Quality use of medicines in neonatal care

a review of measures of quality used to evaluate the appropriateness and rational use of medication within the NICU

Krzyzaniak, Natalia; Bajorek, Beata

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Quality use of Medicines in Neonatal Care: A Review of Measures of Quality used to evaluate the appropriateness and rational use of medication within the NICU

ABSTRACT

With medication error rates in neonatal intensive care units (NICU's) reported to be as high as 91 medication errors per 100 patient admissions, the quality use of medicines (QUM) in this setting is important. Comprising the safe, rational, appropriate and effective use of pharmacotherapy, QUM is integral to achieving medication safety and optimal patient outcomes. To improve QUM in the NICU, the medication use process needs to undergo a quality assessment, using quality measures or indicators. As such, the objectives of this quasi-systematic literature review were to identify the measures used to evaluate QUM within the NICU and to map these against Donabedian's traditional framework of structure, process and outcome. We searched Embase, PubMed, CINAHL, Google Scholar as well as Google for relevant published and grey literature. Overall, a total of 47 quality measures were identified and categorised: 17 structure, 19 process and 11 outcome measures. The most common measures related to: the availability of medication safety technology on the NICU, written policies on the use of high risk medications, medication error and adverse drug event reporting systems, and the provision of education for health professionals involved in the medication use process. However, there were no quality measures specifically designed for medication management in the NICU. The literature does not provide a comprehensive evaluation of the quality of care provided along the medication use process in the NICU. There is a need to develop a quality framework outlining measures that facilitate the appropriate use of medicines in the NICU.

1. INTRODUCTION

Medication safety is of utmost priority in the neonatal intensive care unit (NICU).[1] Medications are heavily utilised within the NICU, with a reported average of 8.6 medications being prescribed per patient.[2] The high-risk characteristics of neonatal patients, including physiological vulnerabilities, varying pharmacokinetics as well as the limited amount of evidence-based information available on the use of pharmacotherapy in infants, increase the complexity of the medication use process.[3-5] In combination with the fast-paced, challenging NICU environment, neonates are at a high risk of medication misadventure with potentially significant consequences that may have long-term impacts upon a child's development.[3] With medication error rates reported in NICU's as high as 91 medication errors per 100 patient admissions, the quality use of medicines (QUM) in this setting is important.[5] Comprising the safe, rational, appropriate and effective use of pharmacotherapy, QUM is integral to achieving medication safety and optimal patient outcomes.[6-8]

In order to improve QUM in the NICU, the medication management process needs to undergo a quality assessment, using quality measures or indicators.[9] Quality indicators are measurable elements that refer to the structure, process and outcomes of pharmacotherapy in the NICU.[9, 10] The medication management process is complex and comprises several phases: prescribing, transcribing, dispensing, administering and monitoring.[11] As such, in order to provide an all-inclusive quality assessment, indicators must consider each aspect of the medication management process. Previous studies describe various measures related to the appropriate use of medications in adult patients, including the Assessing Care of Vulnerable Elders (ACOVE) quality framework, however, there is relatively minimal corresponding literature in other patient groups, particularly neonates.[12] Therefore, the aim of this review was to identify quality measures used to evaluate the medication management process within the NICU. A specific objective was to identify the range of measures used to evaluate the quality use of medicines in the NICU.

2. METHOD

A quasi-systematic review (a review that possesses some elements of a systematic review, including pre-defined selection criteria, however includes grey literature and does not present a critical evaluation of the quality of studies) of the literature was performed and the findings were mapped against Donabedian's framework of structure, process and outcomes.[10, 13-16] A structure of care describes the characteristics of the setting or the organisational framework supporting the process of care, for example, the number of qualified staff, type of hospital, level of NICU. [17, 18] Process refers to the method of healthcare service provision and includes the amount and type of activities performed for the patient. This relates to what is done to the patient, including types of interventions, evidence based treatment regimens, etc.[9, 17-20] Outcomes are classified as the consequences of healthcare and comprise the health status of patients i.e. morbidity, mortality etc.[9]

For the purpose of this review a definition of quality was adapted from the World Health Organisation's (WHO) description of quality in healthcare.[21] This definition was modified to characterise quality relating to the medication use process in the NICU, including the quality of the structure and process systems as well as the outcomes they produce.[21] As such, quality is described across six dimensions, as follows:

- Effective: Using medicines that are evidence-based and which result in improved health outcomes for individuals based on need.
- Efficient: Using medicines in a manner that maximises resource use and minimises waste.
- Accessible: Using medicines in a manner that is timely and provided in a setting where skills and resources are appropriate to therapeutic need.
- Patient-centred: Using medicines in a manner that takes into account the preferences of individual patients.
- Equitable: Using medicines that do not vary in quality because of personal characteristics.
- Safe: Using medicines in a manner that minimise risk and harm to patients. [21]

The review sought to identify quality measures relating to the medication use process in accordance with this definition. Quality measures included guidelines, consensus statements, position statements and quality assessment tools. (Table 1) Furthermore, due to a lack of available literature, the review also included studies that suggested interventions or resources to improve any of the aforementioned dimensions of quality and had the potential to be applied in the future as quality indicators.

Full-text articles were retrieved by searching the following databases: Embase, PubMed, CINAHL and Google Scholar, in the period from March 2015 – March 2016. Citations and reference lists were also hand-searched to find articles that were not identified in the original search. This was supplemented by a Google search to identify relevant grey literature. Articles were selected for the review if they included quality measures/indicators relating to the use of medicines, if the quality indicators were applicable to the NICU and if they stated recommendations for the improvement of medication management. The articles were mapped against Donabedian's domains of health care quality, in three steps. If articles used Donabedian's terms within their findings, they were reviewed to determine their design i.e. study, guideline etc. Secondly, measures were identified as belonging to structure, process or outcome per the definition used in Donabedian's framework or via author verification. Third, these measures were categorized into their corresponding domains on the discretion of Author 1 and were verified by Author 2.

3. SEARCH STRATEGY

A two-tiered search strategy was used. (Figure 1) In Tier 1, a generalised search of the electronic databases was conducted using the MeSH terms: *quality, quality indicators, neonate/infant/newborn*, *NICU*, *medication, medication safety, medication prescribing/transcribing/dispensing/administration/monitoring, patient safety, pharmacist services/pharmaceutical care*. The search terms combined keywords and medical subject headings for neonate, medication safety and quality indicators. The search parameters limited the inclusion of articles relating to the use of medication in NICU, neonatal patients and written in the English language. We applied a date limit so that only recent articles published from the year 2000 or later, i.e. 2000 - 2016 were taken into account. Tier 2 of the search identified relevant sources of grey literature using a Google search of the same terms. Organisations such as WHO, Council of Europe, Society of Hospital Pharmacists Australia, and Australian state/national government protocols in particular were reviewed. The articles retrieved from each tier of searching were pooled for analysis, in-line with the study objectives.

4. RESULTS

A total of 20 sources of information were identified, comprising seven reports [22-28], four studies (including cohort and observational studies)[1, 29-31], one literature review [32], three position statements [33-35], four hospital service standards/guidelines [36-39] and one quality assessment tool developed by the WHO [40]. (Table 2) The literature collected came from the USA (12 of 20 articles) [22-31, 33, 35] and UK (3 of 20 articles) [37-39], with singular reports from the Netherlands [32], Australia [36], New Zealand [1] and Qatar [34]. No randomised control trials were identified in the search.

Overall, the search identified limited published literature comprehensively exploring the quality measures associated with QUM in NICU's. Among the included literature, a total of 47 quality measures were identified and categorised: 17 structure measures, 19 process measures and 11 outcome measures. (Table 3)

4.1 MEASURES OF QUALITY RELATING TO STRUCTURE

Overall, structure measures most commonly related to the staffing and support systems available on the NICU. Three structure measures referred to the presence of a qualified and experienced NICU pharmacist on the ward. A ward-based pharmacist was reported as a key facilitator for the QUM on the NICU, compared to just having access to an externally provided service based in the main hospital pharmacy.[28, 36-39] 'Qualified' was defined in the Scottish and British NICU guidelines as a pharmacist who held postgraduate qualifications in paediatric practice or possessed the equivalent level of skills and knowledge.[37, 38] The National Institute for Health and Care Excellence (NICE) standard also reaffirmed that all NICU pharmacists were required to be sufficiently skilled and compliant with NICU-based competency standards according to each setting's regulations (i.e. British Department of Health Toolkit).[39] Required competencies included possessing comprehensive knowledge of neonatal development, metabolic pathways, as well as pharmacokinetics and pharmacodynamics in neonates.[38] Two resources also reported on the requirement for NICU pharmacists to continue to update their knowledge through continuing education to ensure currency of practice.[33, 38] Additionally, two resources stipulated that there was a need for adequate levels of qualified nursing and medical staff on the NICU, with appropriate workloads and sufficient rest breaks to prevent fatigue errors from occurring.[35, 38] The British Association of Perinatal Medicine (BAPM) guideline recommended that due to the complex needs of infants in the NICU, the ratio of neonatal nurses should be 1 nurse : 1 baby, and medical staff should consist of a minimum of 8 staff comprising specialists, consultants and residents.[38]

The amount of time required and the capacity for pharmacists to provide pharmaceutical care in NICU was also emphasised as a relevant structure measure. The BAPM guideline recommended that NICU pharmacists should allocate at least 10-20 minutes of time (care) per patient-cot as well as attend medical ward rounds and meetings.[38] The Australian standard proposed an alternative method of pharmacist involvement, by allocating pharmacist time to NICU according to the complexity of care within a specific unit (Level 1 – caring for infants with minor conditions with gestations > 37 weeks, Level 2 – caring for newborns with gestations >34 weeks and requiring incubation, oxygen and intravenous therapy, Level 3 – caring for newborns with serious conditions requiring 1:1 nursing care) (Table 1). It was recommended that Level 1 and 2 NICU's required routine

pharmacist access, however Level 3 NICU's required a 24-hour pharmacy support service to be available.[36]

In addition to staffing, four structure measures reported that specific facilities were important requirements for QUM in NICU's. A well-lit work environment, with sufficient work-space, minimal distractions and easily accessible to reference materials was described as optimal for medication safety.[35] Additional important elements also included: space within the unit for medication preparation; and aseptic preparation sites.[36, 38] This was further verified by the WHO quality assessment tool, which specifically recommended that essential medicines (such as caffeine and surfactants) are readily accessible for the timely application of pharmacotherapy.[40]

Structure measures were also associated with the availability of medication management systems. In maintaining medication safety, two guidelines and one quality assessment tool identified the need for evidence-based clinical practice guidelines and protocols for high-risk medications within the NICU to assist with medication selection and administration as well as standard references to assist the general prescribing of medications for neonates.[34, 35, 38, 40] Additionally, it was acknowledged that it was important to have clear, specific policies that were accessible to all healthcare professionals on how medications in the NICU were prescribed, processed, dispensed, administered and monitored.[35] TPN was highlighted as an area requiring additional attention, and it was reported by Grissinger as requiring standardised prescribing methods including pre-printed forms or standard order sets that prompted correct dosing, established three-fold verification of TPN dispensing and administration processes as well as automated dose limit warnings built into pharmacy computer systems.[23] Other measures suggested for the improvement of medication safety included the availability of emergency medication sheets, listing doses by weight, as well as an established neonatal formulary with standardised concentrations of medications to be used in the NICU.[25, 28, 35]

Several resources referred to the utilisation of technology to promote the safe and rational use of medicines. These resources included: barcode verification systems, smart-pumps, computerised physician order entry (CPOE), clinical decision support systems (CDSS), computerised calculation of doses, automated drug dispensing robots and electronic health records.[24-26, 28, 29, 32, 35] Morriss et.al. attributed a barcode verified administration system with reducing the risk of targeted, preventable ADE's in neonatal patients by 47%.[29] Furthermore, in the event of an adverse reaction or medication error, three resources identified that it was essential for the NICU to have a reliable electronic reporting system to document the implicated medications.[33-35, 38] These systems allow for the collection of data regarding the types and causes of error, and allow for the identification of trends in error.[22] McCartney states that electronic database can identify more errors than a paper based reporting method and can facilitate a retrospective analysis of errors.[26] Furthermore, these types of systems enable drug usage data to be tracked. Ellsbury and Ursprung reported that medication misuse could be attributed to failures in collection, reporting and review of drug utilisation data by NICU treating teams.[22] Drug utilisation data provides an insight into patterns of use and allows for benchmarking against other databases.[22]

4.2 MEASURES OF QUALITY RELATING TO PROCESS

Process measures were deemed by de Boer et.al. to be the best method of evaluating quality use of medicines in NICU as they identify factors directly associated with patient care.[41] Process measures relating to NICU medication practice were well-documented within the literature and can be divided into three categories: clinical pharmacist interventions, education/training, and documentation and monitoring of medication-related problems. Clinical pharmacist interventions related to the number and type of interventions performed, including therapeutic drug monitoring, review of patient medication charts, participation in ward rounds, verifying prescriptions, participating in clinical research, and optimising intravenous and TPN therapy.[28, 32-35, 38] The British NICE and BAPM guidelines identified that clinical pharmacist activities improved the quality of medication management in NICU, as these roles improved the rationalisation of resources, reduced costs and reduced medication errors.[38, 39] Four measures related to medication information services and involved pharmacist's providing a medication counselling service to parents, providing general medication information to other NICU professionals, and educating NICU staff on medication protocols. In particular, it was noted that involving parents in the care process was important in achieving quality pharmaceutical care, and required regular communication and consultation with parents in making decisions about pharmacotherapy for their child.[39] Furthermore, only one standard identified the need for pharmacists to advise physicians regarding the use of off-label and unlicensed medicines, including the choice of medication and the type of formulation required.[38] Potentially more attention may be required in this area, as a significant proportion of medications are prescribed off-label or on an unlicensed basis in NICU.

Education was viewed as an important element to the QUM on the NICU in ensuring uniformity and currency of medication management practice.[1, 32-35, 38] Specifically, the National Association of Neonatal Nurses (NANN) position statement highlighted the importance of providing education to NICU staff involved in the medication use process on medication safety principles, the appropriate use of medication delivery devices, calculating doses as well as appropriate prescribing, preparing, and administering of medications.[35] Kunac et.al. highlighted that higher rates of medication errors occurred when new or intern doctors join the neonatal team, however noted training on safe prescribing practices was rarely provided to these staff.[1]

Furthermore, two position statements and one guideline emphasised the importance of the pharmacist in monitoring and reporting and adverse drug events in neonatal patients.[33, 34, 38] It is acknowledged that adverse drug reactions are avoidable when documentation is complete and readily accessible, leading to increased patient safety.[38] In response to any errors that occur, two resources identified that critical incident or root cause analyses should be thoroughly conducted to identify how these errors occurred and to develop strategies and action plans for preventing their recurrence and addressing flaws in the medication use process.[28, 35]

Pain management is highlighted as a high-risk area of practice in the neonatal population, with reports of over-prescribing of opioids as well as adverse effects from opioids. Sharek et.al. suggested process measures to improve pain assessment and management of neonates experiencing pain in the NICU, including the use of pain scales for assessment of patients to determine appropriate pain management as well as the use of pain protocols for patient groups and specific procedures.[30] Additionally, Sullivan et.al. found that the use of a prescribing error feedback programme, which

reported back to prescribers on trends in opioid prescribing errors in their NICU as well as on their own prescribing errors over the previous fortnight, had a relative reduction of opioid prescription errors by 83%.[31]

4.3 MEASURES OF QUALITY RELATING TO OUTCOME

It was reported that, due to multiple treatment modalities and multidisciplinary staff, outcome measures were the most difficult to attribute to the quality use of medicines.[41, 42] However, Kunac et.al. highlighted several outcome measures that were related to QUM in the NICU including: monthly audit of medication charts (with a target of at least 80% of correct time of administration), monthly audit of the labelling of all parenteral fluid/medication lines (to be labelled with access type and fluid/medication being administered, with a target of at least 90% correct labels) and monthly audit of prescribing against prescribing guidelines (target 90%).[1]

Furthermore, important areas of practice identified as being high-risk in neonatal patients included antimicrobial therapy and pain assessment. Outcome measures related to antimicrobial therapy were dedicated to monitoring antibiotics that were used most frequently in the NICU, and which also incurred the most costs, had the greatest risk of toxicity or the greatest risk of inducing antibiotic resistance.[27] Pain management measures related to the number of appropriate pain management interventions prescribed.[30]

Five resources also identified more general outcome measures relevant to the healthcare of the neonatal population.[17, 40, 42-44] The most commonly identified measures referred to the mortality rate of infants in NICU as well as the incidence of patient morbidity, neonatal sepsis and nosocomial infection, the duration of TPN therapy and daily weight gain.[17, 40, 42-44] However, it is unknown to what extent these measures are influenced by medication use or whether they directly reflect quality use of medicines in the NICU.

We also sought to identify outcome measures that were relevant to QUM, but which were not specific to a particular patient population, but which might be relevant to the NICU.[45] These included the number of medication errors, adverse drug events, pharmacist interventions performed, and the costs of drug therapy.[45] Furthermore, another study was identified with outcome measures that may be applicable to the neonatal population.[46] These included: quarterly dispensing errors (target < 5%), drug related problems (target < 10%), pharmacist participation in research projects (target > 1 – publications conferences).[46]

5. DISCUSSION

To our knowledge, this is the only review that identifies the range of quality measures relevant to medication use within the neonatal population. A total of 47 measures within the 20 sources of literature were identified relating to quality use of medicines in the NICU. (Table 3) The majority of these measures referred to the structure and process domains and most commonly described the availability of medication safety technology on the NICU, written policies on the use of high risk medications, medication error and adverse drug event reporting systems, and the provision of education for health professionals involved in the medication use process. The literature collected did not comprehensively address medication management in each phase of the medication use process. Most of the quality measures identified referred to the prescribing of medications, with less

attention paid to medication dispensing and administration. As such, the findings of the review inform the need for a framework of quality measures to be developed that represents quality use of medicines in the NICU. Such a framework would allow for the benchmarking of medication usage in the ward, tracking the performance of medication related processes and identification of areas requiring improvement.

Current studies that identify quality measures in NICU are predominantly based in other fields of healthcare, i.e. nursing, and do not relate to quality use of medicines.[17] One study related to nursing and physician care by Profit et.al., designed the baby-MONITOR quality framework which involved the use of clinical indicators including timely retinopathy of prematurity examinations, oxygen at 36 weeks and rates of first hour hypothermia.[47] Other nursing literature has used general NICU based health indicators to establish the level of quality healthcare being delivered and has measured the number of incubators available, nursing staff levels, incidence of intraventricular haemorrhage and rates of necrotizing enterocolitis.[19, 48, 49]

Studies that do identify medication-based quality measures are not studied within NICU settings. Within the elderly population, several studies emphasise the use of the ACOVE set of quality indicators that measure the processes of pharmaceutical care in both hospitalised and community based settings, including the rates of prescribing appropriate medications, therapeutic drug monitoring, correct transcribing of medication orders and comprehensive discharge summaries.[12, 50] It is unknown whether quality measures assessing medication management in adult patient groups are relevant to medication processes in the NICU. However, it is recognised that specific quality indicators need to be adapted to particular patient groups, for example, in the instance of surgical patients the measurement of the rates of patients receiving suitable peri-operative antibiotic prophylaxis.[41]

Upon birth neonates are already at a high risk of mortality, with a reported two thirds of neonatal deaths occurring within the first week of life.[51] In addition, once admitted to the NICU, patients are also subjected to complex pharmacotherapy regimens, increasing the potential for medication error which may further compromise the health of these patients.[5] Quality indicators are necessary to improve medication safety in the NICU, as they facilitate transparency of medication-use processes and help to benchmark NICU performance.[9, 52] As of yet, there are no reliable and valid quality indicators available in the literature that clearly define and evaluate the quality use of medicines in the NICU. More attention should be paid to the development of measures that assess each phase of the medication use process and address pharmacist as well as nursing and clinician input.

LIMITATIONS

Due to the lack of good-quality literature exploring this area, it is difficult to determine whether the key measures identified are applicable to current practice. Relevant literature from Asia, Africa, South America was not available, precluding a truly global perspective. It is also possible that a large number of studies were excluded due to not being available in the English language.

6. CONCLUSION

Quality measures within the NICU were most frequently identified within the structure and process domains, with limited outcome measures specific to quality use of medicines in the NICU. The most common measures related to: the availability of medication safety technology on the NICU, written policies on the use of high risk medications, medication error and adverse drug event reporting systems, and the provision of education for health professionals involved in the medication use process. However, there were no validated quality indicators specifically evaluating medication use in the NICU. Further research is required to address these gaps in knowledge and develop a quality framework that identifies key quality measures that facilitate appropriate and quality use of medicines in the NICU.

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REFERENCES

1. Kunac DL, Reith DM. Identification of priorities for medication safety in neonatal intensive care. Drug Safety. 2005;28(3):251-61.
2. Daniell A, Darlow B. Audit of drug usage in a regional neonatal intensive care unit. Journal of Paediatrics and Child Health. 1989;25(4):207-10.
3. Dabliz R, Levine S. Medication safety in neonates. American journal of perinatology. 2012;29(1):49-56.
4. Fortescue EB, Kaushal R, Landrigan CP et al. Prioritizing strategies for preventing medication errors and adverse drug events in pediatric inpatients. Pediatrics. 2003;111(4):722-9.
5. Kaushal R, Bates DW, Landrigan C et al. Medication errors and adverse drug events in pediatric inpatients. Jama. 2001;285(16):2114-20.
6. The National Strategy for Quality Use of Medicines. Australian Government Department of Health2004.
7. Quality Use of Medicines & the medicines industry. Medicines Australia. http://medicinesaustralia.com.au/files/2012/05/MA_QUM_External_Reduced.pdf. Accessed 22/09/2015.
8. Quality Use of Medicines (QUM). Department of Health, Australian Government. http://www.health.gov.au/internet/main/publishing.nsf/content/nmp-quality.htm. Accessed 05/10/2015.
9. Smeulers M, Verweij L, Maaskant JM et al. Quality indicators for safe medication preparation and administration: a systematic review. PLoS One. 2015;10(4):e0122695. doi:10.1371/journal.pone.0122695.
10. Donabedian A. Evaluating the quality of medical care. The Milbank memorial fund quarterly. 1966:166-206.
11. Antonucci R, Porcella A. Current pharmacotherapy in the newborn. Research and Reports in Neonatology. 2012;2:85-94.
12. Wierenga PC, Klopotowska JE, Smorenburg SM et al. Quality indicators for in-hospital pharmaceutical care of Dutch elderly patients: development and validation of an ACOVE-based quality indicator set. Drugs & aging. 2011;28(4):295-304.
13. Donabedian A. Special article: The quality of care: How can it be assessed? . Archives of Pathology and Laboratory Medicine. 1997;11(121):1145-50.
14. Martinez-Martin P, Leentjens AF, de Pedro-Cuesta J et al. Accuracy of screening instruments for detection of neuropsychiatric syndromes in Parkinson's disease. Movement Disorders. 2015.
15. Nasser S, Mullan J, Bajorek B. Challenges of older patients' knowledge about warfarin therapy. Journal of primary care & community health. 2012;3(1):65-74.
16. Ryś P, Władysiuk M, Skrzekowska-Baran I et al. Review articles, systematic reviews and meta-analyses: which can be trusted? Polskie Archiwum Medycyny Wewnętrznej. 2009;119(3):148-56.
17. Elverson CA, Samra HA. Overview of Structure, Process, and Outcome Indicators of Quality in Neonatal Care. Newborn and Infant Nursing Reviews. 2012;12(3):154-61.
18. Raven JH, Tolhurst RJ, Tang S et al. What is quality in maternal and neonatal health care? Midwifery. 2012;28(5):e676-e83.
19. Petryshen P, Stevens B. Outcomes management in neonatal nursing clinical practice. Journal of advanced nursing. 1995;22(6):1043-9.
20. Mikeal RL, Brown TR, Lazarus HL et al. Quality of pharmaceutical care in hospitals. American Journal of Health-System Pharmacy. 1975;32(6):567-74.
21. WHO. Quality of Care - A Process for Making Strategic Choices in Health Systems. 2006. http://www.who.int/management/quality/assurance/QualityCare_B.Def.pdf. Accessed 04/03/2015.
22. Ellsbury DL, Ursprung R. A quality improvement approach to optimizing medication use in the neonatal intensive care unit. Clinics in perinatology. 2012;39(1):1-10.
23. Grissinger M. A fatal zinc overdose in a neonate: confusion of micrograms with milligrams. Pharmacy and Therapeutics. 2011;36(7):393.

24. Lemoine JB, Hurst HM. Using smart pumps to reduce medication errors in the NICU. Nursing for women's health. 2012;16(2):151-8.
25. Lucas AJ. Improving medication safety in a neonatal intensive care unit. American journal of health-system pharmacy. 2004;61(1).
26. McCartney PR. Using technology to promote perinatal patient safety. Journal of Obstetric, Gynecologic, & Neonatal Nursing. 2006;35(3):424-31.
27. Patel SJ, Saiman L. Principles and strategies of antimicrobial stewardship in the neonatal intensive care unit. Seminars in perinatology. 2012;36(6):431-6.
28. Simons SL. Designing medication safety in the NICU. Neonatal Network. 2007;26(6):407-8.
29. Morriss FH, Abramowitz PW, Nelson SP et al. Effectiveness of a barcode medication administration system in reducing preventable adverse drug events in a neonatal intensive care unit: a prospective cohort study. The Journal of pediatrics. 2009;154(3):363-8. e1.
30. Sharek PJ, Powers R, Koehn A et al. Evaluation and development of potentially better practices to improve pain management of neonates. Pediatrics. 2006;118(Supplement 2):S78-S86.
31. Sullivan KM, Suh S, Monk H et al. Personalised performance feedback reduces narcotic prescription errors in a NICU. BMJ quality & safety. 2013;22(3):256-62.
32. Chedoe I, Molendijk HA, Dittrich ST et al. Incidence and nature of medication errors in neonatal intensive care with strategies to improve safety. Drug safety. 2007;30(6):503-13.
33. Position Description: NICU Clinical Pharmacist Specialist. University of Kentucky Hospital 2009. http://www.hosp.uky.edu/pharmacy/departpolicy/PH14-45.pdf. 04/03/2015.
34. Clinical Pharmacist Intensive Care (PCICU, PICU, ED and NICU) - Pharmacy. Sidra Medical and Research Center. 2015. http://www.bayt.com/en/job/clinical-pharmacist-intensive-care-pcicu-picu-ed-and-nicu-pharmacy-in-qatar-50043520/. Accessed 04/03/2015.
35. Medication Safety in the Neonatal Intensive Care Unit, Position Statement #3060 National Association of Neonatal Nurses, Chicago. 2014. http://nann.org/uploads/About/PositionPDFS/1.4.7_Medication%20Safety%20in%20the%20NICU.pdf. Accessed 15/02/2016.
36. Neonatal Service Guidelines - Defining Levels of Care in Victorian Hospitals. In: HS, editor. Melbourne: Victorian Government; 2005.
37. Neonatal Care in Scotland: A Quality Framework In: Group NEA, editor.: Scottish Government 2013.
38. BAPM. Service Standards for Hospitals Providing Neonatal Care. Pharmacy. London: BAPM; 2010.
39. NICE. Specialist Neonatal Care Quality Standard. Skilled and Multidisciplinary Staff. Manchester: NICE; 2010.
40. WHO. Making Pregnancy Safer; Assessment tool for the quality of hospital care for mothers and newborn babies. Advanced newborn care (for intensive care units). Copenhagen: WHO; 2009.
41. de Boer M, Ramrattan MA, Boeker EB et al. Quality of Pharmaceutical Care in Surgical Patients. PloS one. 2014;9(7):e101573.
42. Chawla D, Suresh GK. Quality improvement in neonatal care—a new paradigm for developing countries. The Indian Journal of Pediatrics. 2014;81(12):1367-72.
43. PNAE. Paediatric and Neonatal Service and Clinical Quality Indicators. Paediatric Nursing Associations of Europe. 2009. https://www.rcn.org.uk/__data/assets/pdf_file/0020/371351/Paediatric_and_Neonatal_Service_and_Clinical_Quality_Indicators.pdf. Accessed 04/03/2015.
44. Rogowski JA, Horbar JD, Staiger DO et al. Indirect vs direct hospital quality indicators for very low-birth-weight infants. Jama. 2004;291(2):202-9.
45. Cousins D, Kijlstra N, Walser S. Pharmaceutical Care: Policies and Practices for a Safer, More Responsible and Cost Effective Health System. Strasbourg: Directorate for the Quality of Medicines & HealthCare of the Council of Europe; 2012.

46. Martin Conde MT, Monte Boquet E, Morillo Verdugo R. [Quality healthcare and pharmaceutical care practice indicators to HIV+ patient]. Farmacia hospitalaria : organo oficial de expresion cientifica de la Sociedad Espanola de Farmacia Hospitalaria. 2013;37(4):276-85. doi:10.7399/fh.2013.37.4.710.
47. Profit J, Gould J, Zupancic J et al. Formal selection of measures for a composite index of NICU quality of care: Baby-MONITOR. Journal of Perinatology. 2011;31(11):702-10.
48. Ekelem I, Taeusch HW. Defining quality of care indicators for neonatal intensive care units independent of maternal risk factors. Journal of the National Medical Association. 1990;82(5):345.
49. NICU Clinical Quality Data - Cedars Sinai. Cedars Sinai. 2013. http://www.cedars-sinai.edu/Patients/Quality-Measures/Clinical-Areas/NICU-Clinical-Quality-Data.aspx. Accessed 22/06/2015.
50. Higashi T, Shekelle PG, Solomon DH et al. The quality of pharmacologic care for vulnerable older patients. Annals of Internal Medicine. 2004;140(9):714-20.
51. Darmstadt G, Lawn J, Costello A. Advancing the state of the world's newborns. Bulletin of the World Health Organization. 2003;81(3).
52. Hillen JB, Vitry A, Caughey GE. Evaluating medication-related quality of care in residential aged care: a systematic review. SpringerPlus. 2015;4:220. doi:10.1186/s40064-015-0984-9.
53. Clinical indicators. Victorian Government, Australia. http://www.health.vic.gov.au/clinicalengagement/downloads/pasp/clinical_indicators.pdf. Accessed 22/09/2015.
54. Lawrence M, Olesen F. Indicators of Quality in Health Care. European Journal of General Practice. 1997;3(3):103-8. doi:10.3109/13814789709160336.
55. Consensus Statement. http://medical-dictionary.thefreedictionary.com/consensus+statement. Accessed 22/09/2015.
56. Bulajeva A. Pharmaceutical Care Services and Quality Management in Community Pharmacies - An International Study. Helsinki: University of Helsinki; 2010.
57. Key Performance Indicators. Health Information and Performance Authority. http://www.hiqa.ie/healthcare/health-information/key-performance-indicators. Accessed 22/09/2015.
58. Key Performance Indicators. Australia: Department of Health Western Australia2012.
59. Position Statement. http://www.businessdictionary.com/definition/position-statement.html. Accessed 22/09/2015.
60. Guidelines on continuous quality improvement. Faculty of Pain Management ANZCA. http://www.fpm.anzca.edu.au/resources/educational-documents/documents/guidelines-on-continuous-quality-improvement.html. Accessed 22/09/2015.
61. Quality Measures. Centers for Medicare and Medicaid Services. 2016. https://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/QualityMeasures/index.html?redirect=/QUALITYMEASURES/. Accessed 20/05/2016.

Table 1 Definitions of terms used in review

TERM	DEFINITION
CLINICAL INDICATOR	"Measures of elements of clinical care which may, when assessed over time, provide a method of assessing the quality and safety of care at a system level. Can be measures of process, structure and/or outcomes of patient care"[53, 54]
CONSENSUS STATEMENT	"A comprehensive summary of the opinions of a panel of experts about a particular scientific, medical, nursing or administrative issue. Its purpose is to provide guidance to healthcare professionals, particularly on poorly understood or controversial aspects of care"[55]
GUIDELINE	"Systematically developed statements to assist practitioner and patient decisions prospectively for specific clinical circumstances"[54, 56]
KEY PERFORMANCE INDICATOR (KPI)	"Measures of performance that are used by organisations to measure how well they are performing against targets or expectations. KPIs measure performance by showing trends to demonstrate that improvements are being made over time"[57, 58]
POSITION STATEMENT	"A written statement that articulates a position, viewpoint, or policy of a healthcare system or hospital organisation regarding best practices, standard care, or inconclusive evidence-based research".[59]
QUALITY ASSESSMENT TOOL	"A document that provides a semi-quantitative assessment of the quality of care in a variety of key areas, and can be used to assess and monitor the baseline situation and subsequent improvements, thus providing key information before and after interventions to improve quality of care, as well as for incentives and accreditation schemes"[40]
QUALITY IMPROVEMENT	"An organised process that assesses and evaluates health services to improve practice or quality of care"[60]
QUALITY MEASURE	"Quality measures are tools that help measure or quantify healthcare processes, outcomes, patient perceptions, and organizational structure and/or systems that are associated with the ability to provide high-quality health care and/or that relate to one or more quality goals for health care. These goals include: effective, safe, efficient, patient-centered, equitable, and timely care." [61]
QUALITY PHARMACEUTICAL CARE	"The extent to which pharmacy services deliver effective, efficient, patient-centred, equitable and safe pharmacotherapy"[21]
QUALITY STANDARD	"The level of compliance with a criterion or indicator. A standard is set prospectively and stipulates the level of care that a provider must strive to meet"[54, 56]
QUALITY USE OF MEDICINES	"Selecting management options wisely, choosing suitable medicines if a medicine is considered necessary so that the best available option is selected and using medicines safely and effectively to get the best possible results"[6-8]
LEVEL 1 NEONATAL INTENSIVE CARE UNIT (NICU): BASIC	"A nursery that must be capable of assessing, diagnosing and managing uncomplicated pregnancies and: - newborn infants without complications • gestation 37 weeks or greater • birth weight 2,500 grams or greater - newborn infants with minor conditions not requiring additional nursing or specialist medical treatment - newborn infants requiring phototherapy (in consultation with a specialist

	paediatrician)"[36]
LEVEL 2 NICU	"A neonatal unit that must be capable of assessing, diagnosing and managing: - newborn infants without complications • gestation 34 weeks or greater • birth weight 2,000 grams or greater, including growing preterm and convalescing infants - newborn infants requiring incubator care for: • short-term transition problems • mild complications: - oxygen requirement (not exceeding 40%) - apnoea monitoring - blood glucose monitoring - short term intravenous therapy - phototherapy - gavage feeding"[36]
LEVEL 3 NICU	"Neonatal unit that must be capable of assessing, diagnosing and managing all newborn infants requiring neonatal intensive care including infants: - requiring continuing assisted ventilation via an endotracheal tube, and for the 24 hours following endotracheal tube removal - requiring oxygen therapy (more than 60%) for more than four hours - with tracheostomies requiring intermittent positive pressure ventilation (IPPV) or continuous positive airway pressure (CPAP) - requiring a nasopharyngeal tube (without CPAP) to maintain airway patency - requiring an arterial line for continuing blood gas and/or blood pressure monitoring - having frequent seizures - undergoing major surgery, on the day of the procedure and for 48 hours postoperatively, including: • any procedure where a body cavity is opened • repair of neural tube defect • placement of a ventriculoperitoneal shunt or temporary ventricular drainage device - requiring 1:1 nursing care"[36]

Table 2 Summary of findings documenting quality measures related to quality use of medicines within the NICU[1]

INTERNATIONAL GUIDELINES / HOSPITAL SERVICE STANDARDS		
COUNTRY	**PUBLISHING ASSOCIATION**	**GUIDELINE**
Scotland	Neonatal Expert Advisory Group	Neonatal Care in Scotland: A Quality Framework [37]
UK	British Association of Perinatal Medicine	Service Standards for Hospitals Providing Neonatal Care [38]
UK	National Institute for Health and Care Excellence	Specialist Neonatal Care Quality Standard [39]
Australia	Victorian Government	Neonatal Service Guidelines – Defining Levels of Care in Victorian Hospitals [36]
POSITION STATEMENTS ON PHARMACIST ROLES WITHIN NICU		
COUNTRY	**SERVICE PROVIDER**	**ROLE**
USA	University of Kentucky Hospital – Pharmacy Services	NICU Clinical Pharmacist Specialist [33]
USA	National Association of Neonatal Nurses	Medication Safety in the Neonatal Intensive Care Unit – Position Statement #3060 [35]
Qatar	Sidra Medical and Research Center	Clinical Pharmacist Intensive Care (PCICU, PICU, ED and NICU) [34]
QUALITY ASSESSMENT TOOL		
REGION	**PUBLISHING ASSOCIATION**	**TOOL**
Europe	WHO	Making Pregnancy Safer – Assessment tool for the Quality of Hospital Care for Mothers and Newborn Babies [40]
REPORTS/REVIEWS		
COUNTRY	**AUTHOR / YEAR**	**TITLE**
The Netherlands	Chedoe, I., et al. (2007)	*Incidence and Nature of Medication Errors in Neonatal Intensive Care with Strategies to Improve Safety A Review of the Current Literature* [32]
USA	Ellsbury, D. L. and R. Ursprung (2012)	*A quality improvement approach to optimizing medication use in the neonatal intensive care unit* [22]
USA	Grissinger, M. (2011)	*A fatal zinc overdose in a neonate: confusion of micrograms with milligrams* [23]
USA	Lemoine, J. B. and H. M. Hurst (2012)	*Using smart pumps to reduce medication errors in the NICU* [24]
USA	Lucas, A. J. (2004)	*Improving medication safety in a neonatal intensive care unit* [25]
USA	McCartney, P. R. (2006)	*Using technology to promote perinatal patient safety* [26]
USA	Patel, S. J. and L. Saiman (2012)	*Principles and strategies of antimicrobial stewardship in the*

[1] PCICU = Paediatric Cardiac Intensive Care Unit
[2] PICU = Paediatric Intensive Care Unit
[3] ED = Emergency Department
[4] NICU = Neonatal Intensive Care Unit

		neonatal intensive care unit [27]
USA	Simons, S. L. (2007)	*Designing medication safety in the NICU* [28]
STUDIES		
COUNTRY	**AUTHOR**	**TITLE**
New Zealand	Kunac, D. L. and D. M. Reith (2005)	*Identification of priorities for medication safety in neonatal intensive care* [1]
USA	Morriss, F. H., et al. (2009)	*Effectiveness of a barcode medication administration system in reducing preventable adverse drug events in a neonatal intensive care unit: a prospective cohort study* [29]
USA	Sharek, P. J., et al. (2006)	*Evaluation and development of potentially better practices to improve pain management of neonates* [30]
USA	Sullivan, K. M., et al. (2013)	*Personalised performance feedback reduces narcotic prescription errors in a NICU* [31]

Table 3 Summary of Quality Measures associated with the rational and appropriate use of medications in the NICU[2]

QUALITY INDICATORS OF PHARMACEUTICAL SERVICES IN NEONATAL CARE		SOURCE OF INFORMATION
STRUCTURE	• Staffing – full-time/part-time pharmacist [36] • Staffing – nurses and medical staff [35, 38] • Qualifications of pharmacist [37-39] • Experience of pharmacist in NICU [38] • Continuing education of pharmacy practitioners [33, 38] • Well-lit environment, with sufficient workspace, minimal distractions [35] • Availability of aseptic compounding facilities for the formulation of IV and non-standard medications [38] • Availability of facility and instruments for medication preparation [36] • Availability of essential medicines for specific use within NICU [40] • Written policies/protocols/guidelines for high-risk medications i.e. antibiotics, pain-relief, parenteral nutrition [34, 35, 38, 40] • Clear policies on how to prescribe, dispense, administer and monitor medications in the NICU [35] • Neonatal formulary with standard concentrations [25, 28, 35] • Emergency medicines sheets, with listed doses per weight [25, 28] • Standard references for use in the selection, use and evaluation of medications [35] • Medication error and adverse drug event reporting (systems) [33-35, 38] • Collection of drug use data [22] • Availability of safety technology including: CPOE, CDSS, barcode verification, smart pumps, computerised calculation of orders, automated drug dispensing units, electronic health records [24-26, 28, 29, 32, 35]	[36] Australia [34] Qatar [32] The Netherlands [37-39] UK [22, 24-26, 28, 29, 33, 35] USA [40] WHO
PROCESS	• Therapeutic Drug Monitoring [34, 38] • Counselling of parents [33, 34] • Advice on off-label/unlicensed medications [38] • Adverse Drug Event Monitoring and documentation – Identification, Monitoring, Rectifying, Prevention [33, 34, 38] • Medication preparation by pharmacy department [35] • Monitoring of medication orders [33, 34, 38] • Medication errors – Identification, rectifying, prevention [38] • Review, verification and clarification of medication charts [33] • Education/training of health professionals [1, 32-35, 38] • Provision of drug information [34, 38]	[1] New Zealand [34] Qatar [32] The Netherlands [38] UK [28, 30, 31, 33, 35] USA [40] WHO

[1] CPOE = Computerised Physician Order Entry
[2] CDSS = Clinical Decision Support Systems
[3] ETT = Endotracheal Tube
[4] EDQM = European Directorate for the Quality of Medicines
[5] IV = Intravenous
[6] MRSA = Methicillin Resistant Staphylococcus Aureus
[7] NICU = Neonatal Intensive Care Unit
[8] PIV = Peripheral Intravenous
[9] PRN = 'Pro Re Nata' – as needed
[10] STAT = 'Statum' – immediately
[11] TPN = Total Parenteral Nutrition

	• Participation in multi-disciplinary ward rounds and meetings [33, 34] • Optimisation of TPN [38, 40] • Optimisation of IV formulations [38] • Use of pain scales [30] • Use of pain protocols for patient groups and specific procedures [30] • Participation in clinical research [33, 34] • Verification process, medicines and calculations checked by another licensed healthcare professionals before administration [35] • Critical incident /root case analysis [28, 35] • Prescribing error feedback programme [31]	
OUTCOME	• Monthly audit of medication charts with a target of at least 80% correct time of administration (wrong time was defined as more than 1 hour of prescribing for stat/PRN meds, and for regular meds dose not given prior to the next scheduled dose) [1] • Monthly audit of the labelling of all lines – to be labelled with access type and fluid/medication being administered with a target of at least 90% correct labels [1] • Monthly audit of prescribing against prescribing guidelines – target 90% [1] • Episodes of ineffective empiric antibiotic therapy (organism/antibiotic mismatch) [27] • Mean time to target vancomycin trough concentration for infants with known MRSA infection [27] • Proportion of infants receiving appropriate dosing and timing of perioperative prophylaxis [27] • Episodes of antibiotic-associated adverse events [27] • Duration of treatment for culture-negative presumed late onset sepsis [27] • Rates of infections with multi-drug resistant gram-negative infections [27] • Percentage of patients who received at least 1 pain management intervention during heel sticks, PIV insertions, venipunctures, umbilical arterial catheterizations, nasogastric tube placements and ETT suctioning [30] • Percentage of all defined procedures that were treated with a pain treatment intervention [30] **General healthcare outcome measures related to neonatal patients:** • Incidence of nosocomial infection [17, 40, 42] • Incidence of neonatal sepsis [17, 42] • Length of stay [17] • Days on TPN [17, 40] • Growth velocity (daily weight gain) [17, 40] • Mortality rates [17, 42-44] **Pharmacotherapy specific outcome measures as proposed by the EDQM: [45]** • Medication Error rates/reports • Adverse Drug Event rates/reports • Number of pharmaceutical care interventions performed • Dispensing errors rates/reports • Number of parents counselled • Costs of drug therapy • Costs saved	[45] EDQM [42] India [1] New Zealand [43] UK [17, 27, 30, 44] USA [40] WHO

Figure 1 Search Strategy