



Research priorities for children with neurological impairment and medical complexity in high income countries

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Discussion of off-label drugs: off-label use of medication is listed within study results

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ABBREVIATION

CMC Children with medical complexity

AIM To identify the highest-priority clinical research areas related to children with neurological impairment and medical complexity among clinicians and caregivers.

METHOD A modified, three-stage Delphi study using online surveys and guided by a steering committee was completed. In round 1, clinicians and family caregivers suggested clinical topics and related questions that require research to support this subgroup of children. After refinement of the suggestions by the steering committee, participants contributed to 1 (family caregivers) or 2 (clinicians) subsequent rounds to develop a prioritized list.

RESULTS A diverse international expert panel consisting of 49 clinicians and 12 family caregivers provided 601 responses. Responses were distilled into 26 clinical topics comprising 126 related questions. The top clinical topics prioritized for research were irritability and pain, child mental health, disorders of tone, polypharmacy, sleep, aspiration, behavior, dysautonomia, and feeding intolerance. The clinician expert panel also prioritized 10 specific research questions.

INTERPRETATION Study findings support a research agenda for children with neurological impairment and medical complexity focused on addressing clinical questions, prioritized by an international group of clinicians and caregivers.

Diskin, C., Malik, K., Gill, P. J., Rashid, N., Chan, C. Y., Nelson, K. E., Thomson, J., Berry, J., Agrawal, R., Orkin, J., & Cohen, E. (n.d.). Research priorities for children with neurological impairment and medical complexity in high-income countries. *Developmental Medicine and Child Neurology*. <https://doi.org/10.1111/dmcn.15037> (open access)

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Defining the population of interest



Children with medical complexity (CMC): "substantial family-identified service needs, chronic conditions, functional limitations and high health care use".¹



Neurologic impairment (NI): "any neurologic condition primarily arising from the central and/or peripheral nervous systems, lasting at least 12 months (unless death intervenes) AND results in systemic and/or multisystem physiologic impairment that requires pediatric specialty care"²

1. Cohen E, Kuo DZ, Agrawal R, et al. Children With Medical Complexity: An Emerging Population for Clinical and Research Initiatives. *Pediatrics*. 2011
2. Berry JG, Poduri A, Bonkowsky JL, et al. Trends in resource utilization by children with neurological impairment in the United States inpatient health care system: a repeat cross-sectional study. *PLoS Med*. 2012



Background



The literature does not provide a sufficient evidence base to guide many care practices for CMC with NI.



This represents a significant gap in our clinical knowledge.



Objective

To *develop* a list of the top priorities* for clinical research in the CMC with NI, reflecting the *consensus* of an *international expert panel*.

* Priorities: a) clinical topics, b) specific research questions

Methods



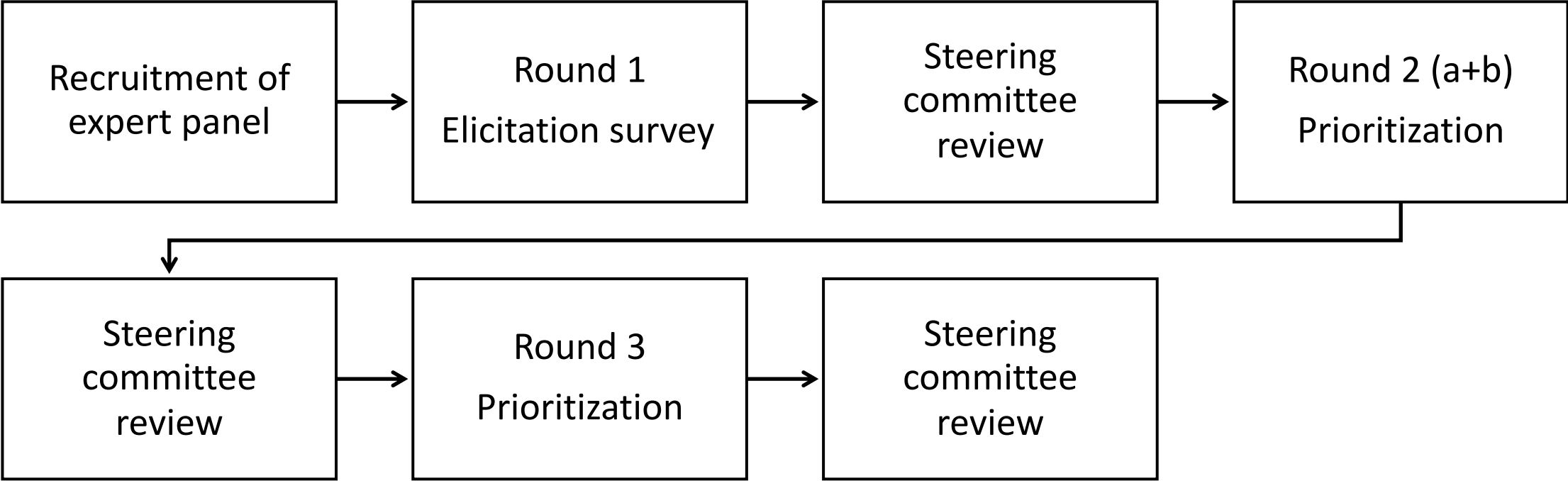
Overarching methods: Modified Delphi (consensus) methodology, involving three web-based surveys



Ethics approval was obtained from SickKids Institutional Review Board

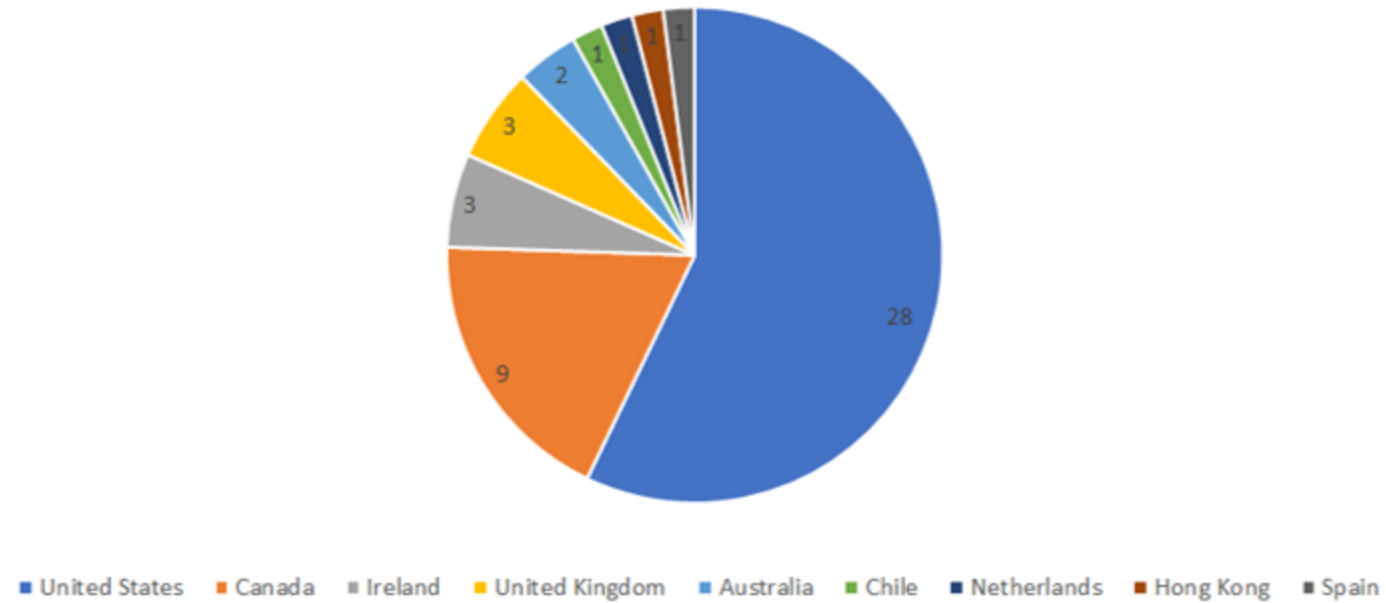


Steering committee – 9 international leaders in complex care from 5 different academic institutions, as well as parent representative



Demographics of clinician expert panel

Geographic location of clinician experts (n=49)



Study participants

Demographics of clinician expert panel, n=49

| Professional role of clinicians | | Current place of clinical practice | |
|---|----|---|----|
| Physician | 42 | Combination (inpatient acute care and outpatient) | 24 |
| Nurse Practitioner | 6 | Outpatient care – primary care | 8 |
| Researcher | 1 | Outpatient care – specialty clinic | 8 |
| Specialty (participants could provide more than one response) | | Inpatient acute care | 2 |
| General Paediatrics | 16 | University | 2 |
| Developmental Paediatrics | 12 | Consulting | 1 |
| Neurodisability | 8 | Home care | 1 |
| Palliative Care | 7 | Inpatient (non-acute) care | 1 |
| Emergency medicine | 2 | | |
| Gastroenterology | 2 | | |
| Orthopaedics | 2 | | |
| Adolescent Medicine | 1 | | |
| Neurology | 1 | | |
| Neurosurgery | 1 | | |
| Primary care | 1 | | |
| Rehabilitation | 1 | | |
| Research only | 1 | | |
| Respirology | 1 | | |

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| Rehabilitation | 1 | | |
| Research only | 1 | | |
| Respirology | 1 | | |



Study participants

Demographics of family caregivers (n=12)

Geographic location

| | |
|--------|---|
| Canada | 9 |
|--------|---|

| | |
|---------|---|
| Ireland | 3 |
|---------|---|

Children's underlying diagnosis

| | |
|----------------|---|
| Cerebral Palsy | 3 |
|----------------|---|

| | |
|--------------|---|
| Brain tumour | 1 |
|--------------|---|

| | |
|--------------|---|
| Brain injury | 1 |
|--------------|---|

| | |
|------------------|---|
| Moebius syndrome | 1 |
|------------------|---|

| | |
|------------|---|
| Trisomy 21 | 2 |
|------------|---|

| | |
|--------------|---|
| Pradar Willi | 1 |
|--------------|---|

| | |
|---------------------------------|---|
| Genetic disorder, not specified | 1 |
|---------------------------------|---|

| | |
|--------------------------------|---|
| Primary mental health disorder | 1 |
|--------------------------------|---|

Technology use

| | |
|-----------------------|---|
| Enteral feeding tubes | 4 |
|-----------------------|---|

| | |
|------------------------|---|
| Respiratory technology | 5 |
|------------------------|---|

| Steps | | | Detail | | | Output | | |
|---------|--|--|--|--|--|--|--|--|
| Round 1 | Elicitation survey Clinicians 49/81 Caregiver 12/12 | | | | | 601 responses 73 clinical topics | | |
| | Steering committee review | | <ol style="list-style-type: none"> 1. Merging similar overlapping topics 2. Excluding topics not relevant to this study (n=34) 3. Inclusion of topics not previously identified (n=1) 4. Incorporation of previously identified research questions (n=1) | | | 26 clinical topics 126 questions | | |
| Round 2 | Round 2a Clinicians 43/49 (87%) Caregiver 6/12 (50%) | | Individual anonymous prioritization of clinical topics | | | Clinical topics prioritized | | |
| | Round 2b Clinicians 43/49 (87%) | | Individual anonymous prioritization of top 7 priority clinical areas and rating of research questions | | | Rating of individual questions | | |
| | Steering committee review | | Exclusion of 1 question (median < 3) and addition of 2 questions suggested by expert panel | | | 49 clinical questions (9 clinical topics) | | |
| Round 3 | Round 3 Clinicians 41/49 (83%) | | Individual anonymous prioritization of each research question in top 9 clinical topics | | | Research questions prioritized | | |

Table 1: Round 2 prioritization of clinical topics (clinical experts [*n*=49] and family caregivers [*n*=12])

| Clinician prioritization | | | | Caregiver prioritization | | | |
|--------------------------|-----------------------------|------------------------|--------------|--------------------------|-----------------------------|-----------------|-----------------|
| Rank | Clinical topic | Frequency ^a | Median (IQR) | Rank | Clinical topic | Frequency score | Median (IQR) |
| 1 | Irritability and pain | 28 | 6 (6–6.5) | 1 | Behavior | 40 | 7 (7–7) |
| 2 | Child mental health | 20 | 6 (4–6) | 2 | Acute LRTI | 37 | 6.5 (6–7) |
| 2 | Disorders of tone | 20 | 6 (5–7) | 3 | Enteral feeding tubes | 36 | 6 (5.25–6.75) |
| 2 | Polypharmacy | 20 | 5 (5–6) | 4 | Sleep | 35 | 5.5 (5–6.75) |
| 2 | Sleep | 20 | 5 (5–6) | 5 | Aspiration | 34 | 6 (6–6) |
| 3 | Aspiration | 19 | 6 (5–6.5) | 5 | Infection control | 34 | 6.5 (5.25–7) |
| 4 | Behavior | 18 | 5 (4–6.5) | 5 | Irritability and pain | 34 | 6.5 (5.25–7) |
| 4 | Dysautonomia | 18 | 5 (4–6) | 6 | Nutrition and growth | 33 | 5 (5–6.5) |
| 4 | Feeding tolerance | 18 | 5 (4–6.5) | 6 | Feeding tolerance | 33 | 6 (5.35–6) |
| 5 | Chronic lung disease | 13 | 5 (4–6) | 6 | Child mental health | 33 | 5.5 (5–6.75) |
| 6 | Nutrition and growth | 12 | 5 (3–6) | 7 | Chronic lung disease | 32 | 5.5 (4.25–6.75) |
| 7 | Acute LRTI | 11 | 5 (3–6) | 8 | Dysautonomia | 31 | 5.5 (4.25–6.75) |
| 8 | Enteral feeding tubes | 10 | 4 (3–5) | 9 | Constipation | 29 | 4 (3.5–6) |
| 8 | Sialorrhea | 10 | 5 (3.5–6) | 9 | GERD | 29 | 5 (3.25–6.75) |
| 8 | Scoliosis | 10 | 4 (3–5.5) | 9 | Polypharmacy | 29 | 5 (3.25–6) |
| 9 | Osteoporosis and osteopenia | 9 | 4 (4–6) | 10 | Sialorrhea | 28 | 5.5 (5.25–6) |
| 10 | Constipation | 8 | 4 (3–5) | 10 | Venous access | 28 | 4.5 (4–5) |
| 10 | Neurogenic bladder | 8 | 4 (3–5) | 11 | Disorders of tone | 27 | 4.5 (2.5–6.5) |
| 11 | GERD | 7 | 4 (4–6) | 11 | Postoperative complications | 27 | 4 (3.25–6.25) |
| 12 | Postoperative complications | 5 | 4 (3–5) | 11 | Peripubertal issues | 27 | 4.5 (2.5–6.5) |
| 12 | Infection control | 5 | 4 (3–5) | 12 | Neurogenic bladder | 26 | 4.5 (3.25–5) |
| 13 | Venous access | 4 | 3 (2–4) | 12 | Scoliosis | 26 | 4.5 (2.5–5.75) |
| 13 | Hip displacement | 4 | 4 (3–5) | 13 | Dental caries | 25 | 5.5 (2.25–5.75) |
| 14 | Hydrocephalus | 3 | 4 (2–5) | 14 | Hip displacement | 24 | 3.5 (2.25–3.25) |
| 14 | Peripubertal issues | 3 | 4 (2.5–5) | 14 | Hydrocephalus | 24 | 3.5 (2–5.75) |
| 15 | Dental caries | 2 | 4 (2.5–4.5) | 15 | Osteoporosis and osteopenia | 23 | 3.5 (2.25–4.75) |

The top clinical topics are shaded. ^aThe frequency score reflects the number of clinical experts who provided the top ranking for each clinical topic. IQR, interquartile range; LRTI, lower respiratory tract infection; GERD, gastroesophageal reflux disease.

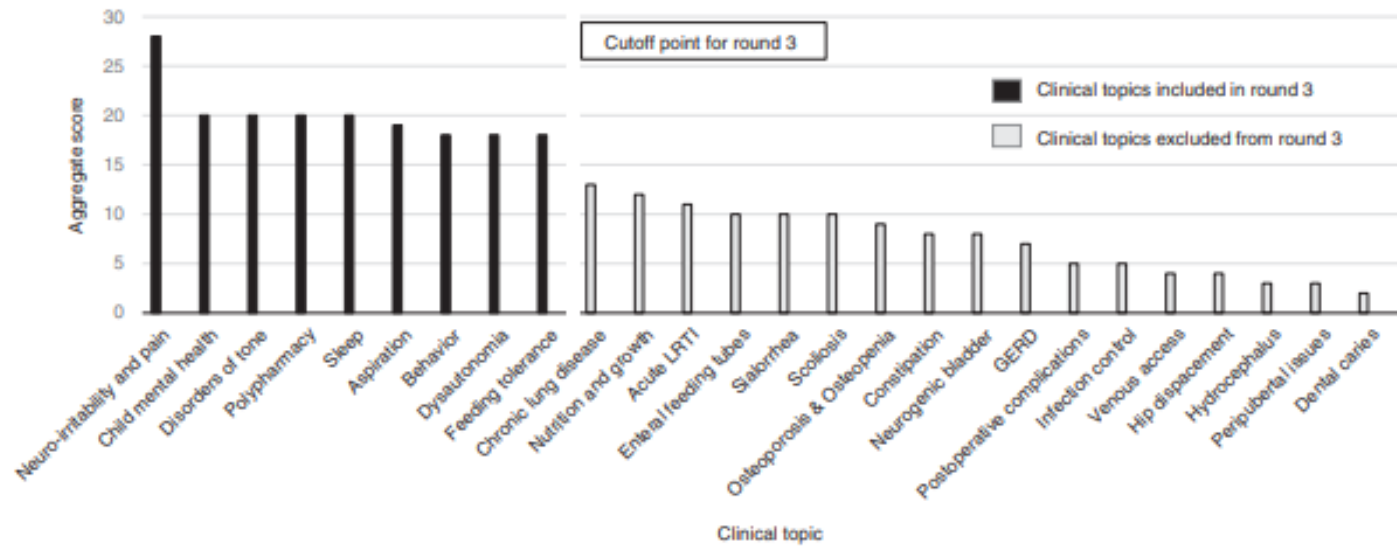


Figure 2: Frequency score of clinical topics by clinical experts. The frequency score calculated by the frequency of inclusion among the top seven of 26 clinical topics developed after round 1 is shown. LRTI, lower respiratory tract infection; GERD, gastroesophageal reflux disease.

Table 2: Top 10 ranked research questions with related clinical topics

| Overall rank | Clinical topic | Research question | Total score | Median (IQR) |
|--------------|-----------------------|--|-------------|--------------|
| 1 | Feeding tolerance | In children with neurological impairment and medical complexity with feeding intolerance, do blenderized formulas (e.g. home or commercially) versus other formula (polymeric or hydrolyzed) improve outcomes (e.g. nutritional health, feeding tolerance, quality of life)? | 229 | 6 (5–7) |
| 2 | Disorders of tone | In children with neurological impairment and medical complexity with dystonia, does baclofen versus baclofen plus gabapentin improve outcomes (e.g. pain, function)? | 228 | 6 (5–6) |
| 3 | Dysautonomia | In children with neurological impairment and medical complexity with autonomic dysfunction, does propranolol versus gabapentin versus clonidine decrease symptoms of autonomic dysfunction (e.g. sweating, temperature dysregulation, blood pressure lability)? | 228 | 5 (5–7) |
| 4 | Irritability and pain | In children with neurological impairment and medical complexity with irritability, does gabapentin versus clonidine improve outcomes (e.g. duration of crying, discomfort)? | 227 | 6 (5–7) |
| 5 | Irritability and pain | In children with neurological impairment and medical complexity with irritability, does cannabidiol and/or tetrahydrocannabinol versus standard therapy (e.g. gabapentin) improve outcomes, for example, duration of crying, discomfort? | 226 | 6 (5–7) |
| 6 | Sleep | In children with neurological impairment and medical complexity with disrupted sleep, does melatonin versus hydroxyzine versus trazodone versus clonidine improve outcomes (e.g. sleep quality, sleep duration, daytime function)? | 225 | 6 (5–6) |
| 7 | Aspiration | In children with neurological impairment and medical complexity, does exclusive enteral (tube) feeding (without oral intake) versus a feeding plan, which includes oral intake, reduce aspiration risk? | 218 | 6 (4–7) |
| 8 | Feeding tolerance | In children with neurological impairment and medical complexity with feeding intolerance, does polymeric formula versus hydrolyzed formula improve outcomes (e.g. nutritional health, feeding tolerance, quality of life)? | 218 | 5 (4–7) |
| 9 | Child mental health | In children with neurological impairment and medical complexity, does screening for mental health issues versus standard (no screening) improve outcomes (e.g. child mental health)? | 217 | 5 (4–6) |
| 10 | Disorders of tone | In children with neurological impairment and medical complexity with dystonia not responsive to medication, does deep brain stimulation versus intrathecal baclofen improve outcomes (e.g. function)? | 216 | 5 (4–6) |

Two prioritized clinical topics did not have a research question ranked in the top 10 (polypharmacy and behavior). The top ranked question for the clinical topic of polypharmacy was 'In CMC and neurological impairment, what are the demographics and clinical predictors of a medication error?' (total score=185; median [IQR]=4 [3–6]). The top ranked question in the clinical topic of behavior was 'In CMC and neurological impairment, what are the demographic and clinical predictors of challenging behavior (e.g. aggression) and emotional dysregulation?' (total score=174; median [IQR]=4 [3–5]). IQR, interquartile range; CMC, children with medical complexity.

Interpretation(A)

- Consensus successful
 - Neurologic and neuropsychiatric topics dominated
 - Other topics such as feeding tolerance and aspiration also prioritized
- Topic generation benefited from parental input
 - Child mental health and behaviour and emotional regulation
 - Infrequently proposed by clinician panel in Round 1
 - But ... behaviour was suggested by caregiver panel

Interpretation(B)

- Some prioritized areas overlapped due to definitional vagaries
 - E.g. neuro-irritability and dysautonomia
 - E.g. aspiration, LRTI and feeding tolerance
- Some topic areas prioritized but difficult to articulate as research questions.
 - E.g. behavioural/mental health
 - ?outcome metrics ?specified interventions
- Intentional focus on clinical questions and not the entire healthcare experience of CMC with NI

Strengths of the study

- Clinician panel
 - All panelists were clinically immersed.
- Diverse, geographical and clinical discipline
- Strong engagement
 - High response rate in Rounds 2 and 3 (88% and 84%)
 - + + + input (126 research questions!)

Limitations of the study

- Limited diversity of caregivers involved
- Caregivers not involved in Round 3
- Clinical topics and related questions were identified as mutually exclusive may not be in practice (e.g. aspiration and LRTI)
- Limited healthcare professional involvement

Conclusion



First step towards a research agenda about CMC with NI focused on the addressing of everyday clinical questions



Reflects the international consensus of both clinicians and caregivers



Engagement with this research agenda may improve the care received by CMC with NI.



Acknowledgements

- Clinician and caregiver participants
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