Data Management and Site-Visit Monitoring of the Multi-Center Registry in the Korean Neonatal Network

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INTRODUCTION

The Korean Neonatal Network (KNN), a nationwide prospective registry of very-low-birth-weight (VLBW, \(<1,500\) g at birth) infants, was launched in April 2013. Data management (DM) and site-visit monitoring (SVM) were crucial in ensuring the quality of the data collected from 55 participating hospitals across the country on 116 clinical variables. We describe the processes and results of DM and SVM performed during the establishment stage of the registry. The DM procedure included automated proof checks, electronic data validation, query creation, query resolution, and revalidation of the corrected data. SVM included SVM team organization, identification of unregistered cases, source document verification, and post-visit report production. By March 31, 2015, 4,063 VLBW infants were registered and 1,693 queries were produced. Of these, 1,629 queries were resolved and 64 queries remain unresolved. By November 28, 2014, 52 participating hospitals were visited, with 136 site-visits completed since April 2013. Each participating hospital was visited biannually. DM and SVM were performed to ensure the quality of the data collected for the KNN registry. Our experience with DM and SVM can be applied for similar multi-center registries with large numbers of participating centers.

Keywords: Clinical Data Management; Site-Visit Monitoring; Prospective Registry; Multi-Center Study

MATERIALS AND METHODS

Clinical data management  
For proper management of clinical data collected for the KNN...
registry, a DM team was organized. The DM team consists of staff neonatologists at the major academic hospitals in the Seoul metropolitan area and clinical research associates (CRAs) at the headquarters hospital. All clinical data of the VLBW infants were entered into the e-CRF established using the iCReaT (Internet based Clinical Research and Trial management system). The iCReaT is a web-based electronic data capture system developed by the Korea CDC. One hundred and sixteen clinical variables are collected from the source documents (electronic or paper medical records) into the e-CRF at each participating hospital. The clinical variables collected are shown in Table 1. All personnel responsible for clinical data entry at each hospital completed a basic educational course officially provided by the Korea CDC for the usage of the iCReaT system. A manual of operation (MOP) for data entry was developed by the KNN short-term registry task force and distributed to all participating hospitals to ensure a clear and uniform definition of each variable by all data entry personnel. Data entry into the e-CRF at each hospital was restricted to the PI or a CRA delegated by the PI of that hospital. The PI must be the staff neonatologist and a CRA delegated by the PI could be another staff neonatologist or attending nurse at the participating hospitals. Rotating residents or fellows were not eligible as CRAs to maintain consistency of data entry.

After clinical data was entered on the e-CRF and confirmed by the PI of the participating hospital, data validation was performed by CRAs in the DM team. The DM process included data cleaning through electronic review using an external program for logic errors, query creation, query resolution, and corrected data revalidation (4). Because the e-CRF developed for the KNN registry included minimal text data, manual data review was not performed. The queries created fell into two categories: data entry errors and reconfirm errors. A reconfirm error occurred when a query was created but the data was confirmed as correct. The detailed process of DM was as follows: 1) the data were checked if they were within a preset range of values according to the distributed MOP for data entry; 2) the data were checked for logic errors using SAS software (SAS® 9.4, SAS Institute, Cary, NC, USA); 3) queries were created using the iCReaT system; 4) the corresponding PI was notified of the creation of queries via e-mail; 5) query resolution and data correction was confirmed; 6) additional queries were created for errors requiring further confirmation; and 7) the corrected data were revalidated and frozen if no further errors were found. A schematic outline of the KNN DM process is illustrated in Fig. 1. Authorization for data entry was given to the PI or a CRA delegated by the PI at the participating hospital, but data confirmation was authorized only by the PI. Data locking was under the authority of CRAs in the DM team at the headquarters hospital. The PI at each participating hospital only had access to the data collected from his or her hospital. Access to the whole data set from all participating hospitals was restricted to the CRAs in the DM team.

**Table 1. Clinical variables collected in the KNN registry**

| Category | Variable |
|----------|----------|
| Identification code | Hospital code, patient code, patient initial, subject initial, birth date, sex, date of entry agreement, age at entry |
| Maternal information | Age, parity, gravidity, amniotic fluid amount, educational status for parents, country of origin for parents, marital status |
| Delivery information | Premature rupture of membrane, antenatal steroid, delivery mode |
| Basic information | Birth date, birth place, admission date, gestational age, apgar score, initial resuscitation at delivery room (oxygen/positive pressure ventilation/intubation/cardiac massage/epinephrine), birth weight/height/head circumference, at admission temperature/pH/base excess |
| Respiratory | Air leak, pulmonary hemorrhage, respiratory distress syndrome, surfactant (use/purpose/place/time/frequency) steroid (use/method/type of drug), at age of 28th day (use for oxygen/ventilator), at 36th week of corrected age (date/oxygen use/ventilator), duration of invasive/noninvasive ventilator/oxygen |
| Cardiovascular | Patent ductus arteriosus (PDA) (medication/type/timing), PDA ligation (date) |
| Central nervous system | Neonatal seizure, intraventricular hemorrhage, post-hemorrhagic hydrocephalus, cystic periventricular leukomalacia |
| Infectious | Congenital infection, bacterial/nonbacterial infection, meningitis, prophylactic antifungal agent use |
| Gastrointestinal | TPN duration, necrotizing enterocolitis (≥ stage 2/operation), idiopathic intestinal perforation (operation) |
| Retinopathy of prematurity | Retinopathy of prematurity (stage/operation/anti-VEGF treatment) |
| Anomaly | Serious congenital anomalies |
| Others | Full feeding day, transfusion of red blood cells |
| Discharge information | Date, hospitalization duration, type of discharge, assistant equipment or treatment, transfer (name of hospital/purpose), death (cause), at discharge (height/weight/head circumference) |

This table was cited from the reference #1.
report production. A total of 55 hospitals had participated in the KNN registry across the country by March 31, 2015. Participating hospitals with more than five registered VLBW infants were subject to SVM. For SVM, an SVM team was organized by dividing the country into the Seoul metropolitan area and six provinces (Fig. 2). In the first half of the registry period, the SVM team consisted of CRAs at headquarters hospital and PIs at participating hospitals located in the Seoul metropolitan area. However, for the second half of the registry period, PIs at participating hospitals in each province joined the SVM team and participated in SVM in their province. All participating hospitals were visited biannually. One or two PIs and one CRA visited one or two hospitals at a time. During SVM, institutional review board (IRB) approval status, informed consents, investigator files, and the e-CRF were checked. The most crucial parts of SVM were the identification of unregistered cases and source document verification. Unregistered cases were identified by comparing the number of VLBW infants admitted to the hospital with the number of created IDs in the e-CRF during a certain period of time. If unregistered cases were found, the reasons for omission were documented. Source documents were electronic medical records at most of the participating hospitals. Five to ten percent of the registered cases (at least five cases) were randomly selected and verified for any differences in 23 predetermined clinical variables between the medical records and e-CRF. After SVM, follow-up letters reporting the results of the site-visit and a corrective action request form were sent to the PI of the hospital by the CRA who conducted the SVM. The requested corrective action was to be completed and the corrective action request form signed and answered by the PI at the hospital within one month after the SVM. The CRA who performed the site-visit confirmed the receipt of the corrective action request form and provided feedback to the PI at the hospital visited.

**Ethics statement**

In all KNN-participating hospitals, a grant for the KNN registry was obtained from the IRB at each participating hospital and consent from the parents of VLBW infants was obtained (MED-OBS-13-014).

**RESULTS**

**Clinical data management**

By March 31, 2015, 4,063 VLBW infants were registered in the KNN registry, with 1,693 queries created since April 2013 (Fig. 3). As of March 31, 2015, 1,629 queries have been resolved and 64 queries remain unresolved. Of the 1,629 created queries, 1,515 queries indicated a data entry error and 114 queries, a reconcile error. A second query was created for 67 cases (Fig. 4). The ratio of the number of queries created to the number of registered VLBW infants was quite different among the participating hospitals, ranging from 6.3% to 211.1% (median, 32.1%). Queries were created in all variables in the e-CRF; but concentrated on several variables. The three most common variables for query creation were the date of 36 weeks postmenstrual age, bronchopulmonary dysplasia, and total duration of invasive mechanical ventilation. Half of the queries were created for these three
variables, from the 116 variables in the e-CRF. The average time between query creation and query resolution also differed greatly among the participating hospitals, ranging from 3 days to 180 days (median, 18 days).

**Site-visit monitoring**

By November 28, 2014, 52 participating hospitals had been visited, with 136 SVMs completed since April 2013. Each participating hospital was visited biannually. In 2013, 37 participating hospitals were visited once between September 5 and December 18. In the first half of 2014, 47 participating hospitals were visited from April 29 to August 4. In the second half of 2014, 52 participating hospitals were visited from October 8 to November 28. The 52 participating hospitals were located throughout the country but were concentrated in the Seoul metropolitan area (32/52) (Fig. 2). By November 28, a total of 42 personnel, including three CRAs at the headquarters hospital and 39 PIs at the participating hospitals, contributed to 136 SVMs in a SVM team since April 2013 (Fig. 5). One PI participated in SVM 1-6 times per year (median, twice per year). Each SVM lasted 2-4 hr. The IRB approval status, informed consents, investigator files, and e-CRF were checked by the visiting CRA, requiring about one hour. Identification of unregistered cases and source document verification were performed by the visiting PI, requiring about 2-3 hr; depending on the number of registered VLBW infants. The reasons for unregistered cases fell into three categories: death of the subject, absence of parental consent, or delayed registration. The problem of deregistration due to death of the subject was resolved by modifications to the study protocol. An updated study protocol enabled the inclusion of dead VLBW infants without parental consent. This updated study protocol was granted by the IRB at each participating hospital. Causes of discrepancy between the source document and the e-CRF fell into four categories: simple entry error, misunderstanding of the inclusion and exclusion criteria, misunderstanding of the definition of the variables, and differing interpretations of clinical findings. Problems identified during source document verification were archived for incorporation into an updated version of the MOP for data entry. The last part of the site-visit was used to interview the PI at each hospital about difficulties in data registration at the hospital. Problems identified during SVM and feedback from the visited hospitals were discussed and incorporated into an updated checklist for subsequent SVMs by the data subcommittee members at periodic off-line meetings.

**DISCUSSION**

The KNN registry project is the first monumental nationwide registry for preterm infants overseen by the Korean Society of Neonatology. As of March 31, 2015, 55 hospitals, including almost all major NICUs in Korea, have participated. DM and SVM were crucial in ensuring data quality in the collection of 116 clinical variables from the 55 participating hospitals. Efforts to ensure data quality began at the e-CRF development stage. A short-term registry task force was formed to select the short-term clinical variables to be collected and prepare a detailed MOP for each variable. Thanks to the detailed MOP for data entry, confusion in data entry at the participating hospitals was markedly reduced. However, discrepancies in the definitions of clinical variables continued to be a problem throughout the registry project. Thus, a complementary on-line bulletin board to answer data entry questions was established and operated by the official KNN registry homepage (http://knn.or.kr/index.jsp). Furthermore, entry errors from misinterpretation of the definition of each variable were found, discussed, and corrected during the site-visits. To reduce errors in the data entry phase, automated proof checks were programmed into the e-CRF. However, these automated proof checks played a limited role (miss-
ing values and simple range checks) in the reduction of data entry errors. Therefore, electronic review for the detection of more complex logic errors was performed using an external program (SAS®) by the CRAs in the DM team at the headquarters hospital after data entry and confirmation by the PIs at the participating hospitals. Queries were created from the data entry errors and sent to the corresponding hospital to be resolved by the PI at his or her hospital. Revalidation of the corrected data was performed by the CRAs in the DM team and second queries were sent to the corresponding hospital when necessary. Through this cycling DM process, data quality could be ensured (5).

The environment of the 55 hospitals participating in the KNN registry varied enormously, not only in the number of NICU beds and attending doctors or nurses, but also in the severities of the conditions of the NICU patients (6). Therefore, a careful understanding of the different environments at each participating hospital was crucial to enroll and maintain as many participating hospitals as possible. In this respect, SVM is an important part of the KNN registry. Thanks to the spontaneous contributions of 39 PIs at participating hospitals, 136 SVMs were performed since the establishment of the KNN registry. The number of participating hospitals increased from 37 to 55 during the project. Of note is the lack of hospitals dropping out of the KNN registry since the beginning of the project. SVM might have encouraged PIs in the participating hospitals to continue registration of VLBW infants. Data quality was also improved through SVM. The identification of unregistered cases at each participating hospital reduced selection bias, which contributes to erroneous conclusions. Source document verification was a crucial part of SVM, along with the identification of unregistered cases. Several errors that were not recognized through the DM process were identified and corrected on-site. Furthermore, confusion over the inclusion or exclusion criteria, definition of the variables, and differing interpretations of the clinical findings were identified and resolved during the site-visit. Although the importance of SVM cannot be emphasized enough, it is not feasible to perform biannual site-visits for 52 participating hospitals due to limited financial and human resources. If not for the voluntary participation of 39 PIs, SVM of the 52 hospitals...
would have been impossible. The KNN registry is a nationwide project, and region-based SVM would be more desirable in the future. In the second half of the registration period, PIs in each province participated in SVM in their province, together with the SVM team from the Seoul metropolitan area. PIs will gradually take over local SVM in their provinces, making the project regionalized and sustainable. Based on the passion and voluntary devotion that the Korean neonatologists have shown in the KNN registry, a more advanced nationwide multi-center research network which targets quality improvement and clinical trials will be able to be established.

Maintenance of data quality is crucial in this multi-center registry project. In the KNN registry, data quality was ensured by clinical DM and SVM. By combining these two approaches, the weakness of each method could be complemented. The experience of the KNN registry using clinical DM and SVM can be applied for similar multi-center registry projects with a large number of participating centers.

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DISCLOSURE

All authors have no potential conflicts of interest.