Establishing the reference interval for pulse oxygen saturation in neonates at high altitudes: protocol for a multicentre, open, cross-sectional study

Bo Wang, Chongde Liu, Yanli Yao, Zhihui Lu, Rong Yu, Zhuoma CaiRen, Zhixiu Wang, Runwu Liu, Yazhen Wu, Zhangbin Yu

ABSTRACT

Introduction Establishing the reference interval for pulse oxygen saturation (SpO₂) is essential for sensitively identifying neonatal hypoxaemia due to various causes. However, the reference interval for high altitudes has not yet been established, and existing studies have many limitations. This study will aim to establish the reference interval for various high altitudes and determine whether preductal and postductal measurements at the same altitude vary.

Methods and analysis This is a multicentre, open, cross-sectional study, which will begin in February 2022. Approximately 2000 healthy full-term singleton neonates will be recruited from six hospitals (altitude ≥2000 m) in Qinghai Province, China. The participating hospitals will use a uniform pulse oximeter type. The measurements will be performed between 24 hours after birth and discharge. During the measurement, the neonate will be awake and quiet. Preductal and postductal measurements will be performed. The measurement time, site and results will be recorded and input, along with the collected basic information, into the perinatal cloud database. We will carry out strict quality control for basic information collection, measurement and data filing. We will perform descriptive statistics on the distribution range of the collected data, determine the lower limit value of the reference interval for each hospital and the corresponding altitude, perform curve fitting for the lower limit value, use the altitude as a covariate for the function corresponding to the fitted curve, establish the prediction equation and ultimately determine the reference intervals of each high altitude location.

Ethics and dissemination Our protocol has been approved by the Medical Ethics Committee of all participating hospitals. We will publish our study results in academic conferences and peer-reviewed public journals.

Trial registration number NCT05115721.

INTRODUCTION

Establishing the reference interval of neonatal pulse oxygen saturation (SpO₂) is conducive to more sensitive identification of hypoxaemia due to sepsis, congenital heart disease and other causes. It could reduce the number of arterial blood gas samples and medical costs and improve the quality of nursing.

The now widely used SpO₂ reference interval for neonates 24 hours after birth has been developed based on data from low altitudes. It is not suitable for neonates at high altitudes because many studies have shown a downward trend in the mean SpO₂ of neonates with the increase in altitude.

Unfortunately, no reference interval has been established for high altitudes, and the existing studies on the topic have many limitations. Obtaining accurate data from a suitable reference population is essential in determining reference intervals, requiring strict criteria to match the reference population characteristics to a normal or healthy population. However, previous studies were deficient in the selection of the reference populations. For example, a study conducted by Guo et al. on neonates born at high altitudes found that the thresholds should be adjusted. However, their study population included premature infants. Another study, performed on a population at an altitude...
of 1371 to 2484 m, found a difference in SpO₂ between preterm and full-term infants with no clinical symptoms and signs.13

Differences in measurement sites might contribute to differences in the results, an aspect many previous studies did not focus on.14,15 A multicentre large sample study from Yunnan, China, found significant differences between preductal and postductal measurements.11 However, the highest altitude in that study was only 2202 m. How the measurement site affects the results at higher altitudes needs further study.

Our previous study found only a few reports on the SpO₂ of neonates 24 hours after birth in areas above 2000 m. We also noted that while these previous studies used the mean±SD to describe the results, their mean±2SD exceeded the theoretical maximum of 100%, indicating that their results were not normally distributed.16 IQRs should have been used so that reliable reference intervals could be derived. Furthermore, previous studies were often limited to a specific altitude. However, the SpO₂ decreases with the increase in altitude,16 so the results of these studies can be applied to the specific altitude studied, while they cannot be generalised and applied to other altitudes.

We designed this multicentre, open, cross-sectional study to solve the many limitations of existing studies and establish the SpO₂ reference interval for healthy neonates 24 hours after birth at several high altitudes. This study will provide the basis for neonatal care and medical decision making at high altitudes.

OBJECTIVE

The primary objective of this study is to establish the reference interval of SpO₂ for healthy neonates 24 hours after birth at high altitudes.

The secondary objective of this study is to observe whether there are statistical differences between preductal and postductal measurements at the same altitude.

METHODS AND ANALYSIS

Study design

This is a multicentre, open, cross-sectional study, which will begin in February 2022. More than 2000 healthy neonates delivered consecutively will be recruited from six participating hospitals in Qinghai, China. This study protocol has been approved by the Medical Ethics Committee of all participating hospitals. All participating hospitals will be required to conduct the study in strict accordance with the established rules. Figure 1 presents a summary of the study process.

Jinan University designed and initiated the study, which is the affiliation body of the promoter (ZY). Qinghai Women and Children’s Hospital is the coordinating centre, the training centre and the affiliation body of the main verification person (CL). This is an open study. We welcome additional eligible hospitals to join this study.

The protocol was drafted in accordance with the recommended statement for standardised study protocol items: Recommendations for Observational Studies statement (online supplemental file 1).

Patient and public involvement

The guardians of the neonates and the public were not involved in the study and/or protocol design. Participation in this study will be entirely voluntary. The findings will be disseminated to the guardians and the public through popular science education, health brochures and academic conferences.

Participants

The six participating hospitals from Qinghai Province, China, form the Qinghai Plateau neonatal multicentre collaborative research group. Basic information of the participating hospitals is shown in table 1. This study is planned to begin on 1 February 2022. Healthy neonates who meet the requirements will be consecutively recruited at the six participating hospitals and will undergo SpO₂ measurements. The recruitment will be stopped when the sample size requirements are met at each altitude point. We expect the study will be completed within a year. The infants clinical management will not be affected by whether their guardians decided to participate, refused participation or withdrew from the study.

Inclusion and exclusion criteria

Inclusion criteria are as follows:

Healthy singleton term infants (≥37 weeks) with no disease-related clinical signs or symptoms (eg, cyanosis, respiratory distress and heart murmur).

Exclusion criteria are as follows:

1. Low birth weight (<2500 g).
2. Need for oxygen.
3. Apgar score <7 at 1 or 5 min.
4. Referred to neonatal intensive care unit or neonatology department for various reasons.
5. Discharged within 24 hours of birth.
6. With confirmed congenital disease in infants.
7. Refused participation.

Figure 1 A flow chart showing the study plan.
Table 1  Participating hospitals basic information

<table>
<thead>
<tr>
<th>Hospital name</th>
<th>Altitude (m)</th>
<th>Number of infants delivered in 2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qinghai University Affiliated Hospital</td>
<td>2261</td>
<td>1356</td>
</tr>
<tr>
<td>Qinghai Red Cross Hospital</td>
<td>2261</td>
<td>8725</td>
</tr>
<tr>
<td>Qinghai Women and Children's Hospital</td>
<td>2261</td>
<td>1471</td>
</tr>
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<td>Geermu People's Hospital</td>
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<td>1274</td>
</tr>
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<td>Yushu Prefecture People's Hospital</td>
<td>3680</td>
<td>2278</td>
</tr>
<tr>
<td>Guoluo Tibetan Autonomous Prefecture People's Hospital</td>
<td>4200</td>
<td>1403</td>
</tr>
</tbody>
</table>

Method of measurement
The neonate should be awake and quiet during the measurement, rather than crying or breast feeding. The measurement environment shall be a well-ventilated quiet room without strong light or electromagnetic field interference. The measurement will be performed between 24 hours after birth and discharge. When measuring, the probe will not be placed on the limbs that have just been used or are presently used to measure blood pressure. The surveyor will first clean the skin at the measuring site and keep it dry. The pulse oximeter’s special probe (sensor) will be wrapped around the neonate’s right hand and any foot. The measurement data of the two sites and the measurement time will be recorded after the SpO2 value and the signal waveform of the pulse oximeter were stable for at least 10s.

Standardised management of the operation
All participating hospitals will use the COVIDIEN 10005941SG pulse oximeter (Covidien Company, USA) with a reusable probe to measure SpO2. Each hospital shall select at least two full-time measuring operators. The coordination centre shall carry out standardised training for all measuring operators on 15 January 2022. Assessment will be conducted after training, and qualification will only be obtained after passing this assessment. The coordination centre will also provide standardised videos to all participating hospitals to facilitate repeated learning.

Each hospital will designate at least one high-level physician as the quality control person, who will conduct on-site operational inspections of the measuring personnel at least once a week in their respective hospitals. If the inspection finds that the operator was unqualified, the operator will be trained again. The coordination centre will conduct on-site inspections at least once a month in all hospitals to check whether the operation process and quality control were qualified.

Data collection
The data collected in this study will be divided into two parts, basic information data and measurement data. These data will be uploaded into the perinatal cloud database (https://www.perinatalcloud.com/) developed by the promoter (ZY). This database can be accessed to upload data from a computer or mobile phone at any time. See online supplemental file 3 for details of data collection.

Standardised management of data
The perinatal cloud database will be managed and operated by Jinan University to ensure data security. Each hospital has its independent account, and operators will only be able to browse and fill in their hospital’s data once logged in. Each subject will be given a unique number that will appear when analysing the data and issuing reports to protect the information of the subjects.
We established a data monitoring committee composed of research group chairpersons from the participating hospitals and the promoter. It has the authority to browse all the data and is responsible for monitoring the progress of the study to ensure compliance with the study plan. It will also recommend stopping further recruitment when the enrolment of a sufficient number of participants at a specific altitude has been met. The committee will hold regular quality control and analysis meetings to evaluate the study progress and whether there are any deviations from the protocol. The committee is also responsible for the overall sampling quality control, recruiting other participating hospitals, organizing training, providing training materials, checking, collating and analysing the data and publishing the study results. If the study design needs to be changed, the committee should apply to the Medical Ethics Committee of Qinghai Women and Children’s Hospital for approval. The ethics committee is independent of sponsors, the promoter or any other entity that might influence their decisions. It is responsible for performing the annual audit of the study.

All collected data will be entered into the online database. See online supplemental file 4 for the specific login and filing steps. The data entry will be completed by the data entry personnel designated at each hospital. These personnel will be trained by the coordination centre and pass an examination before taking up their posts. We have adopted a three-level quality control method to ensure data input accuracy. Each hospital shall designate at least one first-class data quality controller responsible for checking each data entry. The coordination centre shall appoint secondary data quality controllers, one for each hospital. These will sample and inspect weekly at least 30% of the input data during that week. The third quality control level will be assumed by the data committee, which will sample and inspect monthly at least 10% of the input data. We have also established a WeChat group (an instant messaging application) in each hospital to disseminate timely feedback on the inspection results for rectification.

Missing data or withdrawal from the trial
We will apply strict quality control procedures during the data collection and filing process to ensure that no data will be missing from the database.

If a subject’s guardian requested to withdraw during or after the trial, we will fully respect this wish, withdraw the informed consent form, remove the information from the database and proceed to recruit new subjects.

Sample size estimation
The main statistical goal of this study is to establish reliable reference intervals. A large enough sample will be needed to generate precision estimates of extreme percentiles (such as the 2.5th percentile); however, there is no standard method for defining “precision”. Theoretically, the SpO₂ should show normal distribution when the sample size of such a cross-sectional study is large enough. We set the precision of this study, that is, the allowable error D, to 0.1 SD, using two-sided tests with a at 0.05. The required sample at each altitude was estimated by PASS V.15 at 387 infants. Moreover, we increased the sample size by 30% to reduce sampling errors and account for possible subject withdrawals, resulting in a sample size of 503 infants at each altitude. There is no need to expand the sample size by measuring site subgroups because preductal and postductal measurements will be performed on the same neonate. Because of the different volumes of infants delivered at each of the participating hospitals in 2020, we anticipate that the end of study at each altitude will occur at different time points. We expect this project will be completed within a year.

Statistical analysis
First, a normality test will be performed on the SpO₂ data at each altitude. If the data show normal distribution, the mean±SD will be used to describe the distribution of SpO₂. Paired-samples t-test will test for differences between the preductal and postductal data. If the two are statistically similar, the preductal and postductal data for each subject will be averaged, and then the lower limit value for the reference interval of each altitude will be determined. If the two measurements differ statistically, the lower limit value of the reference interval will be determined separately for preductal and postductal data at each altitude. If the data are not normally distributed, the median (IQR) will be used to describe SpO₂ distribution, and Wilcoxon signed-rank test will test for differences between the preductal and postductal measurements. The same principle will determine the lower limit value for the reference interval of each altitude.

After determining each lower limit value, we will visualise it using the altitude as the abscissa and SpO₂ as the ordinate to generate a curve fitting the data points. This will allow us to establish the function corresponding to a fitted curve that uses altitude as a covariate and the prediction equation for the reference interval lower limit value. The prediction equation will output the reference interval lower limit value by inputting the corresponding altitude. If the preductal and postductal will differ statistically, the prediction equation will be established separately for each.

Considering the Guoluo Tibetan Autonomous Prefecture People’s Hospital is located at a significantly higher altitude (4200m) than other hospitals, we expect that the lower limit value of the reference interval at this location will be much lower, which may affect the fitting curve. Therefore, we will perform a subgroup analysis by excluding the data points obtained at this altitude. Finally, we will compare both analyses (ie, the one including and the one excluding this altitude) and select an appropriate curve to determine the optimal prediction equation.

All statistical tests will be two tailed, and p<0.05 will be considered significant. Statistical analysis will be performed using Stata V.16 and Python V.3.8.
DISCUSSION

SpO2 is widely used in the field of neonatology. For example, many countries have included it in a routine screening programme for critical congenital heart disease. However, a prerequisite for all these applications is to have a reliable reference interval. Rao et al. used the standard low altitude interval, that is, 95%, as the threshold, to screen for congenital heart disease in infants at an altitude of 1646 m and found that the false-positive rate was 1.5%, much higher than in the low altitude population. The standard of low altitude is still being used during clinical assessments at high altitudes in China, resulting in misdiagnosing many healthy neonates as having hypoxaemia and the consequent huge waste of medical resources. This is one of the reasons we designed this study. Furthermore, this is the first multicentre investigation of SpO2 reference interval in healthy neonates 24 hours after birth at high altitudes. We will establish a prediction equation to address the inability to establish a uniform reference interval because of the curvilinear decrease in the lower limit value of the SpO2 reference interval with the increase in altitude.

This project is a study on the SpO2 of healthy neonates 24 hours after birth. The SpO2 level fluctuates and is unstable during the first 24 hours after birth because it is the transition stage from fetal to neonatal circulation. Several studies on the use of SpO2 to screen congenital heart disease found that the false positive rate of measuring within 24 hours of birth was significantly higher than that 24 hours after birth, confirming that the SpO2 level within the 24 hours of birth was unstable. Besides, we decided to not include multiple measurements after 24 hours of birth in our protocol. This is because: (1) at 24 hours after birth, the neonate has completed the transition from fetal circulation to neonatal circulation; therefore, at 24 hours after birth of healthy neonates, the SpO2 should be in a stable state; and (2) a large multicentre study of 41,097 measurements at altitudes ranging from 0 to 2500 m showed no differences in multiple SpO2 measurements obtained from 24 hours after birth until discharge. Therefore, our protocol focuses on personnel training and quality control to ensure that each SpO2 measurement is accurate, rather than obtaining multiple measurements.

The measurements in this study will require the neonates to be awake and quiet. It will not consider measurements taken while the infants were asleep. This is because neonates are more prone to apnoea or hypventilation during sleep, resulting in transient periods of hypoxaemia, due to immature control of breathing, and higher compliance of the upper respiratory airway and chest resulting in lower respiratory reserve. While these transient periods of neonatal hypoxaemia might be physiological phenomena, the value of SpO2 measured in this case might be inaccurate, which is why our protocol excludes sleep periods.

This study hopes to determine the reference interval at high altitudes by formulating a predictive equation. Theoretically, the precision of the curve fitting to the data points increases with the distribution of the points through various altitudes, resulting in a more accurate predictive equation. The limitation of this study is that thus far, we have recruited only six hospitals at four altitudes, possibly limiting the accuracy of the prediction equation to be generated. We continue to recruit hospitals at other altitudes to address this limitation.

In conclusion, the results of our study will help medical staff identify hypoxaemia in neonates at high altitudes with higher sensitivity, reducing the misdiagnosis rate and medical burden. It will also provide a theoretical basis for determining thresholds to be used when screening for ailments such as congenital heart disease.

ETHICS AND DISSEMINATION

Each participating hospital should be approved by the local Ethics Committee, and the proof of local approval must be sent to the coordinating centre before recruitment can begin at each hospital. Currently, our protocol has been approved by the Medical Ethics Committee of the six participating hospitals. The staff involved will give a detailed explanation to the guardians of all subjects to ensure they have a comprehensive understanding of the study. Written material will also be provided. If they agree to participate, the guardians will sign informed consent forms. Strict confidentiality will be applied to all data collected. The results of this study will be published in academic conferences and peer-reviewed public journals.

Author affiliations

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Contributors ZY and CL planned the study. ZY and BW designed the study. CL provided ethical support. ZY and BW registered the study. ZY is the promoter. CL is the main coordinator and the main verifier. BW, YY, ZL and YW wrote the study protocol and revised the manuscript. RY, ZC, ZW and RL performed a critical revision of the manuscript. ZY and BW provided statistical analysis. All the authors read and approved the final version.

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Disclaimer The funding body play no role in design and management of the study, collection, analysis and interpretation of data and manuscript preparation.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.
REFERENCES


Supplemental file 1

Standard Protocol Items for Observational Studies (SPIROS)

**Table 1**: Checklist of preliminary items

<table>
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<th>Section and topic</th>
<th>Description / sub-categories</th>
<th>Addressed on page number</th>
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<tr>
<td>i) General Information</td>
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<tr>
<td>Title</td>
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<td>Page number</td>
<td>Page number on each page of protocol</td>
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### ii) Introduction

<table>
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<tr>
<th>Background of study</th>
<th>Scientific background of study</th>
<th>Pages 2-4</th>
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<td>Review of prior research</td>
<td>Summary of all previous relevant research</td>
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<th>Justification for conducting the study</th>
<th>Pages 3-4</th>
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<td>Aim</td>
<td>Broader aims and specific objectives of the study</td>
<td>Page 4</td>
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<tr>
<td>Objective of study</td>
<td>Primary and secondary objectives of study</td>
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### iii) Methods

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<td>Study setting</td>
<td>Description of setting, locations, relevant dates, including periods of recruitment/survey, exposure, follow-up, and data collection.</td>
<td>Pages 4-9</td>
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<td>Schedule of study procedure – Figure or table</td>
<td>Figure 1</td>
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<td>Sample size</td>
<td>Estimated number, calculation and assumptions</td>
<td>Page 9</td>
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<td>Power calculation</td>
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<tr>
<td>Sampling procedure</td>
<td>Description of sampling strategy to ensure representativeness and control of potential bias</td>
<td>Page 9</td>
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### Participants

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<th>Description</th>
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<td>Eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. For matched studies, give matching criteria and number of exposed and unexposed.</td>
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<tr>
<td><strong>Case-control study</strong></td>
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<tr>
<td><strong>Cross-sectional study</strong></td>
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### Variables

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<tr>
<td>Exposures- definition of exposure of interest, Predictors, Potential confounders, Effect modifiers</td>
<td></td>
</tr>
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</table>

Page 5

Pages 6-9
| Data Sources/ Measurement | For each variable of interest, give sources of data and details of methods of assessment (measurement).  
|                           | • Describe comparability of assessment methods if there is more than one group  
|                           | • Data collection points table  
|                           | • Blinding procedure | Pages 5-7 and supplementary file 3  
| Blinding procedure: NA |
| Bias | Describe any efforts to address potential sources of bias | Pages 7-9 |
| More specifically- | • Information bias  
|                           | • Selection Bias  
|                           | • Control for confounding |
| Statistical analysis plan | Method of primary / secondary outcomes and additional analysis  
|                           | • Handling of missing data  
|                           | • Post-hoc analysis | Pages 8-10  
<p>| Post-hoc analysis: NA |
| Handling of withdrawals and lost to follow up | Describe the procedures to be followed when a participant ceases participation in the study prematurely or is lost to follow up | Pages 8-9 |</p>
<table>
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<th>Replacements</th>
<th>Provide information on whether or not participants who discontinue the study will be replaced via additional recruitment to maintain the required sample size.</th>
<th>Pages 8-9</th>
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<tr>
<td>Outcome</td>
<td>Define and describe all primary and secondary outcome or lost to follow up</td>
<td>Pages 6 and 9-10</td>
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</table>
| Database management | • Detail plan of database management including:  
  - Data collection (electronic or paper based),  
  - Source data  
  - Data entry  
  - Data editing  
  - Coding  
  - Data storage  
  - Record retention  
  - Data confidentiality | Pages 7-8 |
| Validation of instrument | Reliability / validity of instrument or plan to establish validation                                                                                                               | Page 7 |
| Follow up    | Plan of follow up and addressing lost to follow up                                                                                                                                      | Page 8 |
| Quality control | • Method of quality control  
  • Monitoring (internal and external)  
  • Training of surveyors | Pages 7-8 |
| Quality assurance | Plan of quality assurance                                                                                                                 | Pages 7-8 |
### Expected outcome/results
A brief description of expected outcome or results

<table>
<thead>
<tr>
<th>iv) Ethical consideration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethical approval</td>
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<tr>
<td>Agreement and consent</td>
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<td>Risk / Harm to participants</td>
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<tr>
<td>Adverse event and Severe adverse event reporting</td>
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</tbody>
</table>

### Reporting and dissemination

<p>| Protocol amendments        | Methods of communicating to investigators/IRBs and documenting | Page 8 |
| Dissemination             | How results will be disseminated to participants, practitioners, public | Page 12 |
| Publication Plan          | Who has right to publish; restrictions; authorship guidelines Open Access | Pages 8 and 12 |
| Reporting of early stopping | Dissemination of results if trial is stopped early (for any reason) | NA |</p>
<table>
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<th>vi) Others</th>
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<td>Limitations</td>
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<tr>
<td>Strength of study</td>
<td>Highlight strengths of proposed study</td>
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<tr>
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<td>List of references cited in protocol</td>
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<td>Data collection forms</td>
<td>Summary table of all forms used for data collection at each point of study</td>
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<td>Sample of informed consent form, translated into local language</td>
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<td>Data sharing policy</td>
<td>To describe how data will be made available in public domain.</td>
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<td>Trial registry</td>
<td>For observational studies also registered as trial</td>
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</table>
| Annexures | Data collection form / instruments  
Informed consent form  
Standard operating procedures (SOPs)  
Detailed Statistical analysis plan (SAP) | supplementary file 2, supplementary file 3, supplementary file 4, Figure 1, and Pages 9-10 |
Informed consent

Dear subject’s guardian:

We invite your baby to participate in a study on "Establishing the reference interval for pulse oxygen saturation in neonates at high altitudes." This study will be jointly carried out in Qinghai Women and Children's Hospital, Qinghai Red Cross Hospital, and other hospitals. It is estimated that 10,000 infants will participate voluntarily. This study has been reviewed and approved by the Medical Ethics Committee of Qinghai Women and Children's Hospital.

Why is this study conducted? Establishing the reference interval for pulse oxygen saturation (SpO$_2$) is essential for sensitively identifying neonatal hypoxemia triggered by various causes. However, the reference interval for high altitudes has not been established yet, and the existing studies have many limitations, such as inadequate selection of study participants. This situation is unfavorable for medical decision-making and nursing work. This study aims to establish the reference intervals for a range of high altitudes.

What do I need to do if I participate in the study? If you are willing to let your baby participate in this study, you need to authorize us to extract the basic information of your baby and his/her mother from the medical records and measure the SpO$_2$ 24 hours after birth for this clinical study. The basic information will include the baby’s mother’s name, age, hospitalization number, hospitalization date, home address, telephone number, and ethnicity. We will also retrieve the baby's name, date of birth, gestational age, sex, mode of delivery, birth weight, and Apgar scores (1 and 5 minutes).

Who should not participate in the study? If your baby is in the following circumstances, it will not be within the scope of this study: 1. Low birth weight (<2,500 g). 2. Need for oxygen. 3. Apgar score < 7 at 1 or 5 minutes. 4. Referred to neonatal intensive care unit or neonatology department for any reason. 5. Discharged within 24 hours of birth. 6. With confirmed congenital disease in utero. 7. If you refuse participation.

What are the risks of participating in the study? The monitoring of SpO$_2$ is a non-invasive nursing method. Its purpose is to identify hypoxemia triggered by various causes early. If the sensor is tied too tightly or the binding time is too long, it might result in skin crush. However, the measurement time in our study is very short, and all measurement personnel are strictly trained, so this risk is very small.

What are the benefits of participating in the study? Your baby will not get additional benefits by participating in this study, but the study results will promote the development of neonatal medicine and provide a basis for better medical decision-making and nursing for future babies.

Do I need to pay to participate in the study? We will not charge additional fees for participating in this study, and we will not pay any fees to guardians participating in the project.

Is personal information confidential? Your medical records will be kept in the hospital, and researchers, research authorities, and the ethics committee will be allowed access to them. Any public report on the results of this study will not disclose your identity. We will make every effort to protect the privacy of your medical data to the extent indicated by law.

Do I have to take part in the study? Participation in this study is completely voluntary. You can decline participation or withdraw from the study at any time during its course, with no effect on the
care of your baby by the healthcare workers.

**Subject's Guardian statement**: I have read the above introduction to this study and understand the risks and benefits of participating in this study. I volunteer to participate in this study.

Office of medical ethics committee Tel: __________

I agree ☐ I reject ☐

Signature of the subject's Guardian: __________ Date: __________

Contact number of the subject's Guardian: __________ Mobile phone number: __________

**Doctor's statement**: I confirm that I have explained the details of this study to the guardian, especially the possible risks and benefits of participating in this study.

Doctor's signature: __________ Date: __________

Doctor's contact number: __________ Mobile phone number: __________

Hospital Name: __________
知情同意书

尊敬的受试者监护人

我们邀请您的宝宝参加“建立高海拔地区新生儿脉搏血氧饱和度的参考区间”课题研究。本研究将在青海妇女儿童医院、青海红十字医院等医院共同开展，估计将有 10000 名受试者自愿参加。本研究已经得到青海妇女儿童医院医学伦理委员会的审查和批准。

为什么要开展本项研究？建立新生儿脉搏血氧饱和度的参考区间对敏锐识别因各种病因引起的低氧血症至关重要。然而，目前在高海拔地区尚未建立参考区间。并且现有的研究存在许多局限性，如选取的对象不合理等。这个现状不利于医疗决策和护理工作的开展。本研究的目的是建立高海拔地区各个高度的新生儿出生 24h 以后的脉搏血氧饱和度的参考区间。

如果参加研究，需要做什么？如果您愿意参加本项研究，您需要授权同意我们提取新生儿及母亲的基本信息以及新生儿出生 24h 后的脉搏血氧饱和度的测量数据进行临床研究。基本信息具体为：母亲的姓名，年龄，住院号，住院日期，家庭住址，手机号码，民族。新生儿的姓名、出生日期、胎龄、性别、分娩方式、出生体重、Apgar 评分（1 分钟、5 分钟）。

哪些人不宜参加研究？如果您的宝宝属于以下情况则不属于此项研究范围：1. 低出生体重(<2500g)，2. 需要吸氧，3. 1 或 5 分钟 Apgar 评分<7，4. 出生后因各种原因转至新生儿重症监护室或新生儿科的新生儿。5. 出生后 24 小时内出院的新生儿。6. 宫内已确诊患先天性疾病的新儿。7. 拒绝同意。

参加研究有哪些风险？脉搏血氧饱和度的监测是一种无创的护理手段。目的是早期识别因各种病因导致的低氧血症，可能的风险是传感器捆绑过紧或者捆绑时间过长导致皮肤压伤，但是我们的研究所测量的时间很短，且所有的测量人员都是经过严格的培训，所以这种风险极小。

参加研究有哪些好处？参加本项研究，您的宝宝不会额外获得好处，但这些研究的结果将会促进新生儿医学的发展，为以后新出生的宝宝提供更好的医疗决策和护理提供依据。

参加研究需要支付有关费用吗？我们不会因参与本研究而额外收取费用，同时也不给予参与课题的监护人支付额外费用。

个人信息是保密的吗？您的医疗记录将保存在医院，研究者、研究主管部门、伦理委员会将被允许查阅您的医疗记录。任何有关本项研究结果的公开报告将不会披露您的个人身份。我们将在法律允许的范围内，尽一切努力保护您个人医疗资料的隐私。

我必须参加研究吗？参加本项研究是完全自愿的，您可以拒绝参加研究，或在研究过程中的任何时间退出本研究，这都不会影响医护人员对您的宝宝的护理。

受试者监护人声明：我已经阅读了上述有关本研究的介绍，对参加本研究可能产生的风险和受益充分了解。我自愿参加本研究。
医学伦理委员会办公室电话：

我同意□ 或拒绝□

受试者监护人签名： ___________________________ 日期： __ __ __ 年 __ __ 月 __ __ 日

受试者监护人联系电话： ___________________________ 手机号： ___________________________

医生声明：我确认已向患者解释了本研究的详细情况，特别是参加本研究可能产生的风险和受益。

医生签名： ___________________________ 日期： __ __ __ 年 __ __ 月 __ __ 日

医生的工作电话： ___________________________ 手机号： ___________________________

医院名称： ___________________________
Supplemental file 3

Content of the collected data

Criteria
Inclusion criteria are as follows:
Healthy singleton term infants (≥37 w) with no disease-related clinical signs or symptoms (e.g., cyanosis, respiratory distress, heart murmur).

Exclusion criteria are as follows:
1. Low birth weight (<2,500 g).
2. Need for oxygen.
3. Apgar score <7 at 1 or 5 minutes.
4. Referred to neonatal intensive care unit or neonatology department for various reasons.
5. Discharged within 24 hours of birth.
6. With confirmed congenital disease in utero.
7. Refused participation.

Information collection process:

Hospital name: ______________

Basic information

Subject's mother information
Name:_________________________ Age:________
Hospitalization number:_________ Hospitalization date:_________
Home address:__________________ Ethnicity:___________
Telephone number:______________

Subject information
Name:_________________________ Date of Birth:________
Gestational age:_______________ Sex:_________
Delivery method:_______________ Birth weight:________
Apgar score, 1 minute: _______ points, 5 minutes: _______ points
Measurement data
Measurement time: ________________, ___ h after birth
State of the neonate at the time of measurement: sleeping/awake but quiet (checked)
Pre-ductal SpO₂: _______%               post-ductal SpO₂: _______%
Chinese version

纳入标准
纳入标准：无临床症状及体征（如发绀、呼吸窘迫、心脏杂音等）的健康单胎足月儿。

排除标准：1.低出生体重(<2500g)，2.需要吸氧，3.1或5分Apgar评分<7，4.出生后因各种原因转至新生儿重症监护室或新生儿科。5.出生后24小时内出院的新生儿。6.宫内已确诊患先天性疾病的新儿生。7.绝对同意。

信息采集流程：

医院名称：
基本信息
姓名：
性别：
年龄：

母亲信息
姓名：
性别：

家庭住址：
电话号码：

新生儿信息
姓名：
性别：
出生日期：

胎龄：
分娩方式：

Apgar评分：1分____分，5分____分

测量数据
测量时间：__________h，生后____h
测量时新生儿的状态：睡/醒/清醒但安静（勾选）
右手经皮氧饱和度：_____%
任意一脚经皮氧饱和度：_____%
Supplemental file 4

Perinatal Cloud Database Filing Steps

Please follow the steps below:

STEP 1 Enter the hospital's exclusive account and password to log into the database.
STEP 2 Click "Add New Case" to generate a unique digital number for this case.
STEP 3 Fill in the basic information of the subject's mother and the subject.
STEP 4 Fill in the measurement data.
STEP 5 Check the entered data.

The following are the detailed steps:

STEP 1 Enter the hospital's exclusive account and password to log into the database.

STEP 2 Click "Add New Case" to generate a unique digital number for this case.

STEP 3 Fill in the basic information of the subject's mother and the subject.

1. Subject's mother information
2. Subject's information

STEP 4 Fill in the measurement data.

STEP 5 Check the entered data.
数据填报请按以下步骤执行：
第一步：输入各家医院专属账号及密码登录数据库。
第二步：点击新增病例，生成此病例唯一数字编码。
第三步：填报受试者的母亲及受试者的基本信息。
第四步：填报测量数据。
第五步：对填报数据进行核对、质控。

以下为详细步骤：
第一步：输入各家医院专属账号及密码登录数据库。
第二步：点击新增病例，生成此病例唯一数字编码。
第三步：填报母亲及新生儿基本信息。

母亲信息

<table>
<thead>
<tr>
<th>母亲姓名</th>
<th>母亲手机号</th>
<th>母亲年龄</th>
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<tr>
<th>住址信息</th>
<th>母亲身份证号</th>
<th>围产云母亲编号</th>
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### 新生儿信息

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<th>两性畸形</th>
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<tr>
<th>分娩方式</th>
<th>阴道分娩</th>
<th>产钳或胎吸产阴道分娩</th>
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<th>天</th>
<th>出生体重</th>
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<tr>
<th>Apgar评分</th>
<th>1分钟</th>
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### 第四步：填报测量数据。

<table>
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<tr>
<th>测量时间</th>
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<thead>
<tr>
<th>测量时患儿情况</th>
<th>睡觉</th>
<th>清醒并安静状态</th>
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<tr>
<th>右手经皮氧饱和度</th>
<th>左手经皮氧饱和度</th>
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### 第五步：对填报数据进行核对、质控。

<table>
<thead>
<tr>
<th>时间</th>
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