

Developing Clinical Guidelines with Scant Evidence. Approaches Taken and Lessons Learnt.

Friedemann Smith, C., Nieto-Hernandez, R., and Abdelhamid, A.

Author Affiliations:

Dr Claire Friedemann Smith (corresponding author and guarantor): Systematic Reviewer, Research and Policy, Royal College of Paediatrics and Child Health, London, UK, WC1X 8SH. Correspondence to cfriedemann86@gmail.com, Telephone: 07806634490.

Dr Rosa Nieto -Hernandez: Clinical Standards Facilitator, Research and Policy, Royal College of Paediatrics and Child Health, London, UK.

Dr Asmaa Abdelhamid: Systematic Reviewer, Norwich Medical School, University of East Anglia, Norwich, UK.

Word count: 1,993

Keywords: Stroke, Child, Guideline, Systematic Review, Delphi

Copyright Statement

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, a worldwide licence to the Publishers and its licensees in perpetuity, in all forms, formats and media (whether known now or created in the future), to i) publish, reproduce, distribute, display and store the Contribution, ii) translate the Contribution into other languages, create adaptations, reprints, include within collections and create summaries, extracts and/or, abstracts of the Contribution, iii) create any other derivative work(s) based on the Contribution, iv) to exploit all subsidiary rights in the Contribution, v) the inclusion of electronic links from the Contribution to third party material where-ever it may be located; and, vi) licence any third party to do any or all of the above.

Competing Interest Statement

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: the project as a whole had financial support from The Stroke Association and no other relationships or activities that could appear to have influenced the submitted work exist.

Transparency declaration

The lead author and guarantor affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Ethical Approval

Ethical approval was not required for this work.

Funding Statement

This work was funded by The Stroke Association. The funder had no influence over the methods used or conclusions drawn in the guideline. The researchers carried out the research independently of the funders.

Checklist

The AGREE checklist has been completed for the full guideline described herein and is available on request.

Statement of contribution

This paper discusses work which was funded by the Stroke Association and developed by the Royal College of Paediatrics and Child Health (RCPCH), which will be launched in May 2017. The funders played no role in the conception, writing or content of this paper but have given their approval for it to be submitted for publishing. CFS and AA were systematic reviewers at the RCPCH (to April 2017

and September 2016 respectively) and were involved in every stage of the development of the guideline. RNH oversaw the development of every stage of the guideline. CFS drafted this manuscript and RNH and AA edited it. All authors approve this manuscript. CFS, RNH, and AA have several years' experience of carrying out systematic reviews for the RCPCH, the Cochrane Collaboration, and numerous other UK universities. The authors declare no conflict of interest. All members of the GDG were required to disclose any conflicts of interest and any conflicts declared will be available in Appendix 2a of the guideline which will be launched in May 2017. CFS is the named guarantor of this work.

Developing Clinical Guidelines with Scant Evidence. Approaches Taken and Lessons Learnt.

Friedemann Smith, C., Nieto-Hernandez, R., and Abdelhamid, A.

BACKGROUND

It is estimated that 400 children suffer from an ischaemic or haemorrhagic stroke in the UK each year with up to 40% dying from it, and approximately 60% of those surviving the initial attack going on to have recurrent strokes (1). Although in recent years the recognition of stroke as a disease that affects children has increased, many still experience delays in diagnosis or misdiagnosis (2, 3). The view that stroke is an illness of the middle-to-late adult years may have also hindered research into stroke in childhood. The need for a clinical guideline was clear, it would provide a practical guide that should aid clinical decision making and improve patient care (4) but when there are gaps in the literature, creating guidelines presents a challenge.

METHODS OF GUIDELINE DEVELOPMENT

A guideline development group (GDG) was established that consisted of clinical experts from specialties relevant to the topic of the guideline, parent representatives whose children had suffered a stroke, and systematic reviewers from the Royal College of Paediatrics and Child Health (RCPCH), following accepted practice (5). The scope of the guideline was drafted, and after stakeholder consultation specific clinical questions were formed.

Systematic review

Clinical questions were grouped into sub-topics and review protocols written. Searches were carried out in five databases; MEDLINE, Embase, PsycInfo, Cochrane Library, and CINAHL, between 1995 and 2016, which were screened and data extracted from relevant studies. Our expectation was that the literature on rehabilitation following stroke in childhood would not be sufficient to answer all of our clinical questions and so our inclusion and exclusion criteria allowed for the inclusion of studies

carried out in children with similar deficits, for example, as a result of acquired brain injury. Despite this, we still found that 36% of all our clinical questions had two or fewer studies on which to base recommendations.

The lack of literature was compounded by the low quality of what was available; observational studies and case series, frequently without control groups, using retrospective medical records reviews were the most common study type. These studies are at a high risk of bias, particularly if the sample was selected from one treatment center, or the data was collected for a purpose other than the objectives of the study, as there is a risk of incomplete or misreporting of the factor(s) of interest (6). With the exception of single case reports we did not, however, exclude lower quality studies based solely on study design, but advised caution when interpreting the results. The decision was taken to exclude single case studies as it was felt that they were more likely to present atypical cases and that there was excessive risk of bias associated with these studies. As we did not exclude any other studies based purely on their quality it was felt that this was a reasonable compromise to try to ensure a minimum degree of quality in the data while limiting the degree to which the anticipated small evidence base was reduced.

To supplement the evidence provided by the systematic review, where recommendations had the potential to change practice, where the management strategy was unclear, or where the experience of parents was required, we used a Delphi panel survey (7) and parent workshops to achieve consensus and add to the evidence base (Figure 1).

[Place Figure 1 here]

Delphi panel survey

The Delphi panel survey included five statements which covered topics such as thrombolysis in children, and management strategies for unruptured arteriovenous malformations. These statements covered areas where there was little published evidence or where the potentially

controversial nature of the topic meant that wider expertise was needed. We assembled the expert panel through the professional bodies of specialties most relevant to the statements. Seventy clinicians responded to an emailed request for input to an online survey in which they rated the five statements on a 10 point Likert scale from 1 – ‘Strongly disagree’ to 10 – ‘Strongly agree’. An option to opt out of responding to a statement was also included as we felt it important that only clinicians with expertise in a relevant area considered each statement and those who did not were not compelled to respond, especially as some of the statements covered highly specialised topics, for example, surgical techniques. We also included an opt out to try to avoid the use of the ‘neutral’ response options in the middle of the scale as a proxy for opting out as these could have masked response trends in either direction. Lastly, a free text box to allow feedback was included with each statement. Consensus was defined as 75% of the participants answering 7-10 on the scale. The panel ran to three rounds of survey, achieving response rates of 99%, 80%, and 77% respectively.

We found that consensus was difficult to achieve for some statements with much of the disagreement being between clinicians of different specialties. The different perspectives of the varying specialties and the lack of trial data to guide opinions meant that responses were often polarised in the initial round, and it was not until two or three rounds of amendments that consensus was achieved. Even so, consensus was not achieved for one statement addressing the usefulness of genetic tests for inherited thrombophilic disorders which suggested that they should not be carried out routinely, as the results would not alter the acute management of a child. In this instance, there was a marked contrast in the responses given by haematologists compared to clinicians from other specialties, with haematologists generally agreeing, and other specialties generally disagreeing with the statement. Since consensus could not be achieved, a non-directive statement was written stating simply that the results of such tests would not change the management of the child. This statement achieved consensus and the guideline will contain a description of the process with a discussion of the implications of carrying out these tests. The four statements that achieved consensus formed recommendations in the guideline.

Parent focus group workshops

We carried out two parent focus group workshops to allow for the views of parents to feed into the guideline and fill the gaps in the literature around the needs of the family from acute to long term care, and when transitioning through life stages. The two workshops ran for three hours and consisted of nine participants with experience of AIS and 12 participants with experience of HS respectively. The experiences of the participants who attended the workshops varied widely in terms of the age at which and time since their child had suffered a stroke, their experiences of diagnosis and treatment, and the health outcomes for the child and therefore their experience of rehabilitation and support services. We presented the participants with summaries of the results of our evidence review and invited them to discuss the findings in the context of their own experiences in small groups. These discussions were broken down into the topic areas 'Information Needs', 'Support Needs', and 'Transition'. The resulting data was analysed using thematic analysis (8) and data saturation was achieved as no themes emerged in the sub-group discussions that were not supported by at least one other sub-group (9). The emerging themes were used to supplement the evidence summary and were either used to support the recommendations that had resulted from the findings of the systematic review, or where strong themes emerged and no supporting published evidence was found, themes formed recommendations in their own right.

Three childhood stroke survivors also attended the workshops and gave an eloquent description of their experience, providing first-hand accounts that are rare in the published literature. By supplementing our literature search in this way, we were able to gather a much richer body of evidence and greater insight into the experiences of children who had suffered a stroke and their families.

Multi-discipline Guideline Development Group

The entire process of guideline development was carried out by a multi-disciplinary GDG. The GDG was made up of clinical experts representing specialties involved in the detection, care, and

rehabilitation of childhood stroke, as well as lay representatives with first-hand experience of childhood stroke, experts in research methods, and representatives of charitable bodies. This enabled the GDG to consider the practical implications of the recommendations from a range of viewpoints. The multi-disciplinary approach also allowed recommendations resulting from different sources to be crafted in a way that was acceptable to all involved. Each recommendation was subject to lengthy discussions around its clinical accuracy, practical implications and the impact it may have on the children, families, and clinical teams who will be encouraged to adopt them.

Where the clinical opinions of the GDG members differed, the recommendation in question was discussed until consensus was reached. As might be expected, disagreement most often arose around the practicalities of implementing the draft recommendations and achieving the right balance between being aspirational in the standard of care that could be achieved while also not being over ambitious. The parent representatives in particular were strong advocates for including recommendations that pushed the boundaries of current clinical practice and as such were vital to creating a guideline that has the potential to have a real impact on the stroke care that children receive.

Guideline write-up

Following the agreement of the recommendations, GDG members wrote introductions for those chapters most closely matching their area of expertise. Following the format used in guidelines produced by the National Institute for Health and Care Excellence (NICE), the systematic reviewers summarised the evidence found for each clinical question including the study designs, numbers of children involved, countries of origin of the papers, and any judgements that were made about the quality of the evidence. A section linking the evidence to the recommendations was then included which provided a brief summary of the discussions that were had around the evidence, and if recommendations were based on the consensus of the GDG, the Delphi survey, the parent focus groups, or a combination thereof, this was stated explicitly in the text.

A chapter on the research implications of the findings of the guideline was also included which outlined the areas that the GDG felt were particularly in need of research as well as the research structures, for example national patient databases, that could facilitate the study of stroke in childhood. It is hoped that clinicians, researchers, and funders interested in this area will use this as a resource to help in the design and identification of research that has the potential to improve the state of the evidence base of childhood stroke.

DISCUSSION

The need for a guideline on stroke in childhood is plain in the varying quality of care described in the literature and by our workshop participants, and in the range of opinions held by clinicians relating to the treatment of this condition. The burden of illness in childhood stroke is arguably greater than in those that occur in adulthood as the child's longer life expectancy translates to a greater number of years living with any resultant deficits (10). Producing an evidence based guideline on childhood stroke, an area that to date has been characterised by under research and extrapolation from the adult literature (11), was a challenge that we overcame by combining and triangulating the often scant published literature with expert consensus gleaned from our GDG, a Delphi study, and parent workshops. As such, we produced a NICE accredited clinical guideline for the complete care pathway of stroke in children that is evidence based, is approved by a large number of clinical and lay experts, is endorsed by a wide range of relevant professional bodies and charities, and draws on the accounts, views, and experiences of a large number of expert health care professionals, childhood stroke survivors, and their families. We suggest that under similar circumstances where there is a need for a clinical guideline but a small or incomplete body of evidence threatens to prevent the creation of the guideline, the methods described above may be used by others to produce robust recommendations.

Competing interests: None

Acknowledgements

We would like to thank the members of the Guideline Development Group, the clinicians who contributed their expertise to the Delphi study, and the parents and children who participated in our workshops, whose invaluable contribution made this guideline possible.

What is known about this topic

- ☐ Stroke in childhood is rarer, and is less well researched and understood in comparison to stroke in adulthood.
- ☐ Evidence based guidelines are valuable to both patients and clinicians as they can help to improve the quality and consistency of patient care.

What this study adds

- ☐ This study is the first clinical guideline for childhood stroke that covers the entire patient pathway for both ischaemic and haemorrhagic stroke.
- ☐ This study uses a variety of methods to triangulate evidence and form robust recommendations.

1. Roach ES, Golomb MR, Adams R, Biller J, Daniels S, deVeber G, et al. Management of Stroke in Infants and Children. *Stroke*. 2008;39(9):2644.
2. Mallick AA, O'Callaghan FJK. The epidemiology of childhood stroke. *European Journal of Paediatric Neurology*. 2010;14(3):197-205.
3. Braun KPJ, Kappelle LJ, Kirkham FJ, DeVeber G. Diagnostic pitfalls in paediatric ischaemic stroke. *Developmental Medicine and Child Neurology*. 2006;48(12):985-90.
4. Cecamore C, Savino A, Salvatore R, Cafarotti A, Pelliccia P, Mohn A, et al. Clinical practice guidelines: what they are, why we need them and how they should be developed through rigorous evaluation. *European Journal of Pediatrics*. 2011;170(7):831-6.
5. Royal College of Paediatrics and Child Health. Setting Standards for Development of Clinical Guidelines in Paediatrics and Child Health. 2016 January 2016.
6. Mann CJ. Observational research methods. Research design II: cohort, cross sectional, and case-control studies. *Emergency Medicine Journal*. 2003;20(1):54-60.
7. Hsu C, Sandford B. The Delphi Technique: Making Sense of Consensus. *Practicle Assessment, Research and Evaluation*. 2007;12(10):1-8.
8. Braun V, Clarke V. Using thematic analysis in psychology. *Qualitative Research in Psychology*. 2006;3(2):77-101.
9. Fusch PI and Ness LR. Are we there yet? Data saturation in qualitative research. *The Qualitative Report*. 2015; 20(9):1408-1416.
10. Greenham M, Gordon A, Anderson V, Mackay MT. Outcome in Childhood Stroke. *Stroke*. 2016;47(4):1159.
11. Tsze DS, Valente JH. Pediatric Stroke: A Review. *Emergency Medicine International*. 2011;2011:10.