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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 (#CHFV 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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8 the manuscript; or the decision to submit the manuscript for publication.
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19 **Keywords:**

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22 Infants, Preterm; Neonatal intensive care unit; Outcomes; Neonatal network;
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24 China; Neonates; Quality improvement
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30 **Abstract (214 words)**

31 **Introduction:** The objective of the Chinese Neonatal Network (CHNN) is to provide
32 a platform for collaborative research, outcomes evaluation, and quality improvement for
33 preterm infants with gestational age less than 32 weeks in China. The CHNN is the first
34 national neonatal network and has the largest geographically representative cohort from
35 neonatal intensive care units (NICUs) in China.
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43 **Methods and analysis:** Individual-level data from participating NICUs will be
44 collected using a unique database developed by the CHNN on an on-going basis from
45 January 2019. Data will be prospectively collected from all infants <32 weeks gestation
46 or <1500 grams birth weight at 58 participating NICUs. Infant outcomes and inter-
47 institutional variations in outcomes will be examined and used to inform quality
48 improvement measures aimed at improving outcomes. Information about NICU
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3 environmental and human resource factors and processes of neonatal care will also be
4 collected and analyzed for association with outcomes. Clinical studies, including
5
6 randomized controlled trials will be conducted using the CHNN data platform.
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10 **Ethics and dissemination:** This study was approved by the ethics review board of
11 Children's Hospital of Fudan University, which was recognized by all participating
12 hospitals. Waiver of consent were granted at all sites. Only non-identifiable patient level
13 data will be transmitted and only aggregate data will be reported in CHNN reports and
14 publications.
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24 **Strengths and limitations of this study**

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

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

22 The specific objectives of CHNN are to: (1) Establish an on-going prospectively
23 collected standardized database of very preterm infants (VPI) with GA <32 weeks or
24 <1500 grams birth weight among NICUs in China, as a platform for surveillance, quality
25 improvement and research, (2) Assess and monitor major outcomes of VPI and their risk
26 determinants, as well as inter-institutional variations in care practices and outcomes to
27 identify clinical practices associated with good or poor outcomes, (3) Implement the
28 Evidence-based Practice for Improving Quality (EPIQ) program to improve quality of
29 care and outcomes, (4) Conduct collaborative research, including epidemiologic, clinical
30 and health services studies and randomized controlled trials.
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47 **Methods and analysis**

48 **Participating hospitals**

49 CHNN was founded in 2018 with 58 participating hospitals from 25 provinces
50 throughout China (Figure 1). CHNN hospitals are tertiary referral hospitals with Grade A
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3 level III NICUs authorized by the Health Administration of China and have recognized
4 expertise in caring for high-risk neonates. They were selected to be representative of
5 different regions of the country, and together they care for approximately 5% of all VPI
6 in China. They include all government-designated neonatal centers of excellence in
7 China, including four national children's medical centers, five regional children's
8 medical centers and 30 provincial perinatal or children's medical centers. The other 19
9 hospitals comprised major referral centers in large cities across China.

20 21 **Patient and Public Involvement**

22 This is a prospective, hospital-based cohort. Data will be collected on all infants
23 <32+0 weeks GA or birth weight <1500g admitted to participating NICUs. Stillborn,
24 delivery room death, and infants transferred to non-participating hospitals within 24
25 hours after birth will be excluded. Readmissions and transfers between participating
26 hospitals will be tracked as data from the same infants. Infants will be followed until
27 NICU discharge/transfer or death. There will be the following 4 sections in establishment
28 and utilization of the CHNN:
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40 Section 1: To establish an on-going prospectively collected standardized database

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42 The CHNN Coordinating and Data Centre is located at the Children's Hospital of
43 Fudan University, Shanghai, China. The Data Center is equipped with dedicated servers
44 that are managed by the Information Technology Department of the Children's Hospital
45 of Fudan University in compliance with hospital, municipal and national standards for
46 data security. A unique scalable customized database with built-in error checking based
47 on MS Access was created in-house. A standard manual of operations and definitions was
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3 provided to all participating centers. Dedicated data abstractors are responsible for data
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5 acquisition in each hospital and centralized training sessions were organized to teach data
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7 abstractors to carry out data collection and uploading to the CHNN database. Data will be
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9 directly entered into a dedicated computer at each hospital and electronically transmitted
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11 to the CHNN Coordinating Center. Only non-identifiable patient information will be
12
13 transferred and only aggregate data results will be reported and published. Data checks
14
15 will be performed quarterly by the coordinating center for quality and completeness, and
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17 site-specific data quality reports will be fed back to each site and data records returned
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19 for corrections if needed. Data quality audit using data re-abstraction of randomly
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21 selected patient charts will be performed annually. Site investigators will be responsible
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23 for data quality control in each site. An annual report will be produced for the network.
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28 Data variables of CHNN were selected by the executive committee, and include
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30 demographic (birth weight, gestation, sex, Apgar score), obstetric/perinatal risk factors
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32 (maternal age, race, education, smoking, drug use during pregnancy, antenatal
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34 care/complications, hypertension, preterm labor/rupture of membranes, diabetes, group B
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36 streptococcus carriage, chorioamnionitis, multiple gestation, antenatal steroids, delivery
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38 mode and presentation, drug treatment, delivery complications and resuscitation), clinical
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40 care (nutrition, assisted respiration, antibiotics, drugs, intravenous lines and catheters,
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42 procedures, surgery), admission illness severity (Transport Risk Index of Physiologic
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44 Stability (TRIPS)), outcomes and resource use. Definitions of variables were
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46 standardized and mapped to the ICD-10[20] and SNOMED[21] dictionaries as
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48 appropriate.
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3 The primary outcome is survival without major morbidity (bronchopulmonary
4 dysplasia (BPD), severe neurological injury (SNI), severe retinopathy of prematurity
5 (ROP), necrotizing enterocolitis (NEC), nosocomial infection (NI)). The secondary
6 outcomes are death, individual major morbidities (as above), patent ductus arteriosus
7 (PDA), air leak syndrome, duration of hospitalization, duration of ventilation, duration of
8 oxygen therapy, use of central catheters, parenteral nutrition, surgery.
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11 Mortality is defined as death due to any cause prior to discharge home. BPD is
12 defined as oxygen requirement at 36 weeks post-menstrual age[22]. SNI is defined as \geq
13 stage 3 intraventricular hemorrhage (IVH) with ventricular dilatation or parenchymal
14 injury (including periventricular leukomalacia) with or without IVH, according to the
15 Papile classification[23]. ROP is defined as \geq stage 3 according to the International
16 Classification[24] or need for laser surgery or intraocular injections of anti-vascular
17 endothelial growth factor agents. NEC is defined as \geq stage 2 according to Bell's
18 criteria[25]. NI is defined as culture-proven sepsis (blood or cerebrospinal fluid positive
19 for pathogenic organism) at >3 days or 72 hours postnatal age[26]. Hemodynamically
20 significant PDA is defined as PDA requiring pharmacological treatment or surgical
21 ligation[27].
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42 Section 2: To assess and monitor major outcomes of VPI and their risk determinants, and
43 inter-institutional variations in care and outcomes
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47 Infant characteristics and outcomes will be summarized as counts and percentages
48 for categorical variables and using the means and standard deviations or the medians and
49 interquartile ranges for continuous variables. Sub-group analysis and inter-institutional
50 comparisons will use the Chi-square test for categorical variables and ANOVA F-test or
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3 Mood's median test for continuous variables. Multivariable logistic regression models
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5 with adjustment for confounders will be used to assess risk factors associated with
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7 outcomes.
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10 To study inter-institutional variations in primary and secondary outcomes, the ratios
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12 and associated 95% confidence intervals (CI) will be calculated, and 'caterpillar plots'
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14 will be used to graphically display differences between participating sites. The 'indirect
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16 standardization' approach will be used to compute the standardized outcome ratios in
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18 order to adjust for multiple baseline characteristics. Each NICU can compare its own
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20 observed rate with the average CHNN rate to identify the relative level of its own unit.
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22 For each outcome, the expected number of events will be computed as the sum of
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24 predicted probabilities from a multivariable model (logistic regression or zero inflated
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26 negative binomial models based on data distribution) derived using data from all NICUs
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28 with adjustment for confounders. NICU standardized outcome ratios will be graphically
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30 displayed using 'funnel' plots with 95% prediction intervals for comparison between
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32 NICUs. Pair-wise comparisons between NICUs will be performed using multivariate
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34 regression models adjusted for confounders. The generalized estimating equation (GEE)
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36 models will be used for adjusting analyses for infant cluster within the CHNN.
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38 Hierarchical random-effects regression models will be used to allow for variation at unit
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40 level. In addition, statistical significance will be evaluated by applying a Bonferroni
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42 correction to account for multiple pair-wise comparisons.
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49 Associations of clinical practices and other factors with outcomes will be assessed
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51 under the general framework of individual patient-level data meta-analyses. Random-
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53 effects models with adjustment for confounding variables and important risk factors will
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3 be used to assess the association and residual variation due to unknown or unmeasured
4 unit-specific factors. These analyses will identify treatment practices and health care
5 services with significant effects on outcomes, which subsequently can be targeted for
6 implementation or improvement. Analyses (two-sided tests) based on 10,000 yearly
7 admissions evaluating the effects of treatments or practices (assuming 50% exposure) on
8 outcomes (incidence 1% to 40%) will be able to detect relative risks of 1.6 to 1.1 with a
9 statistical power of 80% and type I error rate of 5%. This power calculation is based on
10 the anticipated data collection by CHNN during the first year. Safety and outcome
11 improvements will be monitored within each unit using control charts and Chi-square
12 tests for differences from baseline in outcome rates. Multivariable logistic regression
13 analyses will pool data from units within CHNN network to assess changes in outcomes
14 over time with adjustment for potential confounders and important risk factors and
15 accounting for clustering.

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

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37 EPIQ is a multi-faceted system for quality improvement that facilitates
38 implementation of practice change[28]. EPIQ is based on 3 features: (a) systematic
39 review of evidence in the published literature, (b) quantitative and qualitative analysis of
40 outcomes and practices to identify practices associated with good or poor outcomes for
41 targeted change, and (c) use of a collaborative network of clinicians, researchers and
42 administrators to facilitate mutual learning and implement change. In Shanghai, Cao et al.
43 [29] demonstrated that over a 1-year period, EPIQ reduced the rate of ventilator
44 associated pneumonia from 48.84 per 1,000 ventilator-days to 18.50 per 1,000 ventilator-
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3 days ($P<0.001$), and rates of central line associated blood stream infection (CLABSI)
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5 from 16.7 per 1,000 central line days to 5.2 per 1,000 central line days ($P<0.01$).
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8 After the first year of data collection (baseline data), we will implement EPIQ in all
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10 CHNN NICUs and compare the results pre and post EPIQ implementation. A national
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12 infrastructure for collaborative quality improvement will be established. Multi-
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14 disciplinary groups will examine the literature, conduct systematic reviews and examine
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16 hospital specific data in China to develop practice guidelines and bundles of best
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18 practices for implementation in CHNN NICUs. Quarterly cycles of practice change will
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20 be introduced using PDSA (Plan-Do-Study-Act) cycles of rapid change, and outcomes
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22 will be monitored quarterly and results fed back to hospitals. An online Teaching &
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24 Communication web portal will be used to facilitate collaboration between sites. Safety
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26 will be monitored. Multivariable logistic regression analyses will pool data from units to
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28 assess changes in outcomes over time with adjustment for potential confounders and
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30 important risk factors.
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35 Section 4: To conduct collaborative research, including epidemiologic, clinical and health
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37 services studies and randomized controlled trials.
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40 The CHNN database platform will support additional research initiatives, including
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42 epidemiologic, clinical and health services and randomized controlled trials. Research
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44 projects can be initiated by any CHNN member, approved by the CHNN Scientific
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46 Advisory Committee, and coordinated through the CHNN Coordinating Centre, where
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48 data will also be collected and analyzed. In future stages, limited datasets may be released
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50 to investigators using a secure electronic portal system.
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Ethics and dissemination

Central ethics approval was obtained from the Ethics Committee of the Children's Hospital of Fudan University (#CHFUFU 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.

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3 Quality improvement is a key goal, especially for China where neonatal care is still
4 developing and there is significant room for improvement. The adoption of EPIQ will
5 provide a robust system for quality improvement in Chinese NICUs. EPIQ was pioneered
6 by the Canadian Neonatal Network, where Lee et al [28] first demonstrated 44%
7 reduction in nosocomial infection and 15% reduction in bronchopulmonary dysplasia in a
8 multi-center randomized controlled trial, and EPIQ is now practiced in all Canadian
9 NICUs. In a comparative study of outcomes by the International Network for Evaluation
10 of Outcomes (iNEO), the implementation of EPIQ nationally was credited with rapidly
11 improving neonatal outcomes in Canada in comparison with other countries[31,32].
12 Subsequent studies in Canada and China provided confirmation of its efficacy[33-35].
13 Since Chinese NICUs have experience using EPIQ, this will facilitate its implementation
14 in Chinese NICUs and provide a proven method for improving quality of care and
15 outcomes in China. However, we recognize that change can be difficult to implement,
16 especially those that require making financial investments, adding staff, or breaking
17 cultural traditions. Notwithstanding possible early reluctance to follow these
18 recommendations, the strength of evidence produced from the data, the pragmatic nature
19 of the results, and the examples provided by “early adopter” NICUs will be the most
20 persuasive elements of the CHNN collaboration.
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44 The flexibility of the CHNN data platform to accommodate additional studies like
45 randomized controlled trials provides a unique opportunity for Chinese NICUs. China has
46 a large population, which is conducive to conducting multi-center studies rapidly and
47 efficiently. Once the CHNN data platform is fully functional, we anticipate that China
48 will play a leading role in conducting large scale multi-center studies and clinical trials.
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3 In summary, the CHNN collaboration will serve as a strong national platform for
4 collaborative research, outcomes evaluation, and quality improvement for VPI in China.
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6 The knowledge generated will have potential to benefit infants and families in China and
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8 internationally.
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16
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18 Study concept and design: Shoo K Lee, Chen Chao, Mingyan Hei
19

20
21 Drafting of the manuscript: Mingyan Hei, Shoo K Lee
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24 Critical revision of the manuscript for important intellectual content: All authors
25

26
27 Statistical analysis: Yanchen Wang
28

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30 Study supervision: Mingyan Hei, Chao Chen, Shoo K Lee, Wenhao Zhou
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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

2573 words

For peer review only



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.

146x82mm (220 x 220 DPI)

BMJ Open

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 (#CHFUFU 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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7 the study design; the collection, analysis, and interpretation of data; the writing of the
8 manuscript; or the decision to submit the manuscript for publication.
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19 **Keywords:**

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22 Infants, Preterm; Neonatal intensive care unit; Outcomes; Neonatal network;
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24 China; Neonates; Quality improvement
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30 **Abstract (214 words)**

31 **Introduction:** The objective of the Chinese Neonatal Network (CHNN) is to provide
32 a platform for collaborative research, outcomes evaluation, and quality improvement for
33 preterm infants with gestational age less than 32 weeks in China. The CHNN is the first
34 national neonatal network and has the largest geographically representative cohort from
35 neonatal intensive care units (NICUs) in China.
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43 **Methods and analysis:** Individual-level data from participating NICUs will be
44 collected using a unique database developed by the CHNN on an on-going basis from
45 January 2019. Data will be prospectively collected from all infants <32 weeks gestation or
46 <1500 grams birth weight at 58 participating NICUs. Infant outcomes and inter-
47 institutional variations in outcomes will be examined and used to inform quality
48 improvement measures aimed at improving outcomes. Information about NICU
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3 environmental and human resource factors and processes of neonatal care will also be
4 collected and analyzed for association with outcomes. Clinical studies, including
5
6 randomized controlled trials will be conducted using the CHNN data platform.
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10 **Ethics and dissemination:** This study was approved by the ethics review board of
11 Children's Hospital of Fudan University, which was recognized by all participating
12 hospitals. Waiver of consent were granted at all sites. Only non-identifiable patient level
13 data will be transmitted and only aggregate data will be reported in CHNN reports and
14 publications.
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24 **Strengths and limitations of this study**

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

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

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

48 **3.1 Participating hospitals**

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50 CHNN was founded in 2018 with 58 participating hospitals from 25 provinces
51 throughout mainland China (Figure 1). No hospitals in Tibet, Taiwan, and Hong Kong
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3 were included in CHNN. CHNN hospitals are tertiary referral hospitals with Grade A level
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5 III NICUs authorized by the Health Administration of China and have recognized expertise
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7 in caring for high-risk neonates. They were selected to be representative of different
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9 regions of the country but do not include all hospitals providing NICU care to VPI, and
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11 together they care for approximately 5% of all VPI in China. They include all government-
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13 designated neonatal centers of excellence in China, including four national children's
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15 medical centers, five regional children's medical centers and 30 provincial perinatal or
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17 children's medical centers. The other 19 hospitals comprised major referral centers in large
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19 cities across China. Forty-three hospitals were perinatal centers with birthing facilities, and
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21 14 hospitals were freestanding children's hospitals that admitted only outborn infants. The
22
23 median number of NICU beds was 40 (interquartile range [IQR], 30-62), and the median number
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25 of intermediate-level and continuing care neonatal beds was 66 (IQR, 40-91). For perinatal
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27 centers, the median number of annual deliveries was 10 280 (IQR, 6273-15 423). The median
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29 number of full- time equivalent neonatologists was 19 (IQR, 12-27), and the median number of
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31 NICU nurses was 42 (IQR, 30-65)[20].
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40 **3.2 Study population**

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42 This is a prospective, hospital-based cohort. Data will be collected on all infants
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44 <32+0 weeks GA or birth weight <1500g admitted to participating NICUs. Stillborn,
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46 delivery room death, and infants transferred to non-participating hospitals within 24 hours
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48 after birth will be excluded. Readmissions and transfers between participating hospitals
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50 will be tracked as data from the same infants. Infants will be followed until NICU
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52 discharge/transfer or death.
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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 \geq 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 \geq stage 3 according to the International Classification[25] or need for laser surgery or intraocular injections of anti-vascular

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3 endothelial growth factor agents. NEC is defined as \geq stage 2 according to Bell's
4 criteria[26]. NI is defined as culture-proven sepsis (blood or cerebrospinal fluid positive
5 for pathogenic organism) at >3 days or 72 hours postnatal age[27]. Hemodynamically
6 significant PDA is defined as PDA requiring pharmacological treatment or surgical
7 ligation[28].
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17 Objective 2. Assess and monitor major outcomes of VPI and their risk determinants, and
18 inter-institutional variations in care and outcomes
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21 Infant characteristics and outcomes will be summarized as counts and percentages for
22 categorical variables and using the means and standard deviations or the medians and
23 interquartile ranges for continuous variables. Sub-group analysis and inter-institutional
24 comparisons will use the Chi-square test for categorical variables and ANOVA F-test or
25 Mood's median test for continuous variables. Multivariable logistic regression models with
26 adjustment for confounders will be used to assess risk factors associated with outcomes.
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35 To study inter-institutional variations in primary and secondary outcomes, the ratios
36 and associated 95% confidence intervals (CI) will be calculated, and 'caterpillar plots' will
37 be used to graphically display differences between participating sites. The 'indirect
38 standardization' approach will be used to compute the standardized outcome ratios in order
39 to adjust for multiple baseline characteristics. Each NICU can compare its own observed
40 rate with the average CHNN rate to identify the relative level of its own unit. For each
41 outcome, the expected number of events will be computed as the sum of predicted
42 probabilities from a multivariable model (logistic regression or zero inflated negative
43 binomial models based on data distribution) derived using data from all NICUs with
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3 adjustment for confounders. NICU standardized outcome ratios will be graphically
4 displayed using ‘funnel’ plots with 95% prediction intervals for comparison between
5 NICUs. Pair-wise comparisons between NICUs will be performed using multivariate
6 regression models adjusted for confounders. The generalized estimating equation (GEE)
7 models will be used for adjusting analyses for infant cluster within the CHNN. Hierarchical
8 random-effects regression models will be used to allow for variation at unit level. In
9 addition, statistical significance will be evaluated by applying a Bonferroni correction to
10 account for multiple pair-wise comparisons.
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21 Associations of clinical practices and other factors with outcomes will be assessed
22 under the general framework of individual patient-level data meta-analyses. Random-
23 effects models with adjustment for confounding variables and important risk factors will
24 be used to assess the association and residual variation due to unknown or unmeasured
25 unit-specific factors. These analyses will identify treatment practices and health care
26 services with significant effects on outcomes, which subsequently can be targeted for
27 implementation or improvement. Analyses (two-sided tests) based on 10,000 yearly
28 admissions evaluating the effects of treatments or practices (assuming 50% exposure) on
29 outcomes (incidence 1% to 40%) will be able to detect relative risks of 1.6 to 1.1 with a
30 statistical power of 80% and type I error rate of 5%. This power calculation is based on the
31 anticipated data collection by CHNN during the first year. Safety and outcome
32 improvements will be monitored within each unit using control charts and Chi-square tests
33 for differences from baseline in outcome rates. Multivariable logistic regression analyses
34 will pool data from units within CHNN network to assess changes in outcomes over time
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3 with adjustment for potential confounders and important risk factors and accounting for
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10 Objective 3. Implement Evidence-based Practice for Improving Quality (EPIQ) program
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12 to improve quality of care and outcomes
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14 EPIQ is a multi-faceted system for quality improvement that facilitates
15 implementation of practice change[29]. EPIQ is based on 3 features: (a) systematic review
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17 of evidence in the published literature, (b) quantitative and qualitative analysis of outcomes
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19 and practices to identify practices associated with good or poor outcomes for targeted
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21 change, and (c) use of a collaborative network of clinicians, researchers and administrators
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23 to facilitate mutual learning and implement change. In Shanghai, Cao et al. [30]
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25 demonstrated in the multi-center EPIQ-REIN study, that over a 1-year period, EPIQ
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27 reduced the rate of ventilator associated pneumonia from 48.84 per 1,000 ventilator-days
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29 to 18.50 per 1,000 ventilator-days ($P<0.001$), and rates of central line associated blood
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31 stream infection (CLABSI) from 16.7 per 1,000 central line days to 5.2 per 1,000 central
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33 line days ($P<0.01$).
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40 After the first year of data collection (baseline data), we will implement EPIQ in all
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42 CHNN NICUs and compare the results pre and post EPIQ implementation. The EPIQ
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44 program has well established published protocols for training of personnel, coordination,
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46 literature review, risk analysis, identification of target outcomes, implementation and
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48 facilitation of practice changes, monitoring and surveillance, communication and safety
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50 assurance; and CHNN has well trained personnel, teams and organization from the
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52 previous EPIQ-REIN experience[30]. A national CHNN infrastructure for collaborative
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3 quality improvement will be established. Hospitals will be organized into groups that target
4 specific outcomes. Multi-disciplinary groups will examine the literature, conduct
5 systematic reviews and examine hospital specific data in China to develop practice
6 guidelines and bundles of best practices for implementation in CHNN NICUs. Quarterly
7 cycles of practice change will be introduced using PDSA (Plan-Do-Study-Act) cycles of
8 rapid change, and outcomes will be monitored quarterly and results fed back to hospitals.
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10 An online Teaching & Communication web portal will be used to facilitate collaboration
11 between sites, including site visits, discussions and planning.. Safety will be monitored.
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13 Multivariable logistic regression analyses will pool data from units to assess changes in
14 outcomes over time with adjustment for potential confounders and important practice
15 related risk factors, which will be targeted for practice change.
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31 Objective 4. Conduct collaborative research, including epidemiologic, clinical and health
32 services studies and randomized controlled trials.
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35 The CHNN database platform will support additional research initiatives, including
36 epidemiologic, clinical and health services and randomized controlled trials. Research
37 projects can be initiated by any CHNN member, approved by the CHNN Scientific
38 Advisory Committee, and coordinated through the CHNN Coordinating Centre, where data
39 will also be collected and analyzed. In future stages, limited datasets may be released to
40 investigators using a secure electronic portal system.
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51 **3.5 Statistical analysis**

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

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

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52 The CHNN collaboration will be the first national network to examine data from a
53 large cohort of preterm infants that is representative of the different regions of China on an
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3 on-going basis. This is important because China has a huge population, with many regional
4 differences in social, economic and health care development. Unfortunately, the existing
5 literature regarding preterm infants in China has been mostly limited to single-centre
6 studies or multicentre studies with small numbers of participating sites[8,10,30, 31].
7 Findings from this national collaboration will provide a comprehensive picture of outcomes
8 of very preterm infants in Chinese NICUs and establish a strong system for outcomes
9 surveillance and monitoring trends in clinical practices and outcome variations. Data from
10 CHNN will also provide robust estimates for development of clinical practice guidelines
11 and health care recommendations that can be generalizable across the country.
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24 Quality improvement is a key goal, especially for China where neonatal care is still
25 developing and there is significant room for improvement. The adoption of EPIQ will
26 provide a robust system for quality improvement in Chinese NICUs. EPIQ was pioneered
27 by the Canadian Neonatal Network, where Lee et al [29] first demonstrated 44% reduction
28 in nosocomial infection and 15% reduction in bronchopulmonary dysplasia in a multi-
29 center randomized controlled trial, and EPIQ is now practiced in all Canadian NICUs. In a
30 comparative study of outcomes by the International Network for Evaluation of Outcomes
31 (iNEO), the implementation of EPIQ nationally was credited with rapidly improving
32 neonatal outcomes in Canada in comparison with other countries[32,33]. Subsequent
33 studies in Canada and China provided confirmation of its efficacy[34-36]. Since Chinese
34 NICUs have experience using EPIQ, this will facilitate its implementation in Chinese
35 NICUs and provide a proven method for improving quality of care and outcomes in China.
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37 However, we recognize that change can be difficult to implement, especially those that
38 require making financial investments, adding staff, or breaking cultural traditions.
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3 Notwithstanding possible early reluctance to follow these recommendations, the strength
4 of evidence produced from the data, the pragmatic nature of the results, and the examples
5 provided by “early adopter” NICUs will be the most persuasive elements of the CHNN
6 collaboration.
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12 The flexibility of the CHNN data platform to accommodate additional studies like
13 randomized controlled trials provides a unique opportunity for Chinese NICUs. China has
14 a large population, which is conducive to conducting multi-center studies rapidly and
15 efficiently. Once the CHNN data platform is fully functional, we anticipate that China will
16 play a leading role in conducting large scale multi-center studies and clinical trials.
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24 Limitations of CHNN are: (1) The data are from a select group of large tertiary NICUs
25 with the highest level of neonatal care in China, and may not be generalizable to the whole
26 population. (2) Data on parent participation, pain management, skin-to-skin contact care
27 and other important developmental aspects of modern neonatal care are not currently
28 available but will be included in the future (3) Data on resource use is limited.
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38 In summary, the CHNN collaboration will serve as a strong national platform for
39 collaborative research, outcomes evaluation, and quality improvement for VPI in China.
40 The knowledge generated will have potential to benefit infants and families in China and
41 internationally.
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For peer review only

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

2951 words

For peer review only



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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50 **Ethics information**

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This proposal was approved by the Ethics Committee of the Children's Hospital of Fudan University (#CHFUFU 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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7 the study design; the collection, analysis, and interpretation of data; the writing of the
8 manuscript; or the decision to submit the manuscript for publication.
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19 **Keywords:**

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22 Infants, Preterm; Neonatal intensive care unit; Outcomes; Neonatal network;
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24 China; Neonates; Quality improvement
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30 **Abstract (214 words)**

31 **Introduction:** The objective of the Chinese Neonatal Network (CHNN) is to provide
32 a platform for collaborative research, outcomes evaluation, and quality improvement for
33 preterm infants with gestational age less than 32 weeks in China. The CHNN is the first
34 national neonatal network and has the largest geographically representative cohort from
35 neonatal intensive care units (NICUs) in China.
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43 **Methods and analysis:** Individual-level data from participating NICUs will be
44 collected using a unique database developed by the CHNN on an on-going basis from
45 January 2019. Data will be prospectively collected from all infants <32 weeks gestation or
46 <1500 grams birth weight at 58 participating NICUs. Infant outcomes and inter-
47 institutional variations in outcomes will be examined and used to inform quality
48 improvement measures aimed at improving outcomes. Information about NICU
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3 environmental and human resource factors and processes of neonatal care will also be
4 collected and analyzed for association with outcomes. Clinical studies, including
5
6 randomized controlled trials will be conducted using the CHNN data platform.
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10 **Ethics and dissemination:** This study was approved by the ethics review board of
11 Children's Hospital of Fudan University, which was recognized by all participating
12 hospitals. Waiver of consent were granted at all sites. Only non-identifiable patient level
13 data will be transmitted and only aggregate data will be reported in CHNN reports and
14 publications.
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24 **Strengths and limitations of this study**

- 25
26 1. This is the largest prospective, geographically representative, hospital-based cohort
27 study of very preterm infants in China.
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30 2. Data definitions and data collection protocols were standardized.
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33 3. Data were collected on both outcomes and clinical practices to facilitate risk analysis
34 and quality improvement.
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38 4. Limitations include lack of generalizability since participating hospitals were all
39 tertiary hospitals.
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43 5. Outcomes data were not available for infants who were discharged against medical
44 advice, which may bias the results
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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

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3 outcomes in a country and can provide an effective platform for collaborative care, quality
4 improvement (QI), research and knowledge translation^[15-19]. Our goal is to establish a
5 national Chinese Neonatal Network (CHNN) in the People's Republic of China, with a
6 standardized database for collaborative care, quality improvement and research. This
7 manuscript outlines the research protocol for CHNN.
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14 15 16 17 **2. Objectives** 18

19 The specific objectives of CHNN are to: (1) Establish an on-going prospectively
20 collected standardized database of very preterm infants (VPI) with GA <32 weeks or <1500
21 grams birth weight among NICUs in China, as a platform for surveillance, quality
22 improvement and research, (2) Assess and monitor major outcomes of VPI and their risk
23 determinants, as well as inter-institutional variations in care practices and outcomes to
24 identify clinical practices associated with good or poor outcomes, (3) Implement the
25 Evidence-based Practice for Improving Quality (EPIQ) program to improve quality of care
26 and outcomes, (4) Conduct collaborative research, including epidemiologic, clinical and
27 health services studies and randomized controlled trials.
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43 **3. Methods and analysis** 44

45 **3.1 Participating hospitals** 46

47 CHNN was founded in 2018 with 58 participating hospitals from 25 provinces
48 throughout mainland China (Figure 1). No hospitals in Tibet, Taiwan, and Hong Kong were
49 included. CHNN hospitals are tertiary referral hospitals with Grade A level III NICUs
50 authorized by the Health Administration of China and have recognized expertise in caring
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3 for high-risk neonates. They were selected to be representative of different regions of the
4 country but do not include all hospitals providing NICU care to VPI, and together they care
5 for approximately 5% of all VPI in China. They include all government-designated
6 neonatal centers of excellence in China, including four national children's medical centers,
7 five regional children's medical centers and 30 provincial perinatal or children's medical
8 centers. The other hospitals comprise major referral centers in large cities across China.
9
10 Forty-three hospitals were perinatal centers with birthing facilities, and 14 hospitals were
11 freestanding children's hospitals that admitted only outborn infants. The median number of NICU
12 beds was 40 (interquartile range [IQR], 30-62), and the median number of intermediate-level and
13 continuing care neonatal beds was 66 (IQR, 40-91). For perinatal centers, the median number of
14 annual deliveries was 10 280 (IQR, 6273-15 423). The median number of full-time equivalent
15 neonatologists was 19 (IQR, 12-27), and the median number of NICU nurses was 42 (IQR, 30-
16 65)^[20].

3.2 Study population

37 This is a prospective, hospital-based cohort. Data will be collected on all infants
38 <32+0 weeks GA or birth weight <1500g admitted to participating NICUs. Stillborn,
39 delivery room death, and infants transferred to non-participating hospitals within 24 hours
40 after birth will be excluded. Readmissions and transfers between participating hospitals
41 will be tracked as data from the same infants. Infants will be followed until NICU
42 discharge/transfer or death.

3.3 Patient and public involvement

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3 The study responds to patient concerns about quality of care and perceived variation
4 in quality of care among different hospitals. Outcomes of quality improvement initiatives
5 will be published and made available to patients.
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10 11 12 **3.4 Achieving the 4 specific objectives of CHNN**

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

15 16 *Governance*

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18 The executive committee of CHNN comprises 13 senior neonatology leaders
19 representing different regions of the country and include 2 co-chairpersons, 2 vice-
20 presidents, and 3 secretary generals. The committee is responsible for setting policies and
21 research agendas, and oversees the activities and operations of the network and
22 coordinating center.
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30 31 *Coordinating Center and Data Collection*

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33 The CHNN Coordinating and Data Centre is located at the Children's Hospital of
34 Fudan University, Shanghai, China. The Data Center is equipped with dedicated servers
35 that are managed by the Information Technology Department of the Children's Hospital of
36 Fudan University in compliance with hospital, municipal and national standards for data
37 security. A unique scalable customized database with built-in error checking based on MS
38 Access was created in-house. A standard manual of operations and definitions was
39 provided to all participating centers. Dedicated data abstractors under the supervision of
40 the site principal investigator are responsible for data acquisition in each hospital and
41 centralized training sessions were organized to teach data abstractors to carry out data
42 collection and uploading to the CHNN database. Data abstractors enter data directly from
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3 patients charts into a dedicated computer at each hospital and electronically transmitted
4 data to the CHNN Coordinating Center. Only non-identifiable patient information will be
5 transferred and only aggregate data results will be reported and published. Data quality is
6 ensured at multiple levels. The data entry program has built-in error checking. Additional
7 data checks are performed quarterly by the coordinating center for quality and
8 completeness, and site-specific data quality reports will be fed back to each site and data
9 records returned for corrections if needed. Data quality audit using data re-abstraction of
10 randomly selected patient charts will be performed annually. Site investigators will be
11 responsible for data quality control in each site. An annual report will be produced for the
12 network.
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26 *Data Variables*

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

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3 Resource Use Duration of hospitalization, Duration of ventilation,
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5 Duration of oxygen therapy, Use of central catheters,
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7 Parenteral nutrition, Surgery
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11 Abbreviations: SNAP – Score for neonatal acute physiology, TRIPS – Transport risk index
12 of physiologic stability, BPD – bronchopulmonary dysplasia, SNI – severe neurological
13 injury, ROP – retinopathy of prematurity, NEC – necrotizing enterocolitis, NI – nosocomial
14 infection
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21 Objective 2. Assess and monitor major outcomes of VPI and their risk determinants, and
22 inter-institutional variations in care and outcomes
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26 Infant characteristics and outcomes will be summarized as counts and percentages for
27 categorical variables and using the means and standard deviations or the medians and
28 interquartile ranges for continuous variables. Sub-group analysis and inter-institutional
29 comparisons will use the Chi-square test for categorical variables and ANOVA F-test or
30 Mood's median test for continuous variables. Multivariable logistic regression models with
31 adjustment for confounders will be used to assess risk factors associated with outcomes.
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40 To study inter-institutional variations in primary and secondary outcomes, the ratios
41 and associated 95% confidence intervals (CI) will be calculated, and 'caterpillar plots' will
42 be used to graphically display differences between participating sites. The 'indirect
43 standardization' approach will be used to compute the standardized outcome ratios in order
44 to adjust for multiple baseline characteristics. Each NICU can compare its own observed
45 rate with the average CHNN rate to identify the relative level of its own unit. For each
46 outcome, the expected number of events will be computed as the sum of predicted
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3 probabilities from a multivariable model (logistic regression or zero inflated negative
4 binomial models based on data distribution) derived using data from all NICUs with
5 adjustment for confounders. NICU standardized outcome ratios will be graphically
6 displayed using ‘funnel’ plots with 95% prediction intervals for comparison between
7 NICUs. Pair-wise comparisons between NICUs will be performed using multivariate
8 regression models adjusted for confounders. The generalized estimating equation (GEE)
9 models will be used for adjusting analyses for infant cluster within the CHNN. Hierarchical
10 random-effects regression models will be used to allow for variation at unit level. In
11 addition, statistical significance will be evaluated by applying a Bonferroni correction to
12 account for multiple pair-wise comparisons.
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26 Associations of clinical practices and other factors with outcomes will be assessed
27 under the general framework of individual patient-level data meta-analyses. Random-
28 effects models with adjustment for confounding variables and important risk factors will
29 be used to assess the association and residual variation due to unknown or unmeasured
30 unit-specific factors. These analyses will identify treatment practices and health care
31 services with significant effects on outcomes, which subsequently can be targeted for
32 implementation or improvement. Analyses (two-sided tests) based on 10,000 yearly
33 admissions evaluating the effects of treatments or practices (assuming 50% exposure) on
34 outcomes (incidence 1% to 40%) will be able to detect relative risks of 1.6 to 1.1 with a
35 statistical power of 80% and type I error rate of 5%. This power calculation is based on the
36 anticipated data collection by CHNN during the first year. Safety and outcome
37 improvements will be monitored within each unit using control charts and Chi-square tests
38 for differences from baseline in outcome rates. Multivariable logistic regression analyses
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3 will pool data from units within CHNN network to assess changes in outcomes over time
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5 with adjustment for potential confounders and important risk factors and accounting for
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7 clustering.
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12 Objective 3. Implement Evidence-based Practice for Improving Quality (EPIQ) program
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14 to improve quality of care and outcomes
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17 EPIQ is a multi-faceted system for quality improvement that facilitates
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19 implementation of practice change^[29]. EPIQ is based on 3 features: (a) systematic review
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21 of evidence in the published literature, (b) quantitative and qualitative analysis of outcomes
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23 and practices to identify practices associated with good or poor outcomes for targeted
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25 change, and (c) use of a collaborative network of clinicians, researchers and administrators
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27 to facilitate mutual learning and implement change. In Shanghai, Cao et al.^[30] demonstrated
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29 in the multi-center EPIQ-REIN study, that over a 1-year period, EPIQ reduced the rate of
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31 ventilator associated pneumonia from 48.84 per 1,000 ventilator-days to 18.50 per 1,000
32
33 ventilator-days ($P<0.001$), and rates of central line associated blood stream infection
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35 (CLABSI) from 16.7 per 1,000 central line days to 5.2 per 1,000 central line days ($P<0.01$).
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40 After the first year of data collection (baseline data), we will implement EPIQ in all
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42 CHNN NICUs and compare the results pre and post EPIQ implementation. The EPIQ
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44 program has well established published protocols for training of personnel, coordination,
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46 literature review, risk analysis, identification of target outcomes, implementation and
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48 facilitation of practice changes, monitoring and surveillance, communication and safety
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50 assurance; and CHNN has well trained personnel, teams and organization from the
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52 previous EPIQ-REIN experience^[30]. A national CHNN infrastructure for collaborative
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3 quality improvement will be established. Hospitals will be organized into groups that target
4 specific outcomes. Multi-disciplinary groups will examine the literature, conduct
5 systematic reviews and examine hospital specific data in China to develop practice
6 guidelines and bundles of best practices for implementation in CHNN NICUs. Quarterly
7 cycles of practice change will be introduced using PDSA (Plan-Do-Study-Act) cycles of
8 rapid change, and outcomes will be monitored quarterly and results fed back to hospitals.
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10 An online Teaching & Communication web portal will be used to facilitate collaboration
11 between sites, including site visits, discussions and planning.. Safety will be monitored.
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13 Multivariable logistic regression analyses will pool data from units to assess changes in
14 outcomes over time with adjustment for potential confounders and important practice
15 related risk factors, which will be targeted for practice change.
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31 Objective 4. Conduct collaborative research, including epidemiologic, clinical and health
32 services studies and randomized controlled trials.
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35 The CHNN database platform will support additional research initiatives, including
36 epidemiologic, clinical and health services and randomized controlled trials. Research
37 projects can be initiated by any CHNN member, approved by the CHNN Scientific
38 Advisory Committee, and coordinated through the CHNN Coordinating Centre, where data
39 will also be collected and analyzed. In future stages, limited datasets may be released to
40 investigators using a secure electronic portal system.
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51 **3.5 Statistical analysis**

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

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

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52 The CHNN collaboration will be the first national network to examine data from a
53 large cohort of preterm infants that is representative of the different regions of China on an
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3 on-going basis. This is important because China has a huge population, with many regional
4 differences in social, economic and health care development. Unfortunately, the existing
5 literature regarding preterm infants in China has been mostly limited to single-centre
6 studies or multicentre studies with small numbers of participating sites^[8,10,30,31]. Findings
7 from this national collaboration will provide a comprehensive picture of outcomes of very
8 preterm infants in Chinese NICUs and establish a strong system for outcomes surveillance
9 and monitoring trends in clinical practices and outcome variations. Data from CHNN will
10 also provide robust estimates for development of clinical practice guidelines and health
11 care recommendations that can be generalizable across the country.
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24 Quality improvement is a key goal, especially for China where neonatal care is still
25 developing and there is significant room for improvement. The adoption of EPIQ will
26 provide a robust system for quality improvement in Chinese NICUs. EPIQ was pioneered
27 by the Canadian Neonatal Network, where Lee et al^[29] first demonstrated 44% reduction
28 in nosocomial infection and 15% reduction in bronchopulmonary dysplasia in a multi-
29 center randomized controlled trial, and EPIQ is now practiced in all Canadian NICUs. In a
30 comparative study of outcomes by the International Network for Evaluation of Outcomes
31 (iNEO), the implementation of EPIQ nationally was credited with rapidly improving
32 neonatal outcomes in Canada in comparison with other countries^[32,33]. Subsequent studies
33 in Canada and China provided confirmation of its efficacy^[34-36]. Since Chinese NICUs
34 have experience using EPIQ, this will facilitate its implementation in Chinese NICUs and
35 provide a proven method for improving quality of care and outcomes in China. However,
36 we recognize that change can be difficult to implement, especially those that require
37 making financial investments, adding staff, or breaking cultural traditions.
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3 Notwithstanding possible early reluctance to follow these recommendations, the strength
4 of evidence produced from the data, the pragmatic nature of the results, and the examples
5 provided by “early adopter” NICUs will be the most persuasive elements of the CHNN
6 collaboration.
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12 The flexibility of the CHNN data platform to accommodate additional studies like
13 randomized controlled trials provides a unique opportunity for Chinese NICUs. China has
14 a large population, which is conducive to conducting multi-center studies rapidly and
15 efficiently. Once the CHNN data platform is fully functional, we anticipate that China will
16 play a leading role in conducting large scale multi-center studies and clinical trials.
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24 Limitations of CHNN are: (1) The data are from a select group of large tertiary NICUs
25 with the highest level of neonatal care in China, and may not be generalizable to the whole
26 population, (2) There may be biases inherent in large cohort databases of this nature,
27 including reporting bias, selection bias and others, (3) Data on parent participation, pain
28 management, skin-to-skin contact care and other important developmental aspects of
29 modern neonatal care are not currently available but will be included in the future, (4) Data
30 on resource use is limited.
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42 In summary, the CHNN collaboration will serve as a strong national platform for
43 collaborative research, outcomes evaluation, and quality improvement for VPI in China.
44 The knowledge generated will have potential to benefit infants and families in China and
45 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

For peer review only



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