The importance of two-year follow-up assessments in neonatal trials: overcoming the challenges of obtaining data

Identifying developmental delay, early intellectual disability or language problems in infants born preterm may enable earlier intervention and improve outcomes for the child. Two-year follow-up assessments are important but locating and obtaining the information is rarely easy. Researchers on neonatal clinical trials find that locating follow-up information requires a degree of ingenuity. This article considers the experiences gained during conduction of a randomised controlled trial and offers tips on how to enhance the availability and quality of follow-up data.

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Key points

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1. Enhanced developmental surveillance of premature babies up to two years of age may enable earlier identification of future problems.
2. Two-year neurodevelopmental follow-up results can be a valuable resource for future health service planning.
3. Neonatal research is improved by access to follow-up data.
4. Finding this information can be problematic; different pragmatic methods are explored.

Children born prematurely are considered to be at an increased risk of developmental problems and disorders.[1-3] Enhanced developmental surveillance may enable earlier identification of future developmental problems thereby permitting further observation and interventions, which may help mitigate developmental difficulties and allow for more targeted provision of support for these infants.[1-3]

The National Institute for Health and Care Excellence (NICE) is currently consulting on draft guidelines offering greater clarity as to how premature babies should be followed up.[4] The draft consultation document has postulated criteria for enhanced developmental support and surveillance up to two years of corrected gestational age (CGA). It has been suggested within the document that babies born before 30 weeks' gestation constitute one of the groups who would benefit most from increased developmental surveillance in order to indicate future developmental problems for the infant. These draft guidelines recommend:

> "At a minimum, the Parent Report of Children's Abilities – Revised (PARCA-R) is to be used to identify if the child is at risk of global developmental delay, early intellectual disability or language problems."

Apart from the parentally-reported PARCA-R there exist a number of formal assessments, such as Bayley Scales of Infant and Toddler Development (Bayley-III), Schedule of Growing Skills (SOGS) and Griffiths Mental Development Scales.

In general, results from two-year neurodevelopmental follow-up assessments are being viewed as key indicators to the long-term safety and efficacy of treatment administered in the neonatal intensive care unit (NICU). Review of the health status of an infant at this stage may reveal long-term positive or negative effects that may be attributed to a certain process or treatment earlier in the child's life. Robertson[5] has outlined errors in the past that were inadvertently introduced as a result of neonatal care that were not obvious at the time of treatment. As a result, the two-year follow-up assessment is seen as an important outcome for an increasing number of paediatric trials.

PlaNeT-2

This article considers experience gained during the Platelets for Neonatal Transfusion – Study 2 (PlaNeT-2) randomised controlled trial, which compares two different platelet thresholds for prophylactic platelet transfusion to preterm neonates (www.planet-2.com). PlaNeT-2 is a large study of 660 randomised babies, which is funded and sponsored by NHS Blood and Transplant (NHSBT) Research and Development and run by the NHSBT Clinical Trials Unit. The trial is designed to establish where the balance lies between benefit and risk in neonatal platelet transfusion thresholds. While the primary outcome measure is the

proportion of patients who either die or experience a major bleed, up to and including study day 28, one of the most important secondary outcomes is based on a neurodevelopmental assessment of the child at two years CGA.

This article will not consider the actual research findings of PlaNeT-2, which will be published in 2018.

The challenges of finding two-year follow-up information

Researchers on many neonatal clinical trials find that locating follow-up information requires a degree of ingenuity. The 2016 National Neonatal Audit Programme (NNAP) Annual Report on 2015 data[6] revealed that only 60% of premature babies born below 30 weeks' gestation had some health data recorded at a two-year follow-up appointment, although this is an improvement on previous reporting rates. There also appeared to be a variation between neonatal networks entering two-year follow-up data on to BadgerNet – the neonatal electronic health record of all admissions to NHS neonatal units containing data sets for developmental follow-up (www.clevermed.com/badgernet/badgernet-neonatal). Completion levels for two-year follow-up data ranged from 30-90% depending on the network.

The 2016 NNAP report also revealed around 10% of babies experience at least one transfer during their time in the NICU. In the PlaNeT-2 trial the incidence was higher; preliminary findings from 2011 to 2016 appear to indicate that about 25% of babies randomised to the trial transferred out from the recruiting unit at some stage. This higher incidence may be a consequence of the nature of the study cohort – very small and sick premature babies (under 34 weeks' gestation at birth and platelet count below 50x10^9/L) needing specialised care that are transferred to Level 3 units often from outside their own network. Once the babies are stable they are frequently transferred back to their local units nearer to their home. This usually means that the direct contact between trial research clinicians and the families of participating babies is lost.

Tracking recruited babies has revealed that families may move many times before the point of two-year assessment. Some families have moved up to five times within two years and have then been lost to trial follow-up. Other parents may be offered a follow-up appointment but fail to attend.

Improving research outcomes by finding follow-up data: the PlaNeT-2 experience

The PlaNeT-2 trial pathway for obtaining two-year developmental data can be seen in **FIGURE 1**.

All large neonatal trials will probably have some difficulty obtaining two-year developmental follow-up data unless there is sufficient funding to employ a specialist to undertake the assessment in the community or to provide expenses to bring families back to clinics. This is rarely the case in publicly funded research and, therefore, it is essential to consider how to meet this challenge as soon as possible – ideally while developing the initial protocol.

At the outset it is recommended that permission is sought to obtain ethics approval to contact parents at two years' CGA, if required. This could be by email or text (mobile numbers seem to change less frequently than addresses) and may be performed by the site team or central coordinating centre. It has to be clear in the informed consent form (ICF) and patient information leaflet (PIL) that parents are agreeing to the collection of their contact details for storage on a database separate from clinical trial data, based on the understanding that all information will be treated confidentially.

BadgerNet

Once the baby reaches two years' CGA, scrutinising BadgerNet is the easiest way to obtain follow-up data, providing that the assessment has been undertaken and data have been entered. From the outset of the PlaNeT-2 trial, ethics approval was granted for site teams to access BadgerNet for clearly defined research outcomes. Close collaboration with local clinical research teams has enabled collection of the available data. Permission to seek this information was clearly stated in the ICF and PIL. A future hope is that a larger proportion of two-year assessments will be added to the database making collection easier.

PARCA-R

Once the PlaNeT-2 trial management group identified the challenge of getting

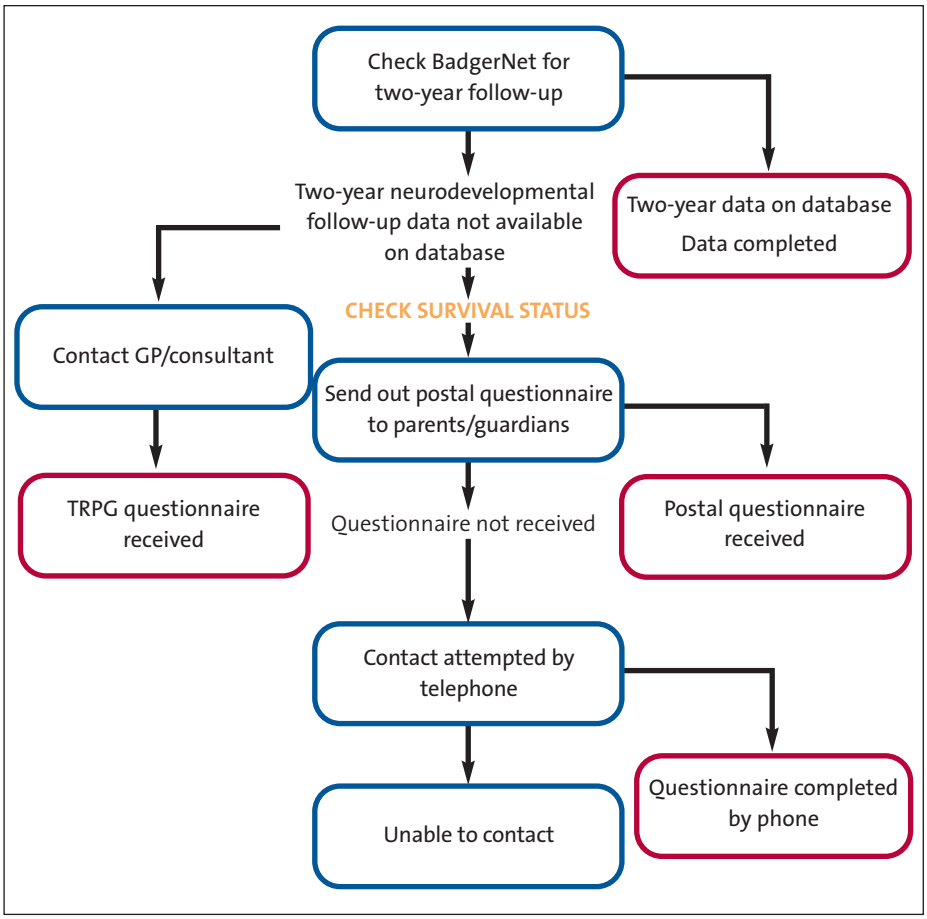

FIGURE 1 The PlaNeT-2 trial pathway for obtaining two-year developmental data.
Key: TRPG = Thames Regional Perinatal Outcome Group.

good quality data through the database, a substantial amendment to the Research Ethics Committee was submitted to enable sending out of the parental report questionnaire, PARCA-R. The PARCA-R questionnaire has been validated for use with very premature infants at two years' CGA[7,8] and it is a useful tool for identifying developmental delay at this stage. The questionnaire can be posted out to parents with a stamped addressed envelope for its return. Ideally a telephone call from their research nurse beforehand will re-engage the family with the trial and offer the possibility of undertaking the questionnaire over the phone, if they prefer. One future consideration is to develop an online version of the PARCA-R with a unique personal identification number for each participant; ensuring adequate data security will be essential.

Questionnaire return rates are shown to be improved if the trial team keeps in touch with parents over the course of the two years, for example, via birthday cards for the infant; this will require ethics approval and confirmation of survival status prior to each contact.

Communication

Developing a good communications strategy between the trial management group and the local researchers is of the utmost importance in the success of any trial. A monthly research nurse teleconference, which initially focused on recruitment to the trial, now increasingly focuses on outstanding follow-up information. The conference calls allow discussion and contributions from participants who share their ideas and these are later featured in a quarterly trial newsletter (**FIGURE 2**).

Using key performance indicators

The PlaNeT-2 data management team generates monthly reports from the trial database to guide other team members on where to focus time and resources. The reports provide progress updates on obtaining data and generate lists of two-year follow-up assessments anticipated within the next month; these are forwarded to site teams to help them concentrate on these particular babies. It is possible to zoom in on individual babies with outstanding follow up, giving the researchers the ability to collaborate with the site team to try and develop new strategies for engaging these particular families.

PlaNeT in Practice

2 year follow up

Those of you who regularly attend the telecons will know we have paid a lot of attention to collecting the 2 year follow up information recently. Although this is a secondary outcome in PlaNeT-2, in many trials this is actually one of the primary outcomes, which demonstrates how important this measure is regarded amongst researchers.

All neonatal trials are finding this data collection very challenging, so as usual with PlaNeT, we are being innovative!

Here are some of your suggestions to get this information:

- **What's the best way of getting the information?**
  So far you have had success by checking Badger, talking to parents at clinics, contacting hospital or community paediatricians, looking at NHS records & by contacting GPs and parents. Site staff can also phone parents to ask for developmental information.
- **If we contact the GP or paediatrician, what do we need to do?**
  We have ethically agreed letters to send out. You will need to send a copy of the ICF & PIL with the request and a SAE (ask Karen or Anna for more information; we can provide SAEs as well).
- **If a baby is older than 2 years old is it worth getting information?**
  Even if the baby is older than 2 years old, we can still use results. Our specialist consultant recently reviewed results from a parent answering questions regarding their baby who is now 5 years old and still managed to get some useful data!
- **If a Bayley's isn't on Badger, does that mean it hasn't been performed?**
  No! One nurse recently phoned parents for follow up information even though the baby is now 4 years old. Their child had actually had a Bayley's assessment but the data was not uploaded onto Badger (this is more likely to happen to the babies randomised earlier in the trial). Luckily the parents had a copy of the Bayley's assessment and sent a copy to the research nurse who forwarded it to us.
- **If there is no Bayley's available how can I get the PARCA questionnaire completed?**

Some nurses have rung parents reminding them of the study and that 2 year follow up was due. They offered to either post the questionnaire to parents or ring at another time to ask the questions over the phone. If they have asked for the questionnaire to be posted, remember to include an SAE (these can be provided by NHSBT — contact Karen or Anna). The parents were also texted later to remind them to complete the questionnaire if it had not been returned. If phoning & time is short, please focus on the section at the end called 'A few extra questions'; these are the most important and should only take a few minutes to answer

Don't forget to check whether each baby is still surviving before direct contact.

If you don't know you may find that the best way to do this is via hospital records, Badger, NHS Spine or GP contact.

PlaNeT-2

FIGURE 2 The PlaNeT-2 quarterly newsletter for the trial team.

Contacting other health professionals

Ethically approved template letters have been introduced for the principal investigators to easily contact consultant colleagues or GPs. Questionnaires are sent out to GPs by site staff with a copy of the PIL that the parent read (or corrected versions if they have been amended) and a copy of the signed ICF, with a stamped addressed envelope for return of the questionnaire. The data obtained from these sources is often incomplete but can still be used to provide a fuller picture of the state of the study cohort at two years' CGA.

Using delayed assessments or other clinical data

On some occasions it is possible to use data even if the child has exceeded two years' CGA. Working with a specialist consultant has enabled the researchers to make the most of available data and for some areas of the assessment it is possible to impute the infant's condition at two years. For example, if a child does not have cerebral palsy at five years, it is safe to say that the child did not have it at two years.

If there is no access to a formal assessment it is still possible to use clinical data or data from other healthcare professionals, such as speech therapists, cardiologists, surgeons or dietitians, for some parts of the questionnaire.

Conclusion

It is incumbent upon researchers to use public funding efficiently and to be innovative in approaches to obtaining good quality data in line with the informed consent given willingly by parents. The trial team has tried a number of methods

for obtaining two-year follow-up information, which has led to improved return rates and better quality data that will ultimately answer the research questions posed, to a higher and more robust standard. Future hopes are for more formal assessments that will be undertaken and entered on to BadgerNet in a more reliable and comprehensive manner. Captured data are a helpful resource for researchers and those involved in planning health and social care services and provide an objective measure of health outcomes.

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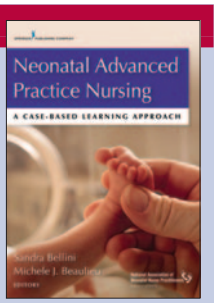
Book review

Neonatal Advanced Practice Nursing – A Case-Based Learning Approach



Sandra Bellini and Michele Beaulieu (eds)
Springer Publishing Company, New York
ISBN: 9780826194152
$85, paperback,
375 pages

It is a joy to read a book on advanced practice dedicated to the role of the ANNP (advanced neonatal nurse practitioner), both in their novice role and through the transition to fully-fledged ANNP. The authors of the various chapters are experienced ANNPs/educators with an interesting scholarly perspective on their chosen topic.

The preface to the book's aim includes the recognition that advanced practice for neonatal care is dynamic and requires a dedication to life-long learning. Each chapter aims to augment didactic learning on subjects such as neonatal physiology, neonatal disorders and disease processes, with case-based studies.

The authors' intentions are to further develop the novice practitioner by enabling integration of factual knowledge and application of scholarly knowledge, which comes with experience. This style of learning is enhanced by the inclusion of a range of case study approaches to engage critical thinking when applying decision-making rationale. Although clearly written for an American audience these aims fit well with a UK-based programme and demonstrate the shared values that underpin neonatal advanced nursing practice in the western world.

The book is set out in sections with each chapter supported by an up-to-date reference list. Section one appropriately focuses on maternal risk factors and other factors that put the fetus at risk. Moving through neonatal transition at birth, it is nicely 'bookended' by a closing discussion on developmental milestones in the first year of life.

Section two, the main part of the text, takes the reader on a journey through the major body systems incorporating background physiology, altered physiology and pathologies. The case studies explore critical thinking and health assessment and diagnostic reasoning, encouraging a wider focus on differential diagnosis.

Towards the back of the book I was pleased to see a section on the 'imposter' phenomenon (feelings of inadequacy, self-doubt and intellectual fraud) that can overwhelm novice ANNPs, and a discussion on how and why this may happen. There is also a thoughtful section on complex communication with families.

The final section of the book discusses both case-based simulation training and the need to continue life-long learning. This is most welcome. For some time I have argued that point for ANNPs in the UK who exit programmes with limited support thereafter. So much so, that I have secured three funded alumni days for trainee ANNPs at Sheffield once they gain their PGDip. Working through this book would be a good learning tool for ANNPs who want to prepare for yearly reviews or Nursing and Midwifery Council validation.

As is to be expected with any American text, there is the caveat of how well clinical decision-making and management of care translates across the pond. Chemistry values are presented differently and guidelines (eg neonatal resuscitation) are not easily transferrable or, indeed, conflict with current UK guidance. This is particularly true about reflection on practice, which is encouraged by both medical and nursing programmes in the UK but is not flagged up much in this text. I wrongly assumed that, as there is an interesting preface discussion on Benner's novice to expert model, I would see more discussion on the role of reflection to explore the wider impacts on practice and care delivery. Most trainee and qualified ANNPs in the UK, who have on average about eight years of nursing practice before embarking on an ANNP programme, should be able to accommodate for these variances in what is an otherwise comprehensive learning tool.

This book would be a welcome addition to any NICU, hospital or university library either as hard copy or online.

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