Combining Electronic Diary Seizure Data with Visit-Based Seizure Data in the MONEAD Study

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ABSTRACT

Electronic diary (eDiary) mobile applications can be a useful tool to collect subject-reported data outside of scheduled study visits. However, integrating eDiary data with data stored in a traditional electronic data capture (EDC) system can present unique challenges. eDiary applications sometimes function under different business rules than traditional EDC systems. Collecting data in different software systems makes linkage of records more difficult, even if a common key exists. This paper describes methods used in the Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs (MONEAD) study to combine daily subject-reported seizure data recorded in an eDiary application with clinically assessed seizure information collected in the study EDC system.

INTRODUCTION

Electronic subject diaries are a commonly used method to collect subject-reported outcomes (1,2). These instruments allow patients to report data directly and closer to the medical moment, when subject recollection is most accurate (1,2). Electronic subject diary (eDiary) mobile applications are an option that facilitates data collection by subjects and eliminates the need for data entry by clinical staff. These applications have additional benefits over paper diaries, namely the presence of an audit trail and the ability to design the application to improve subject compliance and accuracy (2,3).

There are several challenges to eDiary use from a statistical programming perspective. First, there are often large amounts of missing data. Electronic diaries have been shown to have higher rates of compliance than paper diaries (3,4,5,6), but missing data is still a significant challenge. Data entered by subjects are also more likely to contain data entry errors and inconsistencies than data entered by trained clinic staff. This problem can be mitigated but not eliminated by review of the eDiary data during clinic visits and by the querying of discrepancies by data management staff (1,7). Finally, eDiary applications are often separate software packages with fundamentally different architecture than a study’s traditional electronic data capture (EDC) system (2). eDiary applications are designed for frequent data collection and must be usable by subjects with no specialized knowledge of clinical research, while traditional EDC systems are used by clinical research professionals who have undergone training on the software. The incorporation of eDiary data requires careful planning and consideration throughout the entire study.

The MONEAD study is a prospective, observational, multi-center investigation of the effect of antiepileptic drugs on pregnant women with epilepsy and their children. The study includes control groups of non-pregnant women with epilepsy, as well as healthy pregnant women without epilepsy and their children. Pregnant subjects are enrolled during pregnancy followed until 9 months postpartum, and non-pregnant controls are enrolled for 18 months. A traditional EDC system is used to collect data obtained primarily via clinic visits occurring every three months and medical record abstraction. In addition, daily, subject-reported data are captured through the use of an eDiary mobile application. The MONEAD eDiary is used to collect daily seizure data for both pregnant and non-pregnant women with epilepsy, as well as medication, mood and sleep data for all maternal and non-pregnant subjects. Subjects were given an iPod Touch at enrollment with the MONEAD eDiary application installed, or had the option to install the application on their iPhone or other iOS device. Clinic staff reviewed eDiary entries with the subject at every clinic visit as an adjudication mechanism to ensure optimal eDiary compliance and to ensure that all relevant events were properly recorded.

The effect of pregnancy on seizure activity is a primary outcome measure in the MONEAD study, and the combined data from both traditional EDC and eDiary sources is a critical component of this analysis. The programming required to combine data from both sources had several challenges. These include the linking of records between the two systems, how to handle missing seizure records in the eDiary, and
how to treat observations captured via a pop-up window in the eDiary application. The rest of this paper discusses programmatic solutions to each of these issues.

LINKAGE OF RECORDS

The eDiary used in the MONEAD study is a mobile application developed by a different developer than the main study EDC system (hereafter referred to as "traditional EDC system"). This resulted in some challenges linking the two data sources. When a subject with epilepsy enrolls in the MONEAD study, she is asked about the different types of seizures that she experiences, and instructed to give each type of seizure a unique name of her choosing. This name is entered into the traditional EDC system, and in addition, is entered by the same name in the eDiary, which is used by the subject for reporting daily seizure occurrence. The eDiary software assigns each seizure a unique identification number, but this number is not accessible to the subject and is not stored in the traditional EDC system. Data stored in the traditional EDC system (hereafter referred to as "clinic data") and eDiary data are entered under a common subject identification number, which facilitates linking of records. However, linkage of detailed seizure classification data collected at clinic visits with the eDiary seizure data requires comparison between free text fields. The SAS® UPCASE and COMPBL functions can be used, respectively, to change all text to the same case and change multiple consecutive blank spaces to a single space:

```sql
PROC SQL;
CREATE TABLE seizures AS
SELECT ediyary.patid, ediyary.seizure_name AS eDiaryName,
     clinic.seizure_name AS clinicName
FROM ediyary LEFT JOIN clinic
ON ediyary.patid=clinic.patid
   and UPCASE(COMPBL(ediyary.seizure_name))=
     UPCASE(COMPBL(clinic.seizure_name));
QUIT;
```

**Figure 1.** Example of the use of the SQL procedure to join eDiary and clinic data.
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Joining data via a free text field is difficult and prone to error. Use of these functions can improve the accuracy to a degree by removing variations in case and spacing. However, data entry errors by the subjects or the clinic staff are common and many cannot be addressed programmatically after the fact. Programmatic identification of discrepancies between the two free text fields began early in the study. This program identifies the seizures reported in the eDiary that cannot be linked to a record in the seizure classification table in the traditional EDC system:

```
PROC SQL;
  CREATE TABLE ediyary_only AS
    SELECT ediyary.patid, ediyary.seizure_name AS eDiaryName,
           clinic.seizure_name AS clinicName
    FROM ediyary LEFT JOIN clinic
    ON ediyary.patid=clinic.patid
    and upcase(compbl(ediary.seizure_name))=
      upcase(compbl(clinic.seizure_name));
  WHERE clinic.seizure_name IS NULL;

  CREATE TABLE ediyary_queries AS
    SELECT ediyary_only.patid, ediyary_only.eDiaryName,
           clinic.seizure_name AS clinic_names
    FROM ediyary_only LEFT JOIN clinic
    ON ediyary_only.patid=clinic.patid;
  QUIT;

PROC REPORT data=ediary_queries NOWD;
  COLUMNS patid eDiaryName clinic_names;
  DEFINE patid / ORDER "Subject ID";
  DEFINE eDiaryName / ORDER "eDiary Name";
  DEFINE clinic_names / DISPLAY "Name(s) on clinical form";
RUN;
```

**Figure 2.** Output from the REPORT procedure identifying all seizures in the eDiary that cannot be matched to the clinic data. The report also lists all seizure names existing in the traditional EDC system for that subject.

<table>
<thead>
<tr>
<th>Subject ID</th>
<th>eDiary Name</th>
<th>Name(s) on clinical form</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC2</td>
<td>GM</td>
<td>AURA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GRAND MAL</td>
</tr>
</tbody>
</table>

By beginning data cleaning activities early in the study, data linkage problems can be resolved shortly after data is entered, and prior to analysis and data lock, improving data quality.
IMPUTING MISSING DATA

Daily eDiary data collection often results in large amounts of missing data. In the MONEAD study, many study days had no response entered by a given subject. Separate from the daily eDiary report, the traditional EDC system captured subject responses to questions pertaining to joint review of eDiary data between the subject and clinical site staff. Specifically, subjects were asked at each clinic visit whether they had experienced a seizure since the last visit. This question was used to ensure that all seizures were captured in the eDiary, but it can also be used as a source of data for imputation. If the subject reported no seizures since the last visit in the traditional EDC system, the missing eDiary daily seizure data points can be imputed as “no seizure” for that time period. The LAG function allows for easy identification of the previous visit date:

```bash
PROC SORT data=clinic_data;
  BY patid visit_date;

DATA to_impute;
  SET clinic_data;
  BY patid visit_date;
  imputeStart=LAG(visit_date);
  imputeEnd= visit_date-1;
  IF seizure_since_last_visit='N';
RUN;
```

Figure 3. Example of the use of the LAG function to determine the previous visit date

The eDiary data is collected daily, while the clinic visits occur approximately every 90 days. The clinic data must be reshaped into daily data in order to combine the two sources. Once the date of the previous visit is identified, a %DO iterative statement allows the user to create one record per day for each subject visit, starting with the last visit date and ending the day before the current visit:
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```proc sql noprint;
   select count(*) into :numRec from to_impute;
quit;
```

```data impute_all;
   set _null_
   run;
```

```%macro imputing;
   %do i=1 %to &numRec;
      data new_records;
         set to_impute;
         if _n_=&i;
         do date=imputeStart to imputeEnd;
            source='Clinic Data';
            seizureOccurred='N';
            output;
         end;
      end;
   run;
```

```data impute_all;
   set impute_all new_records;
run;
```

```%end imputing;
%mend imputing;
```

Figure 4. Partial data set created by the IMPUTING macro. Records are created for subject ABC1 from 02Jan2014 through 02Jul2014, and 07Oct2014 through 04Jan2015. Records are created for subject ABC2 from 01Jul2014 through 30Oct2014.
This new data set can be combined with the data in the eDiary to impute seizure data for days where the subject did not enter any seizure information. The approach outlined here also constitutes a quality check of the eDiary data, allowing for identification of subjects whose eDiary data conflicts with the data given at the clinic.

**USING POP-UP WINDOW DATA**

One of the advantages of an electronic diary over a paper diary is the ability to prompt subjects to enter data at specific time points. The MONEAD eDiary application includes a pop-up window asking the subject if they had a seizure the previous day. This pop-up appears regardless of whether the subject opens the MONEAD application on their device. While subjects are instructed to open the application and enter detailed seizure information, subjects often fail to comply with these additional data entry steps. In these cases, data from pop-up window becomes a useful data point to determine whether a seizure occurred. Because this pop-up record refers to “yesterday”, additional programmatic steps must be taken to modify the seizure record on the preceding day based off the response to the pop-up. To ensure traceability of records, we re-populate the record ID field with a value that reflects the date of the original record and note the source of the data:

```plaintext
DATA yesterday;
SET ediair;
WHERE seizure_yesterday IN ('Y','N');
recordID = 'P'||STRIP(PUT(date,YYMMDD6.));
source='Pop-up window';

   date=date-1;
   seizureOccurred=seizure_yesterday;
RUN;
```

**Figure 5.** Example of pop-up window data being modified for use in analysis

This data set can be combined with the daily eDiary entries to fill in missing data points. A limitation of the pop-up data is that it does not supply additional detailed seizure data such as type, number or duration of seizures. However, it can still provide some information that would otherwise be missing. To make full use of the benefits of an eDiary, it is important to understand how the software works and what information is being populated in the output data sets.

**CONCLUSION**

Electronic diary data is a valuable supplement to visit-based clinical data collection. When an eDiary is used in a study, the statistical programming team should familiarize themselves with how the software
works and begin planning how to combine the data with the rest of the study data. By starting early in the process, this allows sufficient time to resolve discrepancies in the data and resolve any questions about the data structure. eDiary data requires extra effort to incorporate into analysis, but the clinical data collected makes the effort well worth it.

REFERENCES


ACKNOWLEDGMENTS

The authors would like to thank the clinical principal investigators, Kimford J. Meador and Page B. Pennell, and all members of the MONEAD Study Group, as well as the women and families who have given their time to participate. The MONEAD study is supported by the National Institute of Neurological Disorders and Stroke (NINDS) and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), grant numbers U01-NS038455 and U01-NS050659.

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