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The Chinese Neonatal Network: a national protocol for collaborative research and quality improvement in neonatal care

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TITLE PAGE

Title:

The Chinese Neonatal Network: a national protocol for collaborative research and quality improvement in neonatal care

Running title:

Protocol for CHNN collaborative research in China

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Ethics information

This proposal was approved by the Ethics Committee of the Children's Hospital of Fudan University (#CHFU 2018-296) which was recognized by all participating hospitals. Waiver of consent were granted at all sites.

Abbreviations

BPD	Bronchopulmonary dysplasia
CNN	Canadian Neonatal Network
CHNN	Chinese Neonatal Network
EPIQ	Evidence-based Practice for Quality Improvement
INeo	International Network for Evaluating Outcomes of Neonates
IVH	Intraventricular hemorrhage
NEC	Necrotizing enterocolitis
NI	Nosocomial infection
NICU	Neonatal intensive care unit
ROP	Retinopathy of prematurity
VLBW	Very low birth weight
VPT	Very preterm

Competing Interests

We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

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Keywords:

Infants, Preterm; Neonatal intensive care unit; Outcomes; Neonatal network; China; Neonates; Quality improvement

Abstract (214 words)

Introduction: The objective of the Chinese Neonatal Network (CHNN) is to provide a platform for collaborative research, outcomes evaluation, and quality improvement for preterm infants with gestational age less than 32 weeks in China. The CHNN is the first national neonatal network and has the largest geographically representative cohort from neonatal intensive care units (NICUs) in China.

Methods and analysis: Individual-level data from participating NICUs will be collected using a unique database developed by the CHNN on an on-going basis from January 2019. Data will be prospectively collected from all infants <32 weeks gestation or <1500 grams birth weight at 58 participating NICUs. Infant outcomes and inter-institutional variations in outcomes will be examined and used to inform quality improvement measures aimed at improving outcomes. Information about NICU

environmental and human resource factors and processes of neonatal care will also be collected and analyzed for association with outcomes. Clinical studies, including randomized controlled trials will be conducted using the CHNN data platform.

Ethics and dissemination: This study was approved by the ethics review board of Children's Hospital of Fudan University, which was recognized by all participating hospitals. Waiver of consent were granted at all sites. Only non-identifiable patient level data will be transmitted and only aggregate data will be reported in CHNN reports and publications.

Strengths and limitations of this study

1. The CHNN collaboration is the first national neonatal network in China with the largest geographically representative cohort of preterm infants born at <32 weeks gestation or <1500 grams birthweight in China.
2. Findings will provide comprehensive information about neonatal outcomes in China, and may identify practices contributing to outcome variations in NICUs that can be targeted for quality improvement.
3. The knowledge generated will have potential for national and international impact.
4. Limitations include lack of information from community hospitals that may limit its generalizability.

Introduction

Preterm infants are of significant public health concern worldwide due to their high risk of mortality and morbidities[1][2][3]. The incidence of preterm births at gestational age (GA) less than 32 weeks has increased steadily and approximately 0.2 million are born each year in China[4,5]. In October 2015, China announced a national plan to end the one-child policy that had been implemented for more than 40 years, allowing some couples to have two children. A national descriptive before-and-after comparative study showed that the announcement of China's universal two-child policy was associated with a rise in births in China, and with women giving birth being more likely to be multiparous and to be aged 35 and over[6], with an increased likelihood of preterm births.

The population of China represents almost one fifth of the global population. In China, preterm infant survival in NICUs has significantly improved in recent years[7][8]. Neonatologists in China have made progress in NICU care, and introduced advances such as fresh human milk feeding[9], NICU infection control[10], family-integrated care of preterm infants[11], and better treatment of bronchopulmonary dysplasia in very low birth weight infants[12]. However, previous studies mostly involved small groups of NICUs during a defined research period, and were subject to selection bias. This has led to problems of generalization in the context of the huge Chinese population with regional differences in population characteristics, medical expertise, economic development, and health insurance coverage. It also presents difficulties for translation of clinical evidence into expert consensus practice guidelines[13][14], even though there is strong demand for them in China.

Previous authors have demonstrated that establishing a national neonatal network and database is an important step towards understanding the status of neonatal care and outcomes in a country and can provide an effective platform for collaborative care, quality improvement (QI), research and knowledge translation[15-19]. Our goal is to establish a national Chinese Neonatal Network (CHNN) in the People's Republic of China, with a standardized database for collaborative care, quality improvement and research. This manuscript outlines the research protocol for CHNN.

Objectives

The specific objectives of CHNN are to: (1) Establish an on-going prospectively collected standardized database of very preterm infants (VPI) with GA <32 weeks or <1500 grams birth weight among NICUs in China, as a platform for surveillance, quality improvement and research, (2) Assess and monitor major outcomes of VPI and their risk determinants, as well as inter-institutional variations in care practices and outcomes to identify clinical practices associated with good or poor outcomes, (3) Implement the Evidence-based Practice for Improving Quality (EPIQ) program to improve quality of care and outcomes, (4) Conduct collaborative research, including epidemiologic, clinical and health services studies and randomized controlled trials.

Methods and analysis

Participating hospitals

CHNN was founded in 2018 with 58 participating hospitals from 25 provinces throughout China (Figure 1). CHNN hospitals are tertiary referral hospitals with Grade A

level III NICUs authorized by the Health Administration of China and have recognized expertise in caring for high-risk neonates. They were selected to be representative of different regions of the country, and together they care for approximately 5% of all VPI in China. They include all government-designated neonatal centers of excellence in China, including four national children's medical centers, five regional children's medical centers and 30 provincial perinatal or children's medical centers. The other 19 hospitals comprised major referral centers in large cities across China.

Patient and Public Involvement

This is a prospective, hospital-based cohort. Data will be collected on all infants <32+0 weeks GA or birth weight <1500g admitted to participating NICUs. Stillborn, delivery room death, and infants transferred to non-participating hospitals within 24 hours after birth will be excluded. Readmissions and transfers between participating hospitals will be tracked as data from the same infants. Infants will be followed until NICU discharge/transfer or death. There will be the following 4 sections in establishment and utilization of the CHNN:

Section 1: To establish an on-going prospectively collected standardized database

The CHNN Coordinating and Data Centre is located at the Children's Hospital of Fudan University, Shanghai, China. The Data Center is equipped with dedicated servers that are managed by the Information Technology Department of the Children's Hospital of Fudan University in compliance with hospital, municipal and national standards for data security. A unique scalable customized database with built-in error checking based on MS Access was created in-house. A standard manual of operations and definitions was

provided to all participating centers. Dedicated data abstractors are responsible for data acquisition in each hospital and centralized training sessions were organized to teach data abstractors to carry out data collection and uploading to the CHNN database. Data will be directly entered into a dedicated computer at each hospital and electronically transmitted to the CHNN Coordinating Center. Only non-identifiable patient information will be transferred and only aggregate data results will be reported and published. Data checks will be performed quarterly by the coordinating center for quality and completeness, and site-specific data quality reports will be fed back to each site and data records returned for corrections if needed. Data quality audit using data re-abstraction of randomly selected patient charts will be performed annually. Site investigators will be responsible for data quality control in each site. An annual report will be produced for the network.

Data variables of CHNN were selected by the executive committee, and include demographic (birth weight, gestation, sex, Apgar score), obstetric/perinatal risk factors (maternal age, race, education, smoking, drug use during pregnancy, antenatal care/complications, hypertension, preterm labor/rupture of membranes, diabetes, group B streptococcus carriage, chorioamnionitis, multiple gestation, antenatal steroids, delivery mode and presentation, drug treatment, delivery complications and resuscitation), clinical care (nutrition, assisted respiration, antibiotics, drugs, intravenous lines and catheters, procedures, surgery), admission illness severity (Transport Risk Index of Physiologic Stability (TRIPS)), outcomes and resource use. Definitions of variables were standardized and mapped to the ICD-10[20] and SNOMED[21] dictionaries as appropriate.

The primary outcome is survival without major morbidity (bronchopulmonary dysplasia (BPD), severe neurological injury (SNI), severe retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), nosocomial infection (NI)). The secondary outcomes are death, individual major morbidities (as above), patent ductus arteriosus (PDA),air leak syndrome, duration of hospitalization, duration of ventilation, duration of oxygen therapy, use of central catheters, parenteral nutrition, surgery.

Mortality is defined as death due to any cause prior to discharge home. BPD is defined as oxygen requirement at 36 weeks post-menstrual age[22]. SNI is defined as ≥ stage 3 intraventricular hemorrhage (IVH) with ventricular dilatation or parenchymal injury (including periventricular leukomalacia) with or without IVH, according to the Papile classification[23]. ROP is defined as ≥ stage 3 according to the International Classification[24] or need for laser surgery or intraocular injections of anti-vascular endothelial growth factor agents. NEC is defined as ≥ stage 2 according to Bell's criteria[25]. NI is defined as culture-proven sepsis (blood or cerebrospinal fluid positive for pathogenic organism) at >3 days or 72 hours postnatal age[26]. Hemodynamically significant PDA is defined as PDA requiring pharmacological treatment or surgical ligation[27].

Section 2: To assess and monitor major outcomes of VPI and their risk determinants, and inter-institutional variations in care and outcomes

Infant characteristics and outcomes will be summarized as counts and percentages for categorical variables and using the means and standard deviations or the medians and interquartile ranges for continuous variables. Sub-group analysis and inter-institutional comparisons will use the Chi-square test for categorical variables and ANOVA F-test or

Mood's median test for continuous variables. Multivariable logistic regression models with adjustment for confounders will be used to assess risk factors associated with outcomes.

To study inter-institutional variations in primary and secondary outcomes, the ratios and associated 95% confidence intervals (CI) will be calculated, and 'caterpillar plots' will be used to graphically display differences between participating sites. The 'indirect standardization' approach will be used to compute the standardized outcome ratios in order to adjust for multiple baseline characteristics. Each NICU can compare its own observed rate with the average CHNN rate to identify the relative level of its own unit. For each outcome, the expected number of events will be computed as the sum of predicted probabilities from a multivariable model (logistic regression or zero inflated negative binomial models based on data distribution) derived using data from all NICUs with adjustment for confounders. NICU standardized outcome ratios will be graphically displayed using 'funnel' plots with 95% prediction intervals for comparison between NICUs. Pair-wise comparisons between NICUs will be performed using multivariate regression models adjusted for confounders. The generalized estimating equation (GEE) models will be used for adjusting analyses for infant cluster within the CHNN. Hierarchical random-effects regression models will be used to allow for variation at unit level. In addition, statistical significance will be evaluated by applying a Bonferroni correction to account for multiple pair-wise comparisons.

Associations of clinical practices and other factors with outcomes will be assessed under the general framework of individual patient-level data meta-analyses. Random-effects models with adjustment for confounding variables and important risk factors will

be used to assess the association and residual variation due to unknown or unmeasured unit-specific factors. These analyses will identify treatment practices and health care services with significant effects on outcomes, which subsequently can be targeted for implementation or improvement. Analyses (two-sided tests) based on 10,000 yearly admissions evaluating the effects of treatments or practices (assuming 50% exposure) on outcomes (incidence 1% to 40%) will be able to detect relative risks of 1.6 to 1.1 with a statistical power of 80% and type I error rate of 5%. This power calculation is based on the anticipated data collection by CHNN during the first year. Safety and outcome improvements will be monitored within each unit using control charts and Chi-square tests for differences from baseline in outcome rates. Multivariable logistic regression analyses will pool data from units within CHNN network to assess changes in outcomes over time with adjustment for potential confounders and important risk factors and accounting for clustering.

Section 3: To implement the Evidence-based Practice for Improving Quality (EPIQ) program to improve quality of care and outcomes

EPIQ is a multi-faceted system for quality improvement that facilitates implementation of practice change[28]. EPIQ is based on 3 features: (a) systematic review of evidence in the published literature, (b) quantitative and qualitative analysis of outcomes and practices to identify practices associated with good or poor outcomes for targeted change, and (c) use of a collaborative network of clinicians, researchers and administrators to facilitate mutual learning and implement change. In Shanghai, Cao et al. [29] demonstrated that over a 1-year period, EPIQ reduced the rate of ventilator associated pneumonia from 48.84 per 1,000 ventilator-days to 18.50 per 1,000 ventilator-

days (P<0.001), and rates of central line associated blood stream infection (CLABSI) from 16.7 per 1,000 central line days to 5.2 per 1,000 central line days (P<0.01).

After the first year of data collection (baseline data), we will implement EPIQ in all CHNN NICUs and compare the results pre and post EPIQ implementation. A national infrastructure for collaborative quality improvement will be established. Multi-disciplinary groups will examine the literature, conduct systematic reviews and examine hospital specific data in China to develop practice guidelines and bundles of best practices for implementation in CHNN NICUs. Quarterly cycles of practice change will be introduced using PDSA (Plan-Do-Study-Act) cycles of rapid change, and outcomes will be monitored quarterly and results fed back to hospitals. An online Teaching & Communication web portal will be used to facilitate collaboration between sites. Safety will be monitored. Multivariable logistic regression analyses will pool data from units to assess changes in outcomes over time with adjustment for potential confounders and important risk factors.

Section 4: To conduct collaborative research, including epidemiologic, clinical and health services studies and randomized controlled trials.

The CHNN database platform will support additional research initiatives, including epidemiologic, clinical and health services and randomized controlled trials. Research projects can be initiated by any CHNN member, approved by the CHNN Scientific Advisory Committee, and coordinated through the CHNN Coordinating Centre, where data will also be collected and analyzed. In future stages, limited datasets may be released to investigators using a secure electronic portal system.

Ethics and dissemination

Central ethics approval was obtained from the Ethics Committee of the Children's Hospital of Fudan University (#CHFU 2018-296) and recognized by all participating sites. All participating sites have signed data transfer agreements with the CHNN Coordinating Centre and obtained ethics approval from their affiliated institutions or hospitals to allow sending de-identified data to the CHNN Coordinating Centre in compliance with national, provincial and local hospital regulations for ensuring patient privacy and confidentiality.

Discussion

The CHNN collaboration will be the first national network to examine data from a large cohort of preterm infants that is representative of the different regions of China on an on-going basis. This is important because China has a huge population, with many regional differences in social, economic and health care development. Unfortunately, the existing literature regarding preterm infants in China has been mostly limited to single-centre studies or multicentre studies with small numbers of participating sites[8,10,29,30]. Findings from this national collaboration will provide a comprehensive picture of outcomes of very preterm infants in Chinese NICUs and establish a strong system for outcomes surveillance and monitoring trends in clinical practices and outcome variations. Data from CHNN will also provide robust estimates for development of clinical practice guidelines and health care recommendations that can be generalizable across the country.

Quality improvement is a key goal, especially for China where neonatal care is still developing and there is significant room for improvement. The adoption of EPIQ will provide a robust system for quality improvement in Chinese NICUs. EPIQ was pioneered by the Canadian Neonatal Network, where Lee et al [28] first demonstrated 44% reduction in nosocomial infection and 15% reduction in bronchopulmonary dysplasia in a multi-center randomized controlled trial, and EPIQ is now practiced in all Canadian NICUs. In a comparative study of outcomes by the International Network for Evaluation of Outcomes (iNEO), the implementation of EPIQ nationally was credited with rapidly improving neonatal outcomes in Canada in comparison with other countries[31,32]. Subsequent studies in Canada and China provided confirmation of its efficacy[33-35]. Since Chinese NICUs have experience using EPIQ, this will facilitate its implementation in Chinese NICUs and provide a proven method for improving quality of care and outcomes in China. However, we recognize that change can be difficult to implement, especially those that require making financial investments, adding staff, or breaking cultural traditions. Notwithstanding possible early reluctance to follow these recommendations, the strength of evidence produced from the data, the pragmatic nature of the results, and the examples provided by "early adopter" NICUs will be the most persuasive elements of the CHNN collaboration.

The flexibility of the CHNN data platform to accommodate additional studies like randomized controlled trials provides a unique opportunity for Chinese NICUs. China has a large population, which is conducive to conducting multi-center studies rapidly and efficiently. Once the CHNN data platform is fully functional, we anticipate that China will play a leading role in conducting large scale multi-center studies and clinical trials.

In summary, the CHNN collaboration will serve as a strong national platform for collaborative research, outcomes evaluation, and quality improvement for VPI in China. The knowledge generated will have potential to benefit infants and families in China and internationally.

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Figure legend

Figure 1. Map of 58 participating hospitals in Chinese Neonatal Network

There were 58 member hospitals from 25 provinces in China that are participating in the CHNN. The distribution of the 58 member hospitals is almost geographically throughout the mainland China.

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The Chinese Neonatal Network: a national protocol for collaborative research and quality improvement in neonatal care

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TITLE PAGE

Title:

The Chinese Neonatal Network: a national protocol for collaborative research and quality improvement in neonatal care

Running title:

Protocol for CHNN collaborative research in China

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Ethics information

This proposal was approved by the Ethics Committee of the Children's Hospital of Fudan University (#CHFU 2018-296) which was recognized by all participating hospitals. Waiver of consent were granted at all sites.

Abbreviations

BPD	Bronchopulmonary dysplasia
CNN	Canadian Neonatal Network
CHNN	Chinese Neonatal Network
EPIQ	Evidence-based Practice for Quality Improvement
INeo	International Network for Evaluating Outcomes of Neonates
IVH	Intraventricular hemorrhage
NEC	Necrotizing enterocolitis
NI	Nosocomial infection
NICU	Neonatal intensive care unit
ROP	Retinopathy of prematurity
VLBW	Very low birth weight
VPT	Very preterm

Competing Interests

We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

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Keywords:

Infants, Preterm; Neonatal intensive care unit; Outcomes; Neonatal network; China; Neonates; Quality improvement

Abstract (214 words)

Introduction: The objective of the Chinese Neonatal Network (CHNN) is to provide a platform for collaborative research, outcomes evaluation, and quality improvement for preterm infants with gestational age less than 32 weeks in China. The CHNN is the first national neonatal network and has the largest geographically representative cohort from neonatal intensive care units (NICUs) in China.

Methods and analysis: Individual-level data from participating NICUs will be collected using a unique database developed by the CHNN on an on-going basis from January 2019. Data will be prospectively collected from all infants <32 weeks gestation or <1500 grams birth weight at 58 participating NICUs. Infant outcomes and inter-institutional variations in outcomes will be examined and used to inform quality improvement measures aimed at improving outcomes. Information about NICU

environmental and human resource factors and processes of neonatal care will also be collected and analyzed for association with outcomes. Clinical studies, including randomized controlled trials will be conducted using the CHNN data platform.

Ethics and dissemination: This study was approved by the ethics review board of Children's Hospital of Fudan University, which was recognized by all participating hospitals. Waiver of consent were granted at all sites. Only non-identifiable patient level data will be transmitted and only aggregate data will be reported in CHNN reports and publications.

Strengths and limitations of this study

1. This is the largest prospective, geographically representative, hospital-based cohort study of very preterm infants in China.
2. Data definitions and data collection protocols were standardized.
3. Data were collected on both outcomes and clinical practices to facilitate risk analysis and quality improvement.
4. Limitations include lack of generalizability since participating hospitals were all tertiary hospitals.
5. Outcomes data were not available for infants who were discharged against medical advice, which may bias the results

1. Introduction

Preterm infants are of significant public health concern worldwide due to their high risk of mortality and morbidities[1][2][3]. The incidence of preterm births at gestational age (GA) less than 32 weeks has increased steadily and approximately 0.2 million are born each year in China[4,5]. In October 2015, China announced a national plan to end the one-child policy that had been implemented for more than 40 years, allowing some couples to have two children. A national descriptive before-and-after comparative study showed that the announcement of China's universal two-child policy was associated with a rise in births in China, and with women giving birth being more likely to be multiparous and to be aged 35 and over[6], with an increased likelihood of preterm births.

The population of China represents almost one fifth of the global population. In China, preterm infant survival in NICUs has significantly improved in recent years[7][8]. Neonatologists in China have made progress in NICU care, and introduced advances such as fresh human milk feeding[9], NICU infection control[10], family-integrated care of preterm infants[11], and better treatment of bronchopulmonary dysplasia in very low birth weight infants[12]. However, previous studies mostly involved small groups of NICUs during a defined research period, and were subject to selection bias. This has led to problems of generalization in the context of the huge Chinese population with regional differences in population characteristics, medical expertise, economic development, and health insurance coverage. It also presents difficulties for translation of clinical evidence into expert consensus practice guidelines[13][14], even though there is strong demand for them in China.

Previous authors have demonstrated that establishing a national neonatal network and database is an important step towards understanding the status of neonatal care and outcomes in a country and can provide an effective platform for collaborative care, quality improvement (QI), research and knowledge translation[15-19]. Our goal is to establish a national Chinese Neonatal Network (CHNN) in the People's Republic of China, with a standardized database for collaborative care, quality improvement and research. This manuscript outlines the research protocol for CHNN.

2. Objectives

The specific objectives of CHNN are to: (1) Establish an on-going prospectively collected standardized database of very preterm infants (VPI) with GA <32 weeks or <1500 grams birth weight among NICUs in China, as a platform for surveillance, quality improvement and research, (2) Assess and monitor major outcomes of VPI and their risk determinants, as well as inter-institutional variations in care practices and outcomes to identify clinical practices associated with good or poor outcomes, (3) Implement the Evidence-based Practice for Improving Quality (EPIQ) program to improve quality of care and outcomes, (4) Conduct collaborative research, including epidemiologic, clinical and health services studies and randomized controlled trials.

3. Methods and analysis

3.1 Participating hospitals

CHNN was founded in 2018 with 58 participating hospitals from 25 provinces throughout mainland China (Figure 1). No hospitals in Tibet, Taiwan, and Hong Kong

were included in CHNN. CHNN hospitals are tertiary referral hospitals with Grade A level III NICUs authorized by the Health Administration of China and have recognized expertise in caring for high-risk neonates. They were selected to be representative of different regions of the country but do not include all hospitals providing NICU care to VPI, and together they care for approximately 5% of all VPI in China. They include all government-designated neonatal centers of excellence in China, including four national children's medical centers, five regional children's medical centers and 30 provincial perinatal or children's medical centers. The other 19 hospitals comprised major referral centers in large cities across China. Forty-three hospitals were perinatal centers with birthing facilities, and 14 hospitals were freestanding children's hospitals that admitted only outborn infants. The median number of NICU beds was 40 (interquartile range [IQR], 30-62), and the median number of intermediate-level and continuing care neonatal beds was 66 (IQR, 40-91). For perinatal centers, the median number of annual deliveries was 10 280 (IQR, 6273-15 423). The median number of full- time equivalent neonatologists was 19 (IQR, 12-27), and the median number of NICU nurses was 42 (IQR, 30-65)[20].

3.2 Study population

This is a prospective, hospital-based cohort. Data will be collected on all infants <32+0 weeks GA or birth weight <1500g admitted to participating NICUs. Stillborn, delivery room death, and infants transferred to non-participating hospitals within 24 hours after birth will be excluded. Readmissions and transfers between participating hospitals will be tracked as data from the same infants. Infants will be followed until NICU discharge/transfer or death.

3.3 Patient and public involvement

The study responds to patient concerns about quality of care and perceived variation in quality of care among different hospitals. Outcomes of quality improvement initiatives will be published and made available to patients.

3.4 Achieving the 4 specific objectives of CHNN

Objective 1. Establish an on-going prospectively collected standardized database

Governance

The executive committee of CHNN comprises 13 senior neonatology leaders representing different regions of the country and include 2 co-chairpersons, 2 vice-presidents, and 3 secretary generals. The committee is responsible for setting policies and research agendas, and oversees the activities and operations of the network and coordinating center.

Coordinating Center and Data Collection

The CHNN Coordinating and Data Centre is located at the Children's Hospital of Fudan University, Shanghai, China. The Data Center is equipped with dedicated servers that are managed by the Information Technology Department of the Children's Hospital of Fudan University in compliance with hospital, municipal and national standards for data security. A unique scalable customized database with built-in error checking based on MS Access was created in-house. A standard manual of operations and definitions was provided to all participating centers. Dedicated data abstractors under the supervision of the site principal investigator are responsible for data acquisition in each hospital and

centralized training sessions were organized to teach data abstractors to carry out data collection and uploading to the CHNN database. Data abstractors enter data directly from patients charts into a dedicated computer at each hospital and electronically transmitted data to the CHNN Coordinating Center. Only non-identifiable patient information will be transferred and only aggregate data results will be reported and published. Data quality is ensured at multiple levels. The data entry program has built-in error checking. Additional data checks are performed quarterly by the coordinating center for quality and completeness, and site-specific data quality reports will be fed back to each site and data records returned for corrections if needed. Data quality audit using data re-abstraction of randomly selected patient charts will be performed annually. Site investigators will be responsible for data quality control in each site. An annual report will be produced for the network.

Data Variables

Data variables were selected by the CHNN executive committee (Table 1). Definitions of variables were standardized and mapped to the ICD-10[21] and SNOMED[22] dictionaries as appropriate.Table 1: CHNN data variables

Categories	**Variables**
Demographic	Birth weight Gestation, Sex, Ethnicity, SGA (Small for gestational age)
Obstetric/perinatal Risks	Maternal age Education, Smoking, Drugs in pregnancy, Antenatal care, Antenatal complications, Hypertension Preterm labor, Preterm rupture of membranes, Maternal diabetes, Group B Strep Chorioamnionitis, Multiple gestation, Antenatal steroids, Delivery

	mode Presentation, Drug treatment, Delivery complications, Apgar score, Resuscitation
NICU Care	Admission illness severity (SNAP, TRIPS), Fluids, Nutrition, Assisted respiration, Antibiotics, Drug therapy, Intravenous lines, Catheters Procedures, Surgery
Outcomes	(a) Primary - Survival without major morbidity (BPD, SNI, ROP, NEC, NI) (b) Secondary outcomes – Death , BPD, SNI, ROP, NEC, NI, Patent ductus arteriosus (PDA), Air leak syndrome
Resource Use	Duration of hospitalization, Duration of ventilation, Duration of oxygen therapy, Use of central catheters, Parenteral nutrition, Surgery

Abbreviations: SNAP – Score for neonatal acute physiology, TRIPS – Transport risk index of physiologic stability, BPD – bronchopulmonary dysplasia, SNI – severe neurological injury, ROP – retinopathy of prematurity, NEC – necrotizing enterocolitis, NI – nosocomial infection

Mortality is defined as death due to any cause prior to discharge home. BPD is defined as oxygen requirement at 36 weeks post-menstrual age[23]. SNI is defined as ≥ stage 3 intraventricular hemorrhage (IVH) with ventricular dilatation or parenchymal injury (including periventricular leukomalacia) with or without IVH, according to the Papile classification[24]. ROP is defined as ≥ stage 3 according to the International Classification[25] or need for laser surgery or intraocular injections of anti-vascular

endothelial growth factor agents. NEC is defined as ≥ stage 2 according to Bell's criteria[26]. NI is defined as culture-proven sepsis (blood or cerebrospinal fluid positive for pathogenic organism) at >3 days or 72 hours postnatal age[27]. Hemodynamically significant PDA is defined as PDA requiring pharmacological treatment or surgical ligation[28].

Objective 2. Assess and monitor major outcomes of VPI and their risk determinants, and inter-institutional variations in care and outcomes

Infant characteristics and outcomes will be summarized as counts and percentages for categorical variables and using the means and standard deviations or the medians and interquartile ranges for continuous variables. Sub-group analysis and inter-institutional comparisons will use the Chi-square test for categorical variables and ANOVA F-test or Mood's median test for continuous variables. Multivariable logistic regression models with adjustment for confounders will be used to assess risk factors associated with outcomes.

To study inter-institutional variations in primary and secondary outcomes, the ratios and associated 95% confidence intervals (CI) will be calculated, and 'caterpillar plots' will be used to graphically display differences between participating sites. The 'indirect standardization' approach will be used to compute the standardized outcome ratios in order to adjust for multiple baseline characteristics. Each NICU can compare its own observed rate with the average CHNN rate to identify the relative level of its own unit. For each outcome, the expected number of events will be computed as the sum of predicted probabilities from a multivariable model (logistic regression or zero inflated negative binomial models based on data distribution) derived using data from all NICUs with

adjustment for confounders. NICU standardized outcome ratios will be graphically displayed using 'funnel' plots with 95% prediction intervals for comparison between NICUs. Pair-wise comparisons between NICUs will be performed using multivariate regression models adjusted for confounders. The generalized estimating equation (GEE) models will be used for adjusting analyses for infant cluster within the CHNN. Hierarchical random-effects regression models will be used to allow for variation at unit level. In addition, statistical significance will be evaluated by applying a Bonferroni correction to account for multiple pair-wise comparisons.

Associations of clinical practices and other factors with outcomes will be assessed under the general framework of individual patient-level data meta-analyses. Random-effects models with adjustment for confounding variables and important risk factors will be used to assess the association and residual variation due to unknown or unmeasured unit-specific factors. These analyses will identify treatment practices and health care services with significant effects on outcomes, which subsequently can be targeted for implementation or improvement. Analyses (two-sided tests) based on 10,000 yearly admissions evaluating the effects of treatments or practices (assuming 50% exposure) on outcomes (incidence 1% to 40%) will be able to detect relative risks of 1.6 to 1.1 with a statistical power of 80% and type I error rate of 5%. This power calculation is based on the anticipated data collection by CHNN during the first year. Safety and outcome improvements will be monitored within each unit using control charts and Chi-square tests for differences from baseline in outcome rates. Multivariable logistic regression analyses will pool data from units within CHNN network to assess changes in outcomes over time

with adjustment for potential confounders and important risk factors and accounting for clustering.

Objective 3. Implement Evidence-based Practice for Improving Quality (EPIQ) program to improve quality of care and outcomes

EPIQ is a multi-faceted system for quality improvement that facilitates implementation of practice change[29]. EPIQ is based on 3 features: (a) systematic review of evidence in the published literature, (b) quantitative and qualitative analysis of outcomes and practices to identify practices associated with good or poor outcomes for targeted change, and (c) use of a collaborative network of clinicians, researchers and administrators to facilitate mutual learning and implement change. In Shanghai, Cao et al. [30] demonstrated in the multi-center EPIQ-REIN study, that over a 1-year period, EPIQ reduced the rate of ventilator associated pneumonia from 48.84 per 1,000 ventilator-days to 18.50 per 1,000 ventilator-days ($P<0.001$), and rates of central line associated blood stream infection (CLABSI) from 16.7 per 1,000 central line days to 5.2 per 1,000 central line days ($P<0.01$).

After the first year of data collection (baseline data), we will implement EPIQ in all CHNN NICUs and compare the results pre and post EPIQ implementation. The EPIQ program has well established published protocols for training of personnel, coordination, literature review, risk analysis, identification of target outcomes, implementation and facilitation of practice changes, monitoring and surveillance, communication and safety assurance; and CHNN has well trained personnel, teams and organization from the previous EPIQ-REIN experience[30]. A national CHNN infrastructure for collaborative

quality improvement will be established. Hospitals will be organized into groups that target specific outcomes. Multi-disciplinary groups will examine the literature, conduct systematic reviews and examine hospital specific data in China to develop practice guidelines and bundles of best practices for implementation in CHNN NICUs. Quarterly cycles of practice change will be introduced using PDSA (Plan-Do-Study-Act) cycles of rapid change, and outcomes will be monitored quarterly and results fed back to hospitals. An online Teaching & Communication web portal will be used to facilitate collaboration between sites, including site visits, discussions and planning.. Safety will be monitored. Multivariable logistic regression analyses will pool data from units to assess changes in outcomes over time with adjustment for potential confounders and important practice related risk factors, which will be targeted for practice change.

Objective 4. Conduct collaborative research, including epidemiologic, clinical and health services studies and randomized controlled trials.

The CHNN database platform will support additional research initiatives, including epidemiologic, clinical and health services and randomized controlled trials. Research projects can be initiated by any CHNN member, approved by the CHNN Scientific Advisory Committee, and coordinated through the CHNN Coordinating Centre, where data will also be collected and analyzed. In future stages, limited datasets may be released to investigators using a secure electronic portal system.

3.5 Statistical analysis

All analyses of cohort data will be performed by a team of statisticians (including PhD and MSc statisticians) at the CHNN coordinating center, under the leadership of the CHNN Secretary General supervising the center. For specific research projects, relevant data may be released to the responsible research group for their analysis. Participating sites may perform analysis of their own individual site data.

4. Ethics and dissemination

Central ethics approval was obtained from the Ethics Committee of the Children's Hospital of Fudan University (#CHFU 2018-296) and recognized by all participating sites. All participating sites have signed data transfer agreements with the CHNN Coordinating Centre and obtained ethics approval from their affiliated institutions or hospitals to allow sending de-identified data to the CHNN Coordinating Centre in compliance with national, provincial and local hospital regulations for ensuring patient privacy and confidentiality, and are consistent with international standards. All CHNN studies will not take individual patients, and waiver of consent were granted at all sites. The results of this registry will be disseminated by 3 methods: (1) An annual report will be published and provided to participating hospitals and regional health authorities. (2) Results will be reported at national and international scientific meetings. (3) Results will be published in domestic and international scientific journals.

5. Discussion

The CHNN collaboration will be the first national network to examine data from a large cohort of preterm infants that is representative of the different regions of China on an

on-going basis. This is important because China has a huge population, with many regional differences in social, economic and health care development. Unfortunately, the existing literature regarding preterm infants in China has been mostly limited to single-centre studies or multicentre studies with small numbers of participating sites[8,10,30, 31]. Findings from this national collaboration will provide a comprehensive picture of outcomes of very preterm infants in Chinese NICUs and establish a strong system for outcomes surveillance and monitoring trends in clinical practices and outcome variations. Data from CHNN will also provide robust estimates for development of clinical practice guidelines and health care recommendations that can be generalizable across the country.

Quality improvement is a key goal, especially for China where neonatal care is still developing and there is significant room for improvement. The adoption of EPIQ will provide a robust system for quality improvement in Chinese NICUs. EPIQ was pioneered by the Canadian Neonatal Network, where Lee et al [29] first demonstrated 44% reduction in nosocomial infection and 15% reduction in bronchopulmonary dysplasia in a multi-center randomized controlled trial, and EPIQ is now practiced in all Canadian NICUs. In a comparative study of outcomes by the International Network for Evaluation of Outcomes (iNEO), the implementation of EPIQ nationally was credited with rapidly improving neonatal outcomes in Canada in comparison with other countries[32,33]. Subsequent studies in Canada and China provided confirmation of its efficacy[34-36]. Since Chinese NICUs have experience using EPIQ, this will facilitate its implementation in Chinese NICUs and provide a proven method for improving quality of care and outcomes in China. However, we recognize that change can be difficult to implement, especially those that require making financial investments, adding staff, or breaking cultural traditions.

Notwithstanding possible early reluctance to follow these recommendations, the strength of evidence produced from the data, the pragmatic nature of the results, and the examples provided by "early adopter" NICUs will be the most persuasive elements of the CHNN collaboration.

The flexibility of the CHNN data platform to accommodate additional studies like randomized controlled trials provides a unique opportunity for Chinese NICUs. China has a large population, which is conducive to conducting multi-center studies rapidly and efficiently. Once the CHNN data platform is fully functional, we anticipate that China will play a leading role in conducting large scale multi-center studies and clinical trials.

Limitations of CHNN are: (1) The data are from a select group of large tertiary NICUs with the highest level of neonatal care in China, and may not be generalizable to the whole population. (2) Data on parent participation, pain management, skin-to-skin contact care and other important developmental aspects of modern neonatal care are not currently available but will be included in the future (3) Data on resource use is limited.

In summary, the CHNN collaboration will serve as a strong national platform for collaborative research, outcomes evaluation, and quality improvement for VPI in China. The knowledge generated will have potential to benefit infants and families in China and internationally.

Author Contributions:

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Figure legend

Figure 1. Map of 58 participating hospitals in Chinese Neonatal Network

There were 58 member hospitals from 25 provinces in China that are participating in the CHNN. The distribution of the 58 member hospitals is almost geographically throughout the mainland China.

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The Chinese Neonatal Network: a national protocol for collaborative research and quality improvement in neonatal care

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Protocol for CHNN collaborative research in China

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Ethics information

This proposal was approved by the Ethics Committee of the Children's Hospital of Fudan University (#CHFU 2018-296) which was recognized by all participating hospitals. Waiver of consent were granted at all sites.

Abbreviations

BPD	Bronchopulmonary dysplasia
CNN	Canadian Neonatal Network
CHNN	Chinese Neonatal Network
EPIQ	Evidence-based Practice for Quality Improvement
INeo	International Network for Evaluating Outcomes of Neonates
IVH	Intraventricular hemorrhage
NEC	Necrotizing enterocolitis
NI	Nosocomial infection
NICU	Neonatal intensive care unit
ROP	Retinopathy of prematurity
VLBW	Very low birth weight
VPT	Very preterm

Competing Interests

We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

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Infants, Preterm; Neonatal intensive care unit; Outcomes; Neonatal network; China; Neonates; Quality improvement

Abstract (214 words)

Introduction: The objective of the Chinese Neonatal Network (CHNN) is to provide a platform for collaborative research, outcomes evaluation, and quality improvement for preterm infants with gestational age less than 32 weeks in China. The CHNN is the first national neonatal network and has the largest geographically representative cohort from neonatal intensive care units (NICUs) in China.

Methods and analysis: Individual-level data from participating NICUs will be collected using a unique database developed by the CHNN on an on-going basis from January 2019. Data will be prospectively collected from all infants <32 weeks gestation or <1500 grams birth weight at 58 participating NICUs. Infant outcomes and inter-institutional variations in outcomes will be examined and used to inform quality improvement measures aimed at improving outcomes. Information about NICU

environmental and human resource factors and processes of neonatal care will also be collected and analyzed for association with outcomes. Clinical studies, including randomized controlled trials will be conducted using the CHNN data platform.

Ethics and dissemination: This study was approved by the ethics review board of Children's Hospital of Fudan University, which was recognized by all participating hospitals. Waiver of consent were granted at all sites. Only non-identifiable patient level data will be transmitted and only aggregate data will be reported in CHNN reports and publications.

Strengths and limitations of this study

1. This is the largest prospective, geographically representative, hospital-based cohort study of very preterm infants in China.
2. Data definitions and data collection protocols were standardized.
3. Data were collected on both outcomes and clinical practices to facilitate risk analysis and quality improvement.
4. Limitations include lack of generalizability since participating hospitals were all tertiary hospitals.
5. Outcomes data were not available for infants who were discharged against medical advice, which may bias the results

1. Introduction

Preterm infants are of significant public health concern worldwide due to their high risk of mortality and morbidities[1][2][3]. The incidence of preterm births is 7.3% in China and increasing steadily, with approximately 0.2 million infants born at less than 32 weeks gestational age (GA) born each year[4,5]. In October 2015, China announced a national plan to end the one-child policy that had been implemented for more than 40 years, allowing some couples to have two children. A national descriptive before-and-after comparative study showed that the announcement of China's universal two-child policy was associated with a rise in births in China, and with women giving birth being more likely to be multiparous and to be aged 35 and over[6], with an increased likelihood of preterm births.

The population of China represents almost one fifth of the global population. In China, preterm infant survival in NICUs has significantly improved in recent years[7][8]. Neonatologists in China have made progress in NICU care, and introduced advances such as breast milk feeding[9], NICU infection control[10], family-integrated care of preterm infants[11], and better treatment of bronchopulmonary dysplasia in very low birth weight infants[12]. However, previous studies mostly involved small groups of NICUs during a defined research period, and were subject to selection bias. This has led to problems of generalization in the context of the huge Chinese population with regional differences in population characteristics, medical expertise, economic development, and health insurance coverage. It also presents difficulties for translation of clinical evidence into expert consensus practice guidelines[13][14], even though there is strong demand for them in China.

Previous authors have demonstrated that establishing a national neonatal network and database is an important step towards understanding the status of neonatal care and

outcomes in a country and can provide an effective platform for collaborative care, quality improvement (QI), research and knowledge translation[15-19]. Our goal is to establish a national Chinese Neonatal Network (CHNN) in the People's Republic of China, with a standardized database for collaborative care, quality improvement and research. This manuscript outlines the research protocol for CHNN.

2. Objectives

The specific objectives of CHNN are to: (1) Establish an on-going prospectively collected standardized database of very preterm infants (VPI) with GA <32 weeks or <1500 grams birth weight among NICUs in China, as a platform for surveillance, quality improvement and research, (2) Assess and monitor major outcomes of VPI and their risk determinants, as well as inter-institutional variations in care practices and outcomes to identify clinical practices associated with good or poor outcomes, (3) Implement the Evidence-based Practice for Improving Quality (EPIQ) program to improve quality of care and outcomes, (4) Conduct collaborative research, including epidemiologic, clinical and health services studies and randomized controlled trials.

3. Methods and analysis

3.1 Participating hospitals

CHNN was founded in 2018 with 58 participating hospitals from 25 provinces throughout mainland China (Figure 1). No hospitals in Tibet, Taiwan, and Hong Kong were included. CHNN hospitals are tertiary referral hospitals with Grade A level III NICUs authorized by the Health Administration of China and have recognized expertise in caring

for high-risk neonates. They were selected to be representative of different regions of the country but do not include all hospitals providing NICU care to VPI, and together they care for approximately 5% of all VPI in China. They include all government-designated neonatal centers of excellence in China, including four national children's medical centers, five regional children's medical centers and 30 provincial perinatal or children's medical centers. The other hospitals comprise major referral centers in large cities across China. Forty-three hospitals were perinatal centers with birthing facilities, and 14 hospitals were freestanding children's hospitals that admitted only outborn infants. The median number of NICU beds was 40 (interquartile range [IQR], 30-62), and the median number of intermediate-level and continuing care neonatal beds was 66 (IQR, 40-91). For perinatal centers, the median number of annual deliveries was 10 280 (IQR, 6273-15 423). The median number of full-time equivalent neonatologists was 19 (IQR, 12-27), and the median number of NICU nurses was 42 (IQR, 30-65)[20].

3.2 Study population

This is a prospective, hospital-based cohort. Data will be collected on all infants <32+0 weeks GA or birth weight <1500g admitted to participating NICUs. Stillborn, delivery room death, and infants transferred to non-participating hospitals within 24 hours after birth will be excluded. Readmissions and transfers between participating hospitals will be tracked as data from the same infants. Infants will be followed until NICU discharge/transfer or death.

3.3 Patient and public involvement

The study responds to patient concerns about quality of care and perceived variation in quality of care among different hospitals. Outcomes of quality improvement initiatives will be published and made available to patients.

3.4 Achieving the 4 specific objectives of CHNN

Objective 1. Establish an on-going prospectively collected standardized database

Governance

The executive committee of CHNN comprises 13 senior neonatology leaders representing different regions of the country and include 2 co-chairpersons, 2 vice-presidents, and 3 secretary generals. The committee is responsible for setting policies and research agendas, and oversees the activities and operations of the network and coordinating center.

Coordinating Center and Data Collection

The CHNN Coordinating and Data Centre is located at the Children's Hospital of Fudan University, Shanghai, China. The Data Center is equipped with dedicated servers that are managed by the Information Technology Department of the Children's Hospital of Fudan University in compliance with hospital, municipal and national standards for data security. A unique scalable customized database with built-in error checking based on MS Access was created in-house. A standard manual of operations and definitions was provided to all participating centers. Dedicated data abstractors under the supervision of the site principal investigator are responsible for data acquisition in each hospital and centralized training sessions were organized to teach data abstractors to carry out data collection and uploading to the CHNN database. Data abstractors enter data directly from

patients charts into a dedicated computer at each hospital and electronically transmitted data to the CHNN Coordinating Center. Only non-identifiable patient information will be transferred and only aggregate data results will be reported and published. Data quality is ensured at multiple levels. The data entry program has built-in error checking. Additional data checks are performed quarterly by the coordinating center for quality and completeness, and site-specific data quality reports will be fed back to each site and data records returned for corrections if needed. Data quality audit using data re-abstraction of randomly selected patient charts will be performed annually. Site investigators will be responsible for data quality control in each site. An annual report will be produced for the network.

Data Variables

Data variables were selected by the CHNN executive committee (Table 1). Definitions of variables were standardized and mapped to the ICD-10[21] and SNOMED[22] dictionaries as appropriate. Mortality is defined as death due to any cause prior to discharge home. BPD is defined as oxygen requirement at 36 weeks post-menstrual age[23]. SNI is defined as ≥ stage 3 intraventricular hemorrhage (IVH) with ventricular dilatation or parenchymal injury (including periventricular leukomalacia) with or without IVH, according to the Papile classification[24]. ROP is defined as ≥ stage 3 according to the International Classification[25] or need for laser surgery or intraocular injections of anti-vascular endothelial growth factor agents. NEC is defined as ≥ stage 2 according to Bell's criteria[26]. NI is defined as culture-proven sepsis (blood or cerebrospinal fluid positive for pathogenic organism) at >3 days or 72 hours postnatal age[27]. Hemodynamically

significant PDA is defined as PDA requiring pharmacological treatment or surgical ligation[28].

Table 1: CHNN data variables

Categories	Variables
Demographic	Birth weight Gestation, Sex, Ethnicity, SGA (Small for gestational age)
Obstetric/perinatal Risks	Maternal age Education, Smoking, Drugs in pregnancy, Antenatal care, Antenatal complications, Hypertension Preterm labor, Preterm rupture of membranes, Maternal diabetes, Group B Strep Chorioamnionitis, Multiple gestation, Antenatal steroids, Delivery mode Presentation, Drug treatment, Delivery complications, Apgar score, Resuscitation
NICU Care	Admission illness severity (SNAP, TRIPS), Fluids, Nutrition, Assisted respiration, Antibiotics, Drug therapy, Intravenous lines, Catheters Procedures, Surgery
Outcomes	(a) Primary - Survival without major morbidity (BPD, SNI, ROP, NEC, NI) (b) Secondary outcomes – Death , BPD, SNI, ROP, NEC, NI, Patent ductus arteriosus (PDA), Air leak syndrome

Resource Use	Duration of hospitalization, Duration of ventilation, Duration of oxygen therapy, Use of central catheters, Parenteral nutrition, Surgery

Abbreviations: SNAP – Score for neonatal acute physiology, TRIPS – Transport risk index of physiologic stability, BPD – bronchopulmonary dysplasia, SNI – severe neurological injury, ROP – retinopathy of prematurity, NEC – necrotizing enterocolitis, NI – nosocomial infection

Objective 2. Assess and monitor major outcomes of VPI and their risk determinants, and inter-institutional variations in care and outcomes

Infant characteristics and outcomes will be summarized as counts and percentages for categorical variables and using the means and standard deviations or the medians and interquartile ranges for continuous variables. Sub-group analysis and inter-institutional comparisons will use the Chi-square test for categorical variables and ANOVA F-test or Mood's median test for continuous variables. Multivariable logistic regression models with adjustment for confounders will be used to assess risk factors associated with outcomes.

To study inter-institutional variations in primary and secondary outcomes, the ratios and associated 95% confidence intervals (CI) will be calculated, and 'caterpillar plots' will be used to graphically display differences between participating sites. The 'indirect standardization' approach will be used to compute the standardized outcome ratios in order to adjust for multiple baseline characteristics. Each NICU can compare its own observed rate with the average CHNN rate to identify the relative level of its own unit. For each outcome, the expected number of events will be computed as the sum of predicted

probabilities from a multivariable model (logistic regression or zero inflated negative binomial models based on data distribution) derived using data from all NICUs with adjustment for confounders. NICU standardized outcome ratios will be graphically displayed using 'funnel' plots with 95% prediction intervals for comparison between NICUs. Pair-wise comparisons between NICUs will be performed using multivariate regression models adjusted for confounders. The generalized estimating equation (GEE) models will be used for adjusting analyses for infant cluster within the CHNN. Hierarchical random-effects regression models will be used to allow for variation at unit level. In addition, statistical significance will be evaluated by applying a Bonferroni correction to account for multiple pair-wise comparisons.

Associations of clinical practices and other factors with outcomes will be assessed under the general framework of individual patient-level data meta-analyses. Random-effects models with adjustment for confounding variables and important risk factors will be used to assess the association and residual variation due to unknown or unmeasured unit-specific factors. These analyses will identify treatment practices and health care services with significant effects on outcomes, which subsequently can be targeted for implementation or improvement. Analyses (two-sided tests) based on 10,000 yearly admissions evaluating the effects of treatments or practices (assuming 50% exposure) on outcomes (incidence 1% to 40%) will be able to detect relative risks of 1.6 to 1.1 with a statistical power of 80% and type I error rate of 5%. This power calculation is based on the anticipated data collection by CHNN during the first year. Safety and outcome improvements will be monitored within each unit using control charts and Chi-square tests for differences from baseline in outcome rates. Multivariable logistic regression analyses

will pool data from units within CHNN network to assess changes in outcomes over time with adjustment for potential confounders and important risk factors and accounting for clustering.

Objective 3. Implement Evidence-based Practice for Improving Quality (EPIQ) program to improve quality of care and outcomes

EPIQ is a multi-faceted system for quality improvement that facilitates implementation of practice change[29]. EPIQ is based on 3 features: (a) systematic review of evidence in the published literature, (b) quantitative and qualitative analysis of outcomes and practices to identify practices associated with good or poor outcomes for targeted change, and (c) use of a collaborative network of clinicians, researchers and administrators to facilitate mutual learning and implement change. In Shanghai, Cao et al.[30] demonstrated in the multi-center EPIQ-REIN study, that over a 1-year period, EPIQ reduced the rate of ventilator associated pneumonia from 48.84 per 1,000 ventilator-days to 18.50 per 1,000 ventilator-days ($P<0.001$), and rates of central line associated blood stream infection (CLABSI) from 16.7 per 1,000 central line days to 5.2 per 1,000 central line days ($P<0.01$).

After the first year of data collection (baseline data), we will implement EPIQ in all CHNN NICUs and compare the results pre and post EPIQ implementation. The EPIQ program has well established published protocols for training of personnel, coordination, literature review, risk analysis, identification of target outcomes, implementation and facilitation of practice changes, monitoring and surveillance, communication and safety assurance; and CHNN has well trained personnel, teams and organization from the previous EPIQ-REIN experience[30]. A national CHNN infrastructure for collaborative

quality improvement will be established. Hospitals will be organized into groups that target specific outcomes. Multi-disciplinary groups will examine the literature, conduct systematic reviews and examine hospital specific data in China to develop practice guidelines and bundles of best practices for implementation in CHNN NICUs. Quarterly cycles of practice change will be introduced using PDSA (Plan-Do-Study-Act) cycles of rapid change, and outcomes will be monitored quarterly and results fed back to hospitals. An online Teaching & Communication web portal will be used to facilitate collaboration between sites, including site visits, discussions and planning.. Safety will be monitored. Multivariable logistic regression analyses will pool data from units to assess changes in outcomes over time with adjustment for potential confounders and important practice related risk factors, which will be targeted for practice change.

Objective 4. Conduct collaborative research, including epidemiologic, clinical and health services studies and randomized controlled trials.

The CHNN database platform will support additional research initiatives, including epidemiologic, clinical and health services and randomized controlled trials. Research projects can be initiated by any CHNN member, approved by the CHNN Scientific Advisory Committee, and coordinated through the CHNN Coordinating Centre, where data will also be collected and analyzed. In future stages, limited datasets may be released to investigators using a secure electronic portal system.

3.5 Statistical analysis

All analyses of cohort data will be performed by a team of statisticians (including PhD and MSc statisticians) at the CHNN coordinating center, under the leadership of the CHNN Secretary General supervising the center. For specific research projects, relevant data may be released to the responsible research group for their analysis. Participating sites may perform analysis of their own individual site data.

4. Ethics and dissemination

Central ethics approval was obtained from the Ethics Committee of the Children's Hospital of Fudan University (#CHFU 2018-296) and recognized by all participating sites. All participating sites have signed data transfer agreements with the CHNN Coordinating Centre and obtained ethics approval from their affiliated institutions or hospitals to allow sending de-identified data to the CHNN Coordinating Centre in compliance with national, provincial and local hospital regulations for ensuring patient privacy and confidentiality, and are consistent with international standards. All CHNN studies will not take individual patients, and waiver of consent were granted at all sites. The results of this registry will be disseminated by 3 methods: (1) An annual report will be published and provided to participating hospitals and regional health authorities. (2) Results will be reported at national and international scientific meetings. (3) Results will be published in domestic and international scientific journals.

5. Discussion

The CHNN collaboration will be the first national network to examine data from a large cohort of preterm infants that is representative of the different regions of China on an

on-going basis. This is important because China has a huge population, with many regional differences in social, economic and health care development. Unfortunately, the existing literature regarding preterm infants in China has been mostly limited to single-centre studies or multicentre studies with small numbers of participating sites[8,10,30,31]. Findings from this national collaboration will provide a comprehensive picture of outcomes of very preterm infants in Chinese NICUs and establish a strong system for outcomes surveillance and monitoring trends in clinical practices and outcome variations. Data from CHNN will also provide robust estimates for development of clinical practice guidelines and health care recommendations that can be generalizable across the country.

Quality improvement is a key goal, especially for China where neonatal care is still developing and there is significant room for improvement. The adoption of EPIQ will provide a robust system for quality improvement in Chinese NICUs. EPIQ was pioneered by the Canadian Neonatal Network, where Lee et al[29] first demonstrated 44% reduction in nosocomial infection and 15% reduction in bronchopulmonary dysplasia in a multi-center randomized controlled trial, and EPIQ is now practiced in all Canadian NICUs. In a comparative study of outcomes by the International Network for Evaluation of Outcomes (iNEO), the implementation of EPIQ nationally was credited with rapidly improving neonatal outcomes in Canada in comparison with other countries[32,33]. Subsequent studies in Canada and China provided confirmation of its efficacy[34-36]. Since Chinese NICUs have experience using EPIQ, this will facilitate its implementation in Chinese NICUs and provide a proven method for improving quality of care and outcomes in China. However, we recognize that change can be difficult to implement, especially those that require making financial investments, adding staff, or breaking cultural traditions.

Notwithstanding possible early reluctance to follow these recommendations, the strength of evidence produced from the data, the pragmatic nature of the results, and the examples provided by "early adopter" NICUs will be the most persuasive elements of the CHNN collaboration.

The flexibility of the CHNN data platform to accommodate additional studies like randomized controlled trials provides a unique opportunity for Chinese NICUs. China has a large population, which is conducive to conducting multi-center studies rapidly and efficiently. Once the CHNN data platform is fully functional, we anticipate that China will play a leading role in conducting large scale multi-center studies and clinical trials.

Limitations of CHNN are: (1) The data are from a select group of large tertiary NICUs with the highest level of neonatal care in China, and may not be generalizable to the whole population, (2) There may be biases inherent in large cohort databases of this nature, including reporting bias, selection bias and others, (3) Data on parent participation, pain management, skin-to-skin contact care and other important developmental aspects of modern neonatal care are not currently available but will be included in the future, (4) Data on resource use is limited.

In summary, the CHNN collaboration will serve as a strong national platform for collaborative research, outcomes evaluation, and quality improvement for VPI in China. The knowledge generated will have potential to benefit infants and families in China and internationally.

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Figure legend

Figure 1. Map of 58 participating hospitals in Chinese Neonatal Network

There were 58 member hospitals from 25 provinces in China that are participating in the CHNN. The distribution of the 58 member hospitals is almost geographically throughout the mainland China.

Word Count

3153 words

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146x82mm (220 x 220 DPI)