PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The Chinese Neonatal Network: a national protocol for collaborative research and quality improvement in neonatal care
AUTHORS	Hei, Mingyan; Li, Xiaoying; Shi, Yuan; Cao, Yun; Sun, Jianhua; Wu, Hui; Jiang, Siyuan; Ma, Xiaolu; Wang, Yanchen; Sun, Huiqing; Zhang, Huayan; Du, Li-Zhong; Zhou, Wenhao; Lee, Shoo; Chen, Chao

VERSION 1 – REVIEW

REVIEWER	Hanson, Claudia Karolinska Institute, Dept Public Global Health
REVIEW RETURNED	23-Jun-2021

GENERAL COMMENTS	Thank you providing me the chance to review the protocol paper for an interesting collaboration. I have a few queries which I like to put forward I am missing some details in the method section and I am unsure of the headings The part on the participating hospitals could give more details. In view that this collaboration is about preterms, I would expect to read somewhere about preterm rates and mortality rates in this group. I am also not sure if all hospitals were included or some, thus was there some purposeful selection? I do not understand why the indicators are found in the patient and public involvement section. I believe a better structure and appropriate sub-headings would help. I personally would put the indicators in a table and not the text. I cannot find information who is responsible for data in the first hand, and be more explicit about entering data (staff, data cleark, trained???) and how the platform, eg electronic, e-data base is made. This part is too superficially described. I also do not if there are any data quality assurance systems established, talking about quarterly check is too little specific. Who is part of the executive committee? The part which describes analysis should be found under an appropriate heading. Please add who will do which analysis, some might be done at the hospital level, some by a research team? Please write an appropriate patient and public involvement section, explaining how the public is involved, informed, etc. In relation to the quality improvement: Also here concreteness is missing, who is supporting this QI, is there coaching, and discussions between hospitals, Ethics: I assume you do not take individual patient. Could you add that the ethics approval consented to this? Limitations: Please add on the limitations of the study

	As a minor: fresh human milk is for me a strange term. It is about breast milk?

REVIEWER	Eriksson, Mats Örebro University, Sweden, Faculty of Medicine and Health, School of Health Sciences
REVIEW RETURNED	28-Jun-2021

GENERAL COMMENTS	Dear authors, thank you for the opportunity to review your manuscript, and please excuse me for being a bit late. I have read it with interest and have the following comments: 1. Research ethics. You declare that all the participating units have consented and that only de-identified data will be transferred. But how about the parents? Do they agree to have data about their child recorded in local databases (other than for clinical use)? Please discuss this in relation to Chines legislation and to research ethical standards. 2. The data you collect and the outcome you report are strictly medical. How about data on parent participating, pain management, skin-to-skin contact care and other important features of modern neonatal care? Please elaborate on this in your discussion. 3. This manuscript is submitted as a study protocol, but I find it mainly being a thorough description of how the new network and database are built. I am aware that it is a long step from building this infrastructure to being able to doing actual studies and reporting valid results but I recommend that you discuss possible short-coming and problems in a limitations section.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Claudia Hanson, Karolinska Institute
Comments to the Author:
I am missing some details in the method section and I am unsure of the headings
Reply:
We have revised the headings for clarity and added details to the methods section.

The part on the participating hospitals could give more details. In view that this collaboration is about preterms, I would expect to read somewhere about preterm rates and mortality rates in this group. I am also not sure if all hospitals were included or some, thus was there some purposeful selection?
Reply:
1. We have added additional details about participating hospitals as follows: “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).”
2. We have not reported results here this is a protocol manuscript, not an outcomes manuscript. CHNN outcomes of this cohort study, including mortality and morbidity rates, have been reported

recently by Cao et al, in JAMA Netw Open. 2021;4(8):e2118904.
doi:10.1001/jamanetworkopen.2021.18904.
3. We have expanded the section on Participating Hospitals for added clarity as follows: “CHNN was founded in 2018 with 58 participating hospitals from 25 provinces throughout mainland China (Figure 1). No hospitals in Tibet, Taiwan and Hongkong 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).”

I do not understand why the indicators are found in the patient and public involvement section. I believe a better structure and appropriate sub-headings would help. I personally would put the indicators in a table and not the text.
Reply:
We have revised the headings and placed the indicators under the section entitled “Achieving the 4 specific objectives of CHNN; Objective 1.” We have also placed the indicators in Table 1 as recommended.

I cannot find information who is responsible for data in the first hand, and be more explicit about entering data (staff, data cleark, trained???) and how the platform, eg electronic, e-data base is made. This part is too superficially described. I also do not if there are any data quality assurance systems established, talking about quarterly check is too little specific.
Reply:
We have clarified how the data platform was made and managed, as follows:
“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.”

We have clarified the data entry procedures as follows:
“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 transmit data to the CHNN Coordinating Center. Only non-identifiable patient information will be transferred and only aggregate data results will be reported and published.”

We have clarified the data quality assurance system as follows:
“ 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."

Who is part of the executive committee?
Reply:
We have added a paragraph on governance as follows:
"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."

The part which describes analysis should be found under an appropriate heading. Please add who will do which analysis, some might be done at the hospital level, some by a research team?
Reply:
Details of statistical analysis were described under the section "Achieving the 4 specific objectives of CHNN; Objective 2."
We have added a section on who will perform the Statistical Analysis as follows: "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."

Please write an appropriate patient and public involvement section, explaining how the public is involved, informed, etc.
Reply:
We have added a paragraph as recommended, as follows:
"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."

In relation to the quality improvement: Also here concreteness is missing, who is supporting this QI, is there coaching, and discussions between hospitals？
Reply:
We have added details of the EPIQ methodology for clarity. However, we would like to point out that EPIQ is a well-established program with defined protocols that have been published and which have been used in many countries including Canada, Australia, China, India, and several Latin American countries. The revised text is as follows:
"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[29]. 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.”

Ethics: I assume you do not take individual patient. Could you add that the ethics approval consented to this?
Reply:
No, we do not take individual patient. This has been added to the Ethics section as follows:
“All CHNN studies will not take individual patients, and waiver of consent were granted at all sites.”

Limitations: Please add on the limitations of the study
Reply:
A paragraph of limitations has been added as follows:
“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.”

As a minor: fresh human milk is for me a strange term. It is about breast milk?
Reply:
Sun et al (Scientific Reports 2019,9:941-949) published a pilot clinical trial showing that feeding preterm infants with fresh human breast milk (less than 4 hours following expression) is superior to frozen human breast milk and produces improved outcomes. A full multi-center RCT is currently under way in CHNN.

Reviewer: 2
Dr. Mats Eriksson, Örebro University, Sweden
Comments to the Author:
Dear authors,
thank you for the opportunity to review your manuscript, and please excuse me for being a bit late. I have read it with interest and have the following comments:
1. Research ethics. You declare that all the participating units have consented and that only de-identified data will be transferred. But how about the parents? Do they agree to have data about their child recorded in local databases (other than for clinical use)? Please discuss this in relation to Chinese legislation and to research ethical standards.
Reply:
Ethics approval were provided by all hospitals. Collection and use of data as specified in the study protocol are compliant with all Chinese laws about privacy and use of data and consistent with international standards. Existing databases in other international networks in the International Network for Evaluation of Outcomes (includes Canada, UK, Sweden, Finland, Spain, Italy, Switzerland, Israel, Japan, Australia, New Zealand) also do not require patient consent for collecting and using de-identified infant patient data for research similar to CHNN.

2. The data you collect and the outcome you report are strictly medical. How about data on parent participating, pain management, skin-to-skin contact care and other important features of modern neonatal care? Please elaborate on this in your discussion.
Reply:
Unfortunately, data on parent participating, pain management, skin-to-skin contact care and other important features of modern neonatal care are not currently collected. Relevant discussion has been added in the paragraph on limitations as follows:

"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. This manuscript is submitted as a study protocol, but I find it mainly being a thorough description of how the new network and database are built. I am aware that it is a long step from building this infrastructure to being able to doing actual studies and reporting valid results but I recommend that you discuss possible short-coming and problems in a limitations section.
Reply:
A paragraph on limitations has been added. However, please note that the basic infrastructure and organization has already been built, and the first manuscript on outcomes was published in JAMA Netw Open. 2021;4(8):e2118904. doi:10.1001/jamanetworkopen.2021.18904.

VERSION 2 – REVIEW

REVIEWER	Hanson, Claudia Karolinska Institute, Dept Public Global Health
REVIEW RETURNED	01-Sep-2021

GENERAL COMMENTS	Thank you for giving me the opportunity to review this paper again. Congratulation also to your publication. Sorry to restate some of my comments as I see they have not been clear enough. I expected no results, but that in the introduction section I expect some information stating that preterm birth is a problem in China, thus I expect results from other studies. The issue of structure is not about adding numbers, but having a structure as used in protocols. Sure, the editor should advise, but the structure around objective does not speak to me personally. I would use headings such as setting, participants, variables/outcomes, data collection / data sources. But I have not looked if BMJ open advises a certain structure. There are guidelines out and in your published paper you are adhering also to them. Thank you for expanding on more information on the participating NICUs. However, one important information is still missing: how many of this type of NICUs do exist in China and how many were participating. I am happy with the addition on how data are collected. I would revise the limitation section to stronger also include more on the different types of biases (eg. selection bias, reporting bias, etc). My comment was not about the rational of breastfeeding, but the term "fresh human milk", the international term used is simply breast milk. Hope this helps

REVIEWER	Eriksson, Mats Örebro University, Sweden, Faculty of Medicine and Health, School of Health Sciences
REVIEW RETURNED	10-Sep-2021

GENERAL COMMENTS	Thank you for responding to my questions and concerns. I have no further comments.

VERSION 2 – AUTHOR RESPONSE

I expected no results, but that in the introduction section I expect some information stating that preterm birth is a problem in China, thus I expect results from other studies.
Reply:

We have added additional data as follows: “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].”

The issue of structure is not about adding numbers, but having a structure as used in protocols. Sure, the editor should advise, but the structure around objective does not speak to me personally. I would use headings such as setting, participants, variables/outcomes, data collection / data sources. But I have not looked if BMJ open advises a certain structure. There are guidelines out and in your published paper you are adhering also to them.

Reply:
This is a stylistic comment and does not pertain to content. We have adhered to the format required by BMJ Open and our structure is not dissimilar to other publications of similar nature, e.g. Prakesh S Shah, Shoo K Lee, Kei Lui, Gunnar Sjörs, Rintaro Mori, Brian Reichman, et al and on behalf of the International Network for Evaluating Outcomes of Neonates (iNeo). The International Network for Evaluating Outcomes of very low birth weight, very preterm neonates (iNeo): a protocol for collaborative comparisons of international health services for quality improvement in neonatal care. BMC Pediatrics 2014, 14:110 doi:10.1186/1471-2431-14-110. Unless the editor requires it, we prefer to stay with our current structure.

Thank you for expanding on more information on the participating NICUs. However, one important information is still missing: how many of this type of NICUs do exist in China and how many were participating.
Reply:

Unfortunately, there is lack of information about the number of NICUs in China. According to the Chinese Ministry of Health, in December 2020, there were 1580 Grade A, Level III hospitals in China. This includes general hospitals, maternity hospitals, children’s hospitals, teaching hospitals and others. Some of them have NICUs but it is unclear how many.

I would revise the limitation section to stronger also include more on the different types of biases (eg. selection bias, reporting bias, etc).

Reply:

We have added the following to the limitations “There may be biases inherent in large cohort databases of this nature, including reporting bias, selection bias and others,”

My comment was not about the rational of breastfeeding, but the term “fresh human milk”, the international term used is simply breast milk.

Reply:

The term “fresh human milk” has been replaced with “breast milk”.