal diagnosis and management of over 5000 children and young people each year. We have worked on building satellite sleep clinics and supporting centres further afield with outreach and consultation work. With the knowledge that sleep interventions are a high priority for research, we are delighted to be able to now plan to deliver studies that will comprehensively answer key research questions about which intervention works to improve sleep in children with neurological disorders.

PRIORITY NUMBER 03

How should we best manage emotional well-being in children and young people with neurological conditions?

Examples of Original Uncertainties

"Conduct a UK wide study on quality of life and comorbid anxieties and depression in young adults (13-21years) with epilepsy and their carers with the idea of creating a tool kit to be used in clinics for identifying these issues in clinics" - **Doctor**

"What can I do to control my child's rage attacks to keep him safe and our family safe?" - **Parent**

"Which interventions help children with cerebral palsy and other motor disorders to manage anxiety?" - **Therapist**

Commentary on the question by Dr Catherine Tuffrey & Rhys P. D. Inward

Children with a range of neurological disorders may experience challenges to their emotional well-being. This may be because of the disorder itself, the effect on the wider brain, because of having a disorder which impacts day to day life or the societal response to their disorder. For example, a child or young person with epilepsy may have difficulties as a consequences of an underlying condition which can result in difficulties with learning and emotional regulation, anxiety induced by the unpredictable nature of the condition, the fear of loss of control in front of peers, the response that their peers may have towards their condition, the risk of Sudden Unexpected Death in Epilepsy (SUDEP) and worry about day to day activities such as the impact their epilepsy may have on their careers or learning to drive.

Children and young people with life limiting conditions may be distressed by the loss of previous ability, deterioration in their current abilities and the prospect of early death. Medications used to treat neurological conditions may affect mental health and children and young people may have similar challenges to other children with long term conditions such as painful procedures, hospital admissions and missing school for appointments, all of which may cause distress.

Many of these difficulties do not meet criteria for interventions from Child and Adolescent Mental Health Service (CAMHS) services. There is little research to suggest which interventions may be helpful for different groups of children with different difficulties or how best interventions may be delivered by non-CAMHS professionals. It is not clear whether interventions designed for children without neurological conditions may work in this group, for example, school-based interventions.

Dr Catherine Tuffrey

Consultant Community Paediatrician Southampton

I am a consultant paediatrician, trained in paediatric neurodisability, working in a district community paediatric service. I have a special interest in childhood epilepsy and manage children with epilepsy in addition to other neurodisabilities. My other interests include complex physical disability, sleep difficulties in children with neurodisability and adolescent health and development.

Rhys P. D. Inward

Young Adult Representative and Epidemiologist and Data Scientist, Department of Biology, University of Oxford

As a young person with experience of childhood neurological disease, I have a passion for trying to promote and understand how emotional wellbeing can be best managed within this group. As part of this, I am currently a support, information and research volunteer at the Encephalitis Society and hold several positions in Patient and Public Involvement and Engagement as an individual with lived experience of disease.

Beyond my interest in wellbeing, I am a research scientist within the field of Infectious Diseases. I am mostly interested in using a range of computational and statistical tools, predominately utilising phylogenetics, to uncover and understand biases in key epidemiolocal parameters, the dynamics of viral evolution, and mapping viral spread throughout space and time.

PRIORITY NUMBER 04

What are the most effective strategies to support communication in children and young people with neurological conditions?

(e.g. use of high and low technology augmentative alternative communication (AAC) or improving speech intelligibility)

Examples of Original Uncertainties

"What are the most effective speech and language therapy interventions for children with Down Syndrome and at what ages are they most effective?" - **Doctor**

"What interventions are effective in providing an alternative and augmentative communication system (low or high tech) that meets a child, family and their environments needs so that it is used and not abandoned?" - **Therapist**

"Which treatments work best to improve children's speech intelligibility?" - **Therapist**

Commentary on the question by Catherine Martin

Children and young people with neurological conditions may also have associated speech, language and communication difficulties.

Speech difficulties include dysarthria - difficulty controlling the muscles for speech resulting in slow, imprecise articulation that can be difficult to understand and/or developmental verbal dyspraxia - a motor coordination difficulty also affecting speech intelligibility.

Language difficulties include problems understanding and/or using language. This might be general or include specific difficulties with understanding the meaning of words and learning new words or with combining words together and learning or using grammar.

Communication difficulties include problems with social interaction, knowing how to start conversations with others, how to fix conversations when partners don't understand, how to take turns and keep the conversation going.

Interventions aim to facilitate language and communication development whilst also helping children improve speech intelligibility where this is appropriate. Low tech or paper-based AAC uses photos, pictures or symbols to represent words or concepts of language and provide children with a tool to use to understand or to express a message. High tech or power-based AAC is similar but also includes voice output and enables children access to a large vocabulary organised across dynamic pages sets. Where children have the capacity to develop speech, it is important that they have tailored intervention to maximise their speech production skills.

For children unable to use speech to meet their communication needs, research is necessary to understand the similarities and differences between language development via AAC and language development via verbal speech. This will enable further research to understand how to design interventions in collaboration with families and education staff to enable children to develop their language skills via these alternative tools and reach their potential to understand and use

language in a way that enables social participation. It must also seek to understand when speech interventions are appropriate and how they should be structured and personalised and how children with neurological conditions develop literacy skills to support both speech interventions and use of text-based AAC.

Catherine Martin

Deputy Service Lead. Communication Aid Service East of England (CASEE). Cambridge University Hospitals NHS Foundation Trust, Addenbrooke's Hospital, Cambridge

I am an advanced specialist speech and language therapist and deputy service lead of the Communication Aid Service East of England (CASEE), one of 14 specialised AAC services in England, and I assess for and provide AAC advice to eligible children and adults about the most effective AAC to support their needs and provide powered AAC where this is beneficial. I am interested in researching language development of children using AAC in order to design effective interventions which enable parents, education staff, and speech and language therapists to collaboratively support language and communication development via AAC. I have recently been awarded an NIHR Pre-Doctoral Clinical Academic Fellowship (PCAF) award.

PRIORITY NUMBER 05

What are the most effective medicinal and non-medicinal treatments to manage distressing symptoms (e.g. pain, irritability) in children and young people suffering life limiting neurological conditions?

Examples of Original Uncertainties

"What is the difference in efficacy and side effects between common opioid treatments and whole plant cannabis products for children suffering life limiting pain?" - **Other Family/ Friend**

"What is best treatment for irritability in Batten's disease?" - **Doctor**

Commentary on the question by Dr Emily Harrop

Paediatric Palliative Care (PPC) is defined "as an active and total approach to care, embracing physical, emotional, social and spiritual elements, for children and young people with life-limiting or life-threatening conditions". PPC focuses on enhancement of quality of life, and support for the family; it includes the management of distressing symptoms, provision of respite and care through death and bereavement. Children with life-limiting neurological disorders form a large proportion of the PPC population and their symptoms can be some of the most challenging to manage. Their quality of life may be impacted by a wide range of distressing symptoms including dystonia/ abnormalities of muscle tone, seizures, pain, agitation, secretions, respiratory failure, and gut failure. Despite this, there is little evidence to guide professionals on the best treatment for these symptoms, something which can adversely affect not only the quality of life of the child themselves, but also that of their whole family.

NICE produced guidance for End of Life Care for Infants, Children and Young People (NG61) in 2016, but the sections on symptom management were largely based on the combined opinions of the guidelines committee, due to lack of good quality evidence, and specific research recommendations were made relating to the management of both pain and seizures. The WHO published Guidelines on the management of chronic pain in children in 2020, the evidence relating to the use of opioids in children with palliative care needs was so poor that specific recommendations were made for further studies in 'children with life-limiting conditions or those requiring end-of-life pain management, in inpatient settings and in the community'.

In order to support consistent practice, in the absence of a clear evidence base, the Association of Paediatric Palliative Medicine (APPM) has begun producing guidelines, working with Cochrane Response. A survey of members' priorities led to the choice of seizures, agitation and gut failure as the three most important symptoms to address.

Families often hear informal reports of the benefits of treatments, such as cannabinoids, and in the absence of clear guidance it can be difficult for professionals to contextualise possible emerging / alternative therapies with existing treatments. Furthermore, there is currently wide regional

variability in access to specialist paediatric palliative care, making treatment of challenging symptoms inconsistent. Better understanding of the most effective medicinal and non-medicinal treatments to manage distressing symptoms (e.g. pain, irritability) in children and young people suffering life limiting neurological conditions, will have enormous potential to improve the quality of life of vulnerable and medically complex children in a range of settings.

Dr Emily Harrop

Consultant in Paediatric Palliative Care, Helen and Douglas House, Oxford

As a Consultant in Paediatric Palliative Care, I see first hand the impact of effective symptom management for children with life-limiting neurological disorders. Despite working closely with my local neurology colleagues, optimum symptom control can remain a challenge for children at later stages of their disease, or those with the most complex constellations of symptoms. Allowing a child to achieve their best possible quality of life can make a difference to an entire family. The impact can be felt beyond the life of the child, in its influence on the families' memories of their time together.

Image from the final priority setting workshop in March 2022

PRIORITY NUMBER 06

What are the safest and most effective anti-seizure medications for seizures in new-born babies less than 28 days old?

Examples of Original Uncertainties

"What are the best anti – epileptic drugs for neonatal seizures?" - **Doctor**

"Is levetiracetam safe and effective in acute management of neonates with seizures?" - **Doctor**

"What is the best treatment of neonatal seizures and what measurable parameters determine this?"

"Has anyone studied the effects on the development of children who were prescribed Phenobarbitone as a first line treatment for early onset seizures" - **Doctor**

Commentary on the question by Dr Anthony Hart

Seizures are common in newborn babies and have many causes. Their first-line treatment is phenobarbital, one of the first anti-seizure medicines discovered in 1912. Over the last 100 years, many more anti-seizure medicines have been found and studied in children, young people, and adults. Unfortunately, there have been very few research studies into anti-seizure medicines in newborn babies. One study published in 1999 showed phenobarbital and phenytoin stopped just under half of seizures in newborn babies. The NeoLEV2 study in 2020 showed phenobarbital was better than levetiracetam in a small group of babies.

One of the reasons why there are so few studies in newborn babies is because their seizures are impossible to diagnose accurately without brain monitoring. We need to look at creative ways to design studies that are not overly complicated or expensive to run. We also need to think about what the best outcome measure for our studies is. The authors of the NeoLEV2 study themselves said, "the end point of greatest concern in neonatal seizure trials is long term neurodevelopmental outcome, and not seizure cessation. A drug that is less effective in achieving seizure cessation but leads to better neurodevelopmental outcome through neuroprotective effect or lack of neurotoxicity, may be the preferred first line treatment option." But there are no large studies that look at developmental outcome in detail. As a result, we do not know which drug works best in newborn babies and which cause harm. After phenobarbital, the choice of next drug and dose will depend on where a baby is cared for and by whom. Our knowledge of anti-seizure medicines in newborn babies is decades behind older children and adults, and needs to improve.

Dr Anthony Hart

Consultant Neonatal Neurologist, Sheffield

I am a consultant paediatric neurologist with an interest in brain disorders affecting the unborn and newborn babies. I am particularly interested in how our care can improve developmental outcome in newborn babies, including diagnosis and treatment of seizures. This work will need collaboration with many different professional groups, including neonatologists, neurophysiologists, neuroradiologists, child development experts, physiotherapists, and pharmacologists, to name a few.

Which medications should be used, and in what sequence, in the management of muscle stiffness (hypertonia) in children and young people?

Examples of Original Uncertainties

"Is Gabapentin an effective treatment for dystonia? How does it compare to other drug treatments for dystonia ? (e.g. trihexyphenidyl)" - **Doctor**

"There is anecdotal evidence amongst my daughter's peers, that the development of Dystonic Muscle spasms often develops around puberty. Also speaking with older people with cerebral palsy, there is anecdotal evidence that not only did they develop problems with Dystonic Muscle Spasms around the time of puberty, that they noticed a reduction or complete resolution in them whilst being pregnant with their children. Could this be linked to hormones and could some sort of hormone therapy or treatment help?" - **Parent**

"What are the most effective medications for managing spasticity and dystonia? What 'order' should they be used in?" - **Doctor**

Commentary on the question by Dr Paul Eunson

Muscle stiffness in children occurs most commonly when children have suffered a brain injury just before or around the time of birth but can also occur through problems with brain development during pregnancy, and by diseases and injuries affecting the brain later on in childhood.

Muscle stiffness is often found together with muscle weakness and poor control of movements resulting in the child having difficulty learning functional skills such as sitting, crawling, walking, self-feeding and writing. Muscle stiffness may also cause pain and the presence of pain probably has the biggest effect on quality-of-life as assessed by children themselves. In the form of muscle stiffness called dystonia painful spasms are very common and ideal management addresses both the muscle stiffness and the pain

There is little in the way of high quality research evidence on when to treat muscle stiffness, what drugs to use, at what dose and in what order. Recent published guidelines have relied on clinical consensus.

This priority interacts with priority 10 as successful management of muscle stiffness may influence what orthosis and other aids are effective and acceptable to the child. In the same way, it may influence what early interventions are used as in priority 1.

The drugs that are currently used to reduce muscle stiffness in children have potential side-effects which can limit the dose used or result in withdrawal of treatment. Having better quality information on how to use these drugs, and looking at how reduction in muscle stiffness improves activity, participation and quality-of-life for the child and family would be a significant step forward. Agreement on what outcome measures to use and engaging young people and families in designing studies would ensure that what we measure is important for the child.

All involved with research in this field can now focus on this key question.

PRIORITY NUMBER 07

Dr Paul Eunson

Paediatric Neurologist and Hospice Doctor, Children's Hospices Across Scotland

I was a consultant paediatric neurologist in Edinburgh from 1996 to 2020 and then moved to Dundee until October 2021. In my career, my particular clinical and research interest was in working with children with cerebral palsy and complex neurodisability, many of these have muscle stiffness.

I worked closely with and was very grateful for the support I received from colleagues in the therapy disciplines, orthopaedic surgery and neurosurgery. I am now working in the children's hospices and hospice outreach service in Scotland.

Are medications (e.g. antibiotics and/or immune treatments) effective in the management of PANS/PANDAS?

(Paediatric Acute-onset Neuropsychiatric Syndrome/Paediatric Acute-onset Neuropsychiatric Disorders Associated with Streptococcal infection)

Examples of Original Uncertainties

"Use of NSAIDs seems to help with pans pandas flare up, what mechanism helps this to work" - **Parent**

"What are reliable treatments for PANS?" - **Parent**

"What is the role of antibiotics in the treatment of Pans/Pandas and how long should they be prescribed for?" - **Parent**

"It has become clear that steroid bursts help reduce sudden onset symptoms such as tics, eating disorders, frequent urination, anxiety, OCD etc. How does this work and what other medications would achieve the same response?" - **Parent**

"As IVIG is regarded as appropriate treatment elsewhere for PANDAS, why is it not considered in the UK? " - **Parent**

Commentary on the question by Vicky Burford

At present, awareness within the UK medical community of Paediatric Acute-onset Neuropsychiatric Syndrome/Paediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infection (PANS/PANDAS) is low. Symptoms are not restricted to OCD, movement or eating disorders but, as part of the diagnostic criteria, also include anxiety, emotional lability and/or depression, irritability, aggression, severe oppositional behaviours, behavioural (developmental) regression, sudden deterioration in school performance (impaired cognitive functioning), motor or sensory abnormalities, sleep disturbances, enuresis or urinary frequency. The sudden onset of these multiple symptoms is typically acute and severe and should not be explained by other psychiatric conditions.

The impairment in the day-to-day functioning of children with these conditions ranges from significant to incapacitating or even life threatening. Untreated, these children are often incapable of leaving their homes to go to school or play with their friends. Intrusive thoughts and compulsions cripple their ability to function normally. Some children are unable to wear any clothes, eat, sleep or be hugged by their parents. Some children self-harm, experience hallucinations and attempt suicide. Prior to onset, these children were free from such significant and life changing symptoms.

We are trying to understand the most effective ways to treat these conditions. Internationally, these conditions are treated by multidisciplinary teams that can include neurologists, immunologists, psychiatrists, rheumatologists, infectious disease specialists and paediatricians. The use of antibiotics, anti-inflammatories

PRIORITY NUMBER 08

and other immunomodulatory treatments are recommended. The evidence for the efficacy of such treatments is provided by small scale trials which have only focussed on single symptom response, case studies, clinical knowledge and patient feedback. Given the severity of the symptoms experienced, and their impacts upon all areas of functioning, it is imperative that we fully evaluate the most effective antibiotics and/or immune treatment protocols for these conditions through robust clinical trials.

Vicky Burford

Chair of Trustees, PAN PANDAS UK

PANS PANDAS UK
awareness support education
www.panspandasuk.org

Treatment approaches recommended internationally for PANS/PANDAS are not widely adopted in the UK. However, my patients diagnosed with probable PANS often show significant improvements in their overall presentation when treated with non-steroidal anti-inflammatory drugs, antibiotics and/or short courses of oral prednisolone but may then regress when these are stopped. These children and young people deserve appropriate multidisciplinary assessment and management (including with medications), but in the absence of recognised UK guidelines this is currently problematic. I strongly believe that recognised guidelines including the possible use of the treatments (non-steroidal anti-inflammatory drugs, antibiotics and/or short courses of oral prednisolone) described, are needed. To achieve this, we really require robust studies to be carried out to evaluate the most effective treatments.

Professor Rajat Gupta

Consultant Paediatric Neurologist
Honorary Professor, Aston University and University of Birmingham
Head of Specialist Clinical Teaching Academy & Deputy Lead Paediatrics, University of Birmingham
Programme Medical Director, Pharmacist Independent Prescribing PgCert, Aston University
Regional Co-Lead for West Midlands & England Area Officer - Midlands, RCPCH

Parents report that their children (who meet the diagnostic criteria for PANS/PANDAS) are significantly improved whilst being treated with antibiotics and/or anti-inflammatories - to the extent that they are able to attend school when previously were unable to do so and/or are functioning at a higher level. In the absence of NICE guidelines there is currently no consistency in how clinicians assess and treat these children, leading to a lack of treatment, inappropriate treatment or an inequity of treatment. Whilst psychological interventions can sometimes be helpful, in PANS and PANDAS these talking therapies do not treat the underlying immune disorder and as such a more holistic approach is required that ensures physical and mental health interventions are both offered to address the underlying cause and the consequences of these conditions.

Diane Palmer

Associate Director of Nursing, Norfolk and Suffolk NHS Foundation Trust
British Journal of Nursing 'Nurse of the Year 2022'

Which psychological interventions are most effective in children and young people who have functional neurological disorders?

Examples of Original Uncertainties

"Is psychology and CBT input started in the paediatric age range any more effective than in adults for improving functional neurological symptoms" - **Doctor**

"Outcome of targeted psychological intervention e.g. CBT in outcome for FND" - **Doctor**

Commentary on the question by Dr Laavanya Damodaran

Functional neurological symptom disorder, also called conversion disorder is a very good example of a condition where neurologists and psychiatrists work together in assessing and managing the symptoms that children and young people present with. Symptoms can be in the form of changes in consciousness, speech, sensation and movements of our body that is not better explained by a physical condition and yet they cause significant impairment in many aspects of day-to-day functioning for that individual.

We are trying to better understand the manner of causation of this condition so we can provide effective interventions. However, some of the examples of factors we identify as contributing to the symptoms commonly are a pre-existing neurological condition, stress at school due to learning needs, bullying experiences, subtle language problems, struggling to recognise and communicate difficulties within school, when there are family stressors, functional symptoms in family members, anxiety in parents etc. Hence, therapeutic interventions should be tailored as per the findings of a biopsychosocial diagnostic formulation. Research in the area of therapeutic interventions for family as well as education for staff within school & health setting is as important as therapeutic interventions for children and young people.

Dr Laavanya Damodaran

Consultant Paediatric Liaison & Neuropsychiatrist, Birmingham

I am a liaison psychiatrist at a tertiary paediatric hospital and provide care for children with functional neurological symptoms. I find that collaborative working by multidisciplinary team members providing care and intervention in a non-judgemental manner improves patient experience and helps build trust, enhancing engagement in therapeutic interventions & therefore recovery. Hence research in finding out the most effective therapeutic intervention would also depend on the environmental conditions in which the intervention is delivered.

PRIORITY NUMBER 10

What are the best non-medicinal interventions (including therapies, orthotics e.g. splints, high and low technology supports) for children and young people with motor disorders?

Examples of Original Uncertainties

"What allied therapies improve outcome in children with cerebral palsy or acquired brain injury?" - **Doctor**

"Has there been any research done into the impact of holistic therapies on children with hemiplegia?" - **Parent and 3rd sector charity professional**

"For parents of children with neurodisabilty, what is the impact of undertaking long term parent-delivered therapies on parent and family wellbeing?" - **Therapist**

Commentary on the question by Dr Sarah Crombie

Allied health professionals (AHPs) such as occupational therapists, physiotherapists and speech and language therapists regularly support children with motor disorders, for example cerebral palsy or acquired brain injury, to improve outcomes. AHPs deliver varying interventions to promote a child's functional skills and participation in everyday life throughout their childhood years. These may focus on gross and fine motor development of skills, everyday functional tasks and activities of daily living, oral-motor function and communication. These therapeutic interventions may be delivered directly by therapists themselves but commonly in collaboration with parents, carers or education staff to maximise the impact of therapy throughout the child's life.

There has been research into the effectiveness of some interventions particularly for children with cerebral palsy. However, as highlighted in Priority Number 1, high quality research is lacking in many areas of therapy intervention which may be due to the heterogeneity of this clinical population (both within cerebral palsy as well as with other neurological conditions) as well as the many confounding variables influences outcomes such as family and environmental differences.

Therefore, many uncertainties remain not only in the effectiveness of the type of therapy delivered but for which population they are most effective, the dosage required to achieve optimal outcomes, who is best placed to deliver the therapy e.g. therapist, parent, school staff, timing of delivery in terms of age and the most effective environment for the intervention to take place. Additionally, there has been less research into interventions for children who are non-ambulant and have complex needs.

Dr Sarah Crombie

Clinical Specialist Physiotherapist, Chailey Heritage Clinical Services

I am a clinical specialist physiotherapist working at Chailey Clinical Services, Sussex Community NHS Foundation Trust, a specialist service for children and young people with neurodisability. I work in a multidisciplinary healthcare team primarily in the motor disorder service and am involved in research studies into therapy interventions for children with cerebral palsy. I aim to work with children and their parents, carers and education staff towards the achievement of the child's personal goals to promote their participation, function, health and well-being outcomes. With increasing evidence into the effectiveness of therapy interventions for different population groups, parents, young people and clinicians can be more confident that the child receives the most effective, targeted interventions at the right time in their lives.

IMPACT AND NEXT STEPS

The top ten list generated from this PSP has identified research questions of significant importance regarding interventions for children and young people with neurological conditions, their families and professionals working with them. There is a balance regarding questions about specific conditions, a variety of interventions for more common conditions, and questions regarding interventions for co-morbidities relevant to children and young people with many neurological disorders.

It reflects priorities of multiple stakeholder groups and will inform researchers and funders to drive meaningful future research and improvement in clinical care for children and young people with childhood neurological disorders.

This has been an important starting point for the BPNA research milestone. BPNA and the Research Committee are committed to fostering patient and public involvement. The successful completion of this project and its outcomes will support the BPNA research agenda to direct future research paths, of both clinical and societal relevance, making sure that the needs of end users are properly addressed.

The BPNA research committee will draw the attention of the public, academic researchers and funding authorities to the questions selected in this process. We invite the PSP outcomes to be presented at the next BPNA annual conference in 2023 in Edinburgh at the Presidential Session. The results will also be advertised on the BPNA website and circulated to all its members via our regular newsletter.

We plan to further analyse the selected questions and translate them into research questions and proposals. We will ensure that the PSP steering and expert groups are part of this process, but we also encourage other BPNA members, from the research committee and beyond, with expertise in individual questions to support this process, bringing in additional ideas and accurately translating questions.

Acquisition of funding is a crucial part of this process. The BPNA research committee with the PSP leads will approach funding agencies including NIHR. We also believe that continuous inclusion of patients and carers is an important step throughout this process. Our ultimate goal is to influence research practice and make sure that we articulate not only the top 10 questions, but all the questions which were brought to our attention through this process.

Dr Sam Amin

Chair of Research, British Paediatric Neurology Association
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Image from the final priority setting workshop in March 2022

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