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Review

Seizure diaries for clinical research and practice: Limitations and future prospects

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ABSTRACT

Purpose: An NINDS-sponsored conference in April of 2011 reviewed issues in epilepsy clinical trials. One goal was to clarify new electronic methods for recording seizure information and other data in clinical trials.
Methods: This selective literature review and compilation of expert opinion considers advantages and limitations of traditional paper-based seizure diaries in comparison to electronic diaries.
Key findings: Seizure diaries are a type of patient-reported outcome. All seizure diaries depend first on accurate recognition and recording of seizures, which is a problem since about half of seizures recorded during video-EEG monitoring are not known to the patient. Reliability of recording is another key issue. Diaries may not be at hand after a seizure, lost or not brought to clinic visits. On-line electronic diaries have several potential advantages over paper diaries. Smartphones are increasingly accessible as data entry gateways. Data are not easily lost and are accessible from clinic. Entries can be time-stamped and provide immediate feedback, validation or reminders. Data can also can be graphed and pasted into an EMR. Disadvantages include need for digital sophistication, higher cost, increased setup time, and requiring attention to potential privacy issues. The Epilepsy Diary by *epilepsy.com* and Irody, Inc. has over 13,000 registrants and *SeizureTracker* over 10,000, and both are used for clinical and research purposes. Some studies have documented patient preference and increased compliance for electronic versus paper diaries.
Seizure diaries can be challenging in the pediatric population. Children often have multiple seizure types and limited reporting of subjective symptoms. Multiple caregivers during the day require more training to produce reliable and consistent data.
Diary-based observational studies have the advantages of low cost, allowing locus-of-control by the patient and testing in a "real-world" environment. Diary-based studies can also be useful as descriptive "snapshots" of a population. However, the type of information available is very different from that obtained by prospective controlled studies. The act of self-recording observations may itself influence the observation, for example, by causing the subject to attend more vigilantly to seizures after changing medication.
Pivotal anti-seizure drug or device trials still mostly rely on paper-based seizure diaries. Industry is aware of the potential advantages of electronic diaries, particularly, the promise of real-time transmission of data, time-stamping of entries, reminders to subjects, and potentially automatic interfaces to other devices. However, until diaries are validated as research tools and the regulatory environment becomes clearer, adoption of new types of diaries as markers for a primary study outcome will be cautious.
Significance: Recommendations from the conference included: further studies of validity of epilepsy diaries and how they can be used to improve adherence; use and further development of core data sets, such as the one recently developed by NINDS; encouraging links of diaries to electronic sensors; development of diary privacy and legal policies; examination of special pediatric diary issues; development of principles for observational research from diaries; and work with the FDA to make electronic diaries more useful in industry-sponsored clinical trials.

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1. Introduction

Most clinical trials of epilepsy therapies include seizure frequency, as documented on calendar diaries, as a primary outcome variable. This places self-reported diaries at a pinnacle of importance in the development of new treatments for epilepsy, but little information exists on the accuracy or validity of these tools. On April 30, 2011, the National Institutes of Neurological Diseases and Stroke (NINDS) of the United States National Institutes of Health sponsored a conference on clinical trials in the field of epilepsy, at which seizure diaries were discussed. This article reviews seizure diaries as they now exist and possible directions for the near future.

Diaries are a form of so-called patient-reported outcomes [33]. The Food and Drug Administration (FDA) has provided guidance, in general, on the development of PROs [13]. A review of patient-reported outcomes (PROs) in epilepsy [35] listed 61 articles involving design and validation of PROs, including scales for Quality of Life, Seizure Severity and Psychosocial Inventories but none analyzing diaries, which is perhaps the most fundamental PRO. Under ideal circumstances, diaries developed for research and clinical trials would also be useful for direct patient care [15]. Seizure diaries have already been found to be useful for patient-based prediction of subsequent seizures [19]. However, diaries designed primarily for clinical care or seizure prediction are not the subject of this review.

2. What information should be recorded in a seizure diary?

Before using a seizure diary, subjects need to prospectively describe and codify their various seizure types, in conjunction with study organizers. Patients have the capability of naming their own seizures as they perceive them. For example, seizure type "A" might be described as a feeling of déjà vu; type "B" would be representative of déjà vu followed by confusion, lip-smacking and fumbling; and type "C" would reflect an event of loss of consciousness with falling and shaking. Subjects will be instructed to record the type (A, B or C) and quantity of each seizure type in a suitable calendar box for each study day. A blank box for a calendar date may be presumed to reflect no seizures on that day, although this may not be acceptable in all cases, and some studies require active affirmation by checking a box to indicate that no seizures occurred on a particular day. Paper diary calendars are usually collected at study visits or mailed at intervals to a study center.

National Institutes of Neurological Diseases and Stroke (NINDS) has developed a set of common data element forms to encourage consistent data collection in epilepsy clinical trials. The recommended seizure diary form can be found at http://www.commondataelements.ninds.nih.gov. The form includes the following instructions:

1. Take this diary home and use it every day to keep track of your seizures.
2. The staff will review your seizures with you and each seizure type will be assigned a special code.
3. If you have a seizure, record the number of seizures and the type of seizure (using the assigned code) on the diary.
4. If you do not have any seizures on that day, mark the 'no seizure' box.
5. Bring the seizure diary with you to every appointment.

In a daily calendar covering 31 days per page, subjects are asked to check a box marking "no seizures" or to write down the number of seizures they had each day for each of their seizure types.

Some study diaries record additional details, including: duration or severity of seizures, seizure clustering, time of a woman's menstrual cycle, missed medications, extra medications, precipitating factors, medication regimen, medication side effects and mood. While documentation of seizure type and frequency is the industry standard (and the basic requirement from the FDA) for providing proof of efficacy of therapies, it should be noted that this information alone is far from comprehensive in understanding longitudinal relationships of seizure events. In addition, since clinical trials often only capture data on the number (frequency) of seizures, significant changes in severity of seizures and other co-morbidities may be completely missed. Comorbidities are usually captured in standard adverse event reporting systems.

Because of the variability of questions posed in clinical trials, one type of diary will not apply for all clinical studies. Trying to anticipate all possible needed information would result in requesting so much information on the calendar that it would become impractical to use. The best diaries collect only the information that is needed for a particular clinical or research question, with an efficient and user-friendly design. The NINDS Common Data Element Diary comprises a "core" of data, such as seizure counts, that would likely be required for any studies or clinical care situations. This information can be supplemented as needed by additional required data for particular uses.

3. Potential problems with seizure diaries

Table 1 lists the potential problems with interpretation of seizure diaries.

Entering information in diaries requires at least moderate intellectual capability and literacy, which is not present in all patients with epilepsy. However, the increasing penetration of smartphones indicates that most people will have usable input platform in the near future. Studies restricted to those capable of using paper or electronic diaries may introduce selection bias into the trials. Caregivers can assist with diary entries, but caregivers are rarely in contact with the subjects on a continuous basis and therefore may miss some seizures. Paper diaries are prone to being misplaced or lost and have no easy method for backup and reconstruction of information.

4. Electronic diaries

Electronic diaries provide an alternative to the traditional paper-based seizure diaries. These may be implemented on dedicated handheld devices or as software loaded on a standard smartphone or another commercially available device. Such devices potentially allow programming to improve data validity, real-time transmission of data, reminders to subjects, and other features. However, handheld devices and smartphones may also be lost, although some allow uploads of data when patients are connected to wireless networks.

Adherence (compliance) is a key issue in epilepsy care, and it applies equally to taking medications and completing a seizure diary. Entering information in near-real-time could be expected to improve both compliance and accuracy. Many epilepsy clinicians have witnessed patients frantically filling out diaries in a clinic waiting room. Glueckauf and associates [17] evaluated the consistency of seizure frequency estimates by 32 individuals with medication-resistant partial seizures

Table 1
Potential problems with interpretation of seizure diaries.

Subjects may be unable to understand or complete instructions to use a diary
Subjects may be noncompliant with diary maintenance
Recall of seizures for recording may be faulty if entry is delayed
Physical diaries can be lost or not brought to clinic visits
Awareness of seizures may be inaccurate
Subjects can record "false positive" events that are not seizures
Subjects may record adverse events in the diaries, requiring queries to resolve inconsistencies
Entries may be made by family or caregivers
Privacy issues

and by 17 caregivers. Retrospective seizure frequency estimates were given for the two prior months, followed by prospective completion of a seizure diary for one month. The patients estimated seizure frequencies of 8.5 for the two retrospective months and demonstrated a median of 9.0 seizures for the prospective month. In contrast, caregivers estimated 5.0, 4.0 and 1.0 seizure per month, respectively, for the two retrospective and one prospective months. This study suggests consistency of recall by patients but not by their caregivers. The study does not address the question of whether seizure counts were accurate. A blank page in a seizure diary could equally signify no seizures or a failure to record seizures. However, ensuring that a diary is easily accessible (in an electronic mobile form) increases the likelihood of better compliance and reporting accuracy.

Studies of diaries for other medical conditions, including weight loss [2], hypertension [10] and diabetes [32] indicate that diaries with interactive feedback capabilities may actively increase compliance with a treatment program. A meta-analysis of Internet-based diaries and intervention programs for various conditions [34] emphasizes the role of interactive feedback for increasing compliance. Furthermore, accurate completion of a seizure diary correlates with compliance in taking seizure medications [39].

One element of diary reliability is test–retest accuracy, which was investigated by Neugebauer in 1989 [29]. Phone calls were made to 84 subjects keeping a paper seizure diary, asking them to report the number of seizures written for the previous day without looking at the diary. Failure to put an entry or an uninterpretable entry in the diary was observed in 30 of 84 subjects. Among those who recorded an interpretable entry, 64 of 66 seizures were correctly recalled on the day after the seizure. This suggests that compliance with the initial recording task is the primary barrier; thus, modern diary methods may be designed to promote a patient or caregiver response in a maximally timely manner, using such techniques as electronic, mobile, or messaging reminders.

Limited awareness of seizures is another fundamental problem for reporting accuracy. A study in an epilepsy monitoring unit by Blum and colleagues [3] found that 61% of seizures were not recognized by patients, according to questioning soon after a seizure. Only 15% of patients were reliably aware of each of their seizures, and 30% were never aware of any seizures. Kerling and colleagues [23] observed that 44% of seizures in 30 patients went undetected by patients in a video-EEG monitoring unit. This was especially true for seizures originating in the left temporal region or occurring during sleep. A study in a Canadian monitoring unit by Poochikian-Sarkissian and coworkers [31] found that only 44.5% of complex partial and secondarily generalized tonic-clonic seizures were recognized by the patients. Heo and associates [20] reported 23% of patients to be unaware of their seizures, and Hoppe and colleagues [21] observed patients failing to document 55.5% of all recorded seizures. Finally, DuBois and associates [11] found that only 77% of patients in an epilepsy monitoring unit could correctly recall whether or not they had a seizure in the previous 24 h.

Inpatient video-EEG studies of seizure awareness may not reflect awareness in an outpatient setting. In 2001, Tatum and colleagues [38] reviewed outpatient 16-channel ambulatory EEG monitoring from 502 patients to compare EEG confirmation of seizures with patient-recorded diary information. A total of 47 records comprised recordings of partial seizures, among which 18 (38.3%) had seizures that were unrecognized by the patient. Conversely, 86.6% of the recordings included push-button event markers by the patient or family in the absence of concurrent EEG changes, although such absence does not rule out true partial seizures. The use of a diary may itself introduce a response bias for increased reporting of events; one study reported that even healthy individuals reported more frequent occurrences of pain when asked to review a symptom diary daily [14].

If missed seizures are distributed evenly over all treatment arms of a study, then randomized comparison trials might still be expected to be valid, provided that sample size calculations account for missing or inaccurate data. No information is available to validate or refute an assumption of proportionally missing diary seizure data among different treatment arms. Treatments theoretically may affect recall of seizures differently, for example, if a medication impairs memory in comparison with placebo or if a medication converts complex partial seizures that are poorly recalled to simple partial seizures that are better recalled. Epidemiological and observational studies of seizure frequencies in different populations always will be significantly affected by inaccurate seizure counts.

Tonic-clonic seizure detection can be performed automatically by devices based upon bed-shaking [4] or accelerometer detection of shaking of a wristwatch [24,27]. Video algorithms can detect rhythmical movements associated with tonic-clonic seizures [6,8,22]. Partial or secondarily generalized seizures produce tell-tale changes in heart rate [26] or ambient sounds [12]. Seizure detection based upon EEG pattern recognition is well-established [18] but requires wearing EEG electrodes. Pivotal clinical trials have not yet incorporated automatic seizure detection as the primary endpoint, but linking automated seizure detection to study databases or online diaries (see below) seems a fruitful future direction. Methods for validating and confirming the automatic detection would be required.

5. Seizure diaries in pediatric populations

Use of seizure diaries can be challenging in the pediatric population. First, children with epilepsy may be more likely than adults to have multiple seizure types. Accurate description, categorization and labeling of each seizure type (as described above) are especially crucial for children. Since younger children may not have the cognitive capacity to recognize and report seizures, the data collection must be done by caregiver's observation. Children often have multiple caregivers (parents, teachers, coaches, etc.) and schedules that change throughout a year (school, vacation, etc.), so accurate seizure tracking will require that all caregivers are able to recognize the child's seizures and be reliably compliant with reporting. An online diary would need to be accessible by multiple caregivers, or seizure data could be compiled and entered by the primary caregiver. Although dedicated parents or adult caregivers may intuitively be more accurate reporters than the patients, the logistical aspects of continuous monitoring of children will make diary reporting challenging.

Studies in other domains have suggested that parent-reported diaries can be highly accurate when compared with objective measures, but parents may be more likely to report certain types of events [1]. Similarly, parents may have a tendency to either over- or under-report their child's symptoms [36].

6. Epilepsy diaries for clinical practice

Two web-based diaries have recently come into clinical use for people with epilepsy, *My Epilepsy Diary* by Irody, Inc. at *epilepsy.com* and *Seizure Tracker* at *SeizureTracker.com*. Both of these diaries are free, nonprofit services for the epilepsy community. As of March, 2012, *My Epilepsy Diary* had 13,052 user accounts, two-thirds of which were in the United States, 571,504 logged transactions, 86,840 seizure events, 41,070 reported side effects, and 169,513 medication-related (compliance) events. About 50% of transactions were communicated by smartphones (iPhone and Android-based) showing the usefulness of these platforms for a diary. As of February, 2012, *Seizure Tracker* had 10,235 user accounts, 500,391 logged transactions, 337,485 seizure events, and 23,285 medication-change entries. About 37% of user accounts on *Seizure Tracker* were collecting epilepsy-related information on individuals under the age of 12. Approximately 2.25% of user accounts were collecting information on individuals over the age of 61. Both programs allow simple methods for logging seizures of different types, medication dosages, events by time of day and duration, graphical reports and tabular summaries.

Side effect type and level can also can be documented, along with missed or additional medications. A physician portal in *My Epilepsy Diary* allows the medical care team to have permission to access an individual patient's diary or to receive summary e-mails. *My Epilepsy Diary* can issue electronic reminders when it is time to take particular pills, reorder pharmacy prescriptions or attend a doctor's visit. The *Seizure Tracker* iPhone/iTouch application allows users to easily mark the time of seizure onset, time the event and video record the event all in real time. A mobile device application is offered on the *My Epilepsy Diary* platform for both iPhone and Android. This functionality capitalizes on the inherent advantages of mobile technology and the ability for real-time reporting. The Internet has worldwide reach, so English cannot be assumed to be the only relevant language. *My Epilepsy Diary* supports Spanish, Italian and French, in addition to English. Fig. 1 illustrates screenshots from the two on-line diaries. Neither of these diaries has been fully validated for compliance with 21 CFR, part 11, but some features have been implemented: for example, the *Seizure Tracker* clinical trial tool and *My Epilepsy Diary* have data audit trails to make sure no data are lost or modified, even if accidentally deleted. Additional development might be required to allow back-end integration with study sponsor databases and ensure isolation of study data.

What evidence is there that online diaries meet the potential advantages listed in Table 2? No comparison has yet been published for paper versus on-line seizure diaries but lessons can be extrapolated from diary studies of other medical conditions. Gaertner and associates [16] performed a randomized crossover study of paper diaries versus on-line diaries for tracking pain symptoms over a month. Patient satisfaction was "remarkably higher" for the electronic palmtop diary. The electronic diary was used more frequently and was less subject to retrospective fabrication of information. A study of 60 children, ages 8 to 16, with headaches or arthritis randomized data collection either to an electronic or paper diary. Use of the electronic diary provided

Table 2
Potential advantages and disadvantages of electronic seizure diaries for clinical research.

Advantages
• Accessible via smartphones or computers
• Flexible methods of entry, depending on patient preference
• Can be adapted (e.g., images) for low literacy or pediatric populations
• Not easily lost and can be queried from clinic
• Easier and more consistent patient entry choices
• Use is preferred by most patients
• Can graph data over time
• Allows date- and time-stamped entries
• Can transmit to medical team (if both parties so wish)
• Minimize transcription errors
• Can validate entry and prevent out-of-range entries
• Can be potentially integrated into other online or social media platforms
• Can paste into the electronic medical record
• Can enable reminder functions: medication, diary entry, seizure reporting, visits
• Real-time calculation of trial exit criteria
• Can link to biosensors, such as seizure detectors
• Can utilize electronic training on the diary
• Allows observational research on populations
Disadvantages
• More complicated and not understood by all patients
• Increased device cost (unless using an existing cellphone)
• Handheld devices can be broken
• Increased study setup time
• Current systems may not be sufficiently validated for regulatory submission
• Privacy issues must be handled properly

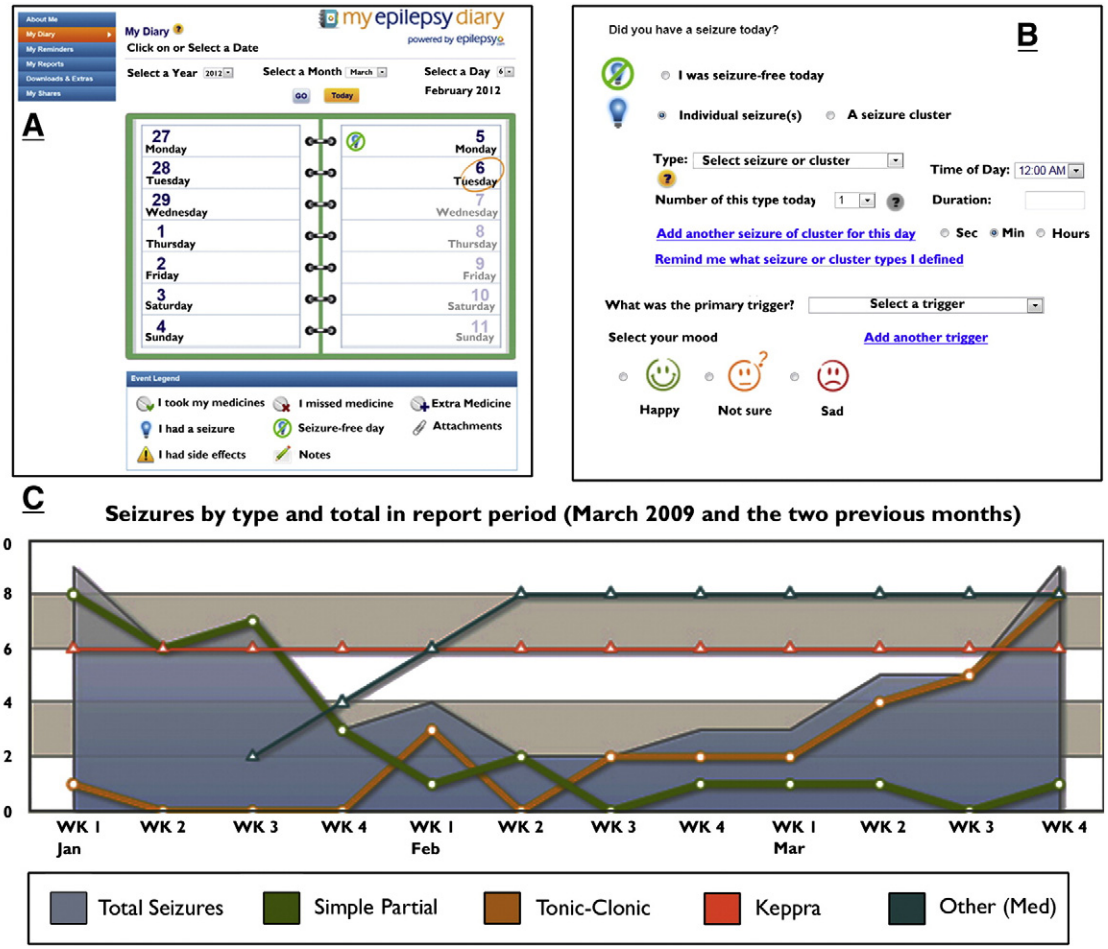

Fig. 1. A. Calendar page of *My Epilepsy Diary*, allowing entry of information about individual seizures. B. After choosing a date from the calendar screen, the user describes characteristics of the seizure. C. A chart of seizure frequencies and medications is illustrated from *Seizure Tracker*. Similar charts, not shown, are available in *My Epilepsy Diary*.

significantly greater numbers of diary entries and better accuracy of entries. A gender difference was evident in satisfaction rates, with boys rating electronic diaries higher than did girls. A crossover trial of 36 patients with chronic pain randomized to use of a paper or electronic diary for two weeks found no differences in the type of information collected but patients reported the electronic diary to be easier to use ($p<0.0001$).

Electronic diaries can assist with evaluation of compliance and data integrity, since electronic entries can be time-stamped. A comparison of compliance for electronic and paper diaries was performed in a population of patients with pain [37]. Subjects were told to enter pain levels at specific times for three times per day for three weeks with simultaneous use of both an electronic and paper diary. Paper diaries indicated 90% compliance within 15 min before or after the assigned time for recording pain information. Actual time of entry detected by the electronic diary showed timeliness of entry in only 11%. This demonstrates that the entry of recording time for the paper diaries was inaccurate.

Online diaries can be accessed by desktop or laptop computers and by handheld devices such as personal digital assistants, iPhones or Android-based phones. Dale and Hagan [9] performed a systematic review of studies using handheld electronic diary collection versus paper diaries. Among nine identified studies, five reported better compliance with handheld devices and one better compliance with a written diary. Two studies reported saving substantial staff time with electronic data collection. Three of three studies reported greater data accuracy with handheld entry, and four of four studies found a user preference for electronic data recording. Several studies reported technical problems with the handheld method, although technology has improved in the five years since the study was completed.

Several practical issues arise with use of an electronic diary for clinical epilepsy care. Only relatively sophisticated patients or caregivers are candidates for electronic data entry. Practically speaking, both a desktop computer and a smartphone are required because so many seizures take place away from a home computer and data delayed tends to become data not recorded. Copying a paper diary into an on-line diary is double-work and usually not a sustainable method. Patients must be made to understand that the medical team is not constantly monitoring the diary or they will be disappointed by silence after "that big seizure." Patients should use their usual communication channels to report urgent problems. In most cases, excepting the rare physician who wants to be aware of every seizure in near-real-time, data reports should be at time of a clinic visit. Diary data can be printed, graphed and brought to clinic as physical paper, e-mailed (according to HIPAA rules) or brought on a disk. *My Epilepsy Diary* also allows designated physicians direct read-only access to the on-line patient data, which can be copied into the electronic medical record.

On-line diaries present several unique potential privacy issues. The Health Insurance Portability and Accountability Act (HIPAA) requires that medical records meet certain privacy laws and regulations. On-line diaries and other patient-controlled sites such as Microsoft Health Vault® (which is integrated with *My Epilepsy Diary*) and the discontinued Google Health® are not HIPAA-covered entities because they do not provide medical care. On-line health sites do, nevertheless, require a certain level of security, confidentiality and explanation of policies and safeguards to the user. Even with the best security, information on a site containing health data can become public. Such a possibility is minimized by using non-identifiable usernames and passwords. Sites such as *My Epilepsy Diary* and *Seizure Tracker* should and do comply with privacy regulations as a personal medical record service, including separation of personal from medical information, timely backing up of data and protection of the server against intrusions.

Studies utilizing on-line or mobile electronic diaries must take steps to ensure security standards are met for both patient data transmission and storage. Validation of data integrity and privacy for such systems are requirements.

7. Epilepsy diaries for research

Communication and data storage in modern times increasingly involves electronic rather than written data entry and preservation. Computer databases for tracking clinical trials have been available for decades, although not necessarily with primary data entry by the study participants. Electronic data entry is now beginning to be used without concurrent paper diaries, since translation of paper to electronic diaries increases work and introduces translation errors.

Potential advantages and disadvantages of electronic versus paper diaries are listed in Table 2.

Diaries collect large amounts of data but usually in an uncontrolled and non-standardized manner. Standardized diaries, either paper or electronic, might provide unique opportunities for multicenter and population-based longitudinal research in epilepsy [5]. Epilepsy research using diaries can be either investigator-supervised, such as diaries in randomized controlled trials of new epilepsy therapies or in prospective observational studies, or unsupervised, as with post-hoc analysis of self-reported anonymous diaries [25]. In supervised studies, diary information is validated by medical personnel and supplemented by the medical record. In clinical trials, although the subject provides seizure descriptions and seizure counts, the investigator reviews the diary for accuracy, confirms the symptoms, and classifies the seizure types based on semiology, results of prior EEGs and neuroimaging studies. This increases diary validity and usually improves response rates, as subjects can be reminded to complete diaries. De-identified bulk analysis of diary data can be employed for observational research and to focus hypotheses. For example, a study of seizure timing [19] in 71 patients with drug-resistant seizures showed that a 30-day diary could predict subsequent seizures over the next 30 days with 72% sensitivity and 80% specificity. Diaries were able to characterize injuries from seizures in a study of 631 epilepsy patients and 592 cohort controls [7]. Risks of an accident were found to be higher than the general population but usually mild and uninfluenced by seizure type.

Standardized diaries can also improve the efficiency of clinical trials of new therapies [9]. The prospective baseline period prior to randomization can sometimes be shortened by incorporating a retrospective baseline with seizure counts from a diary. Electronic diaries that wirelessly collect real-time data on seizures and adverse effects could enable innovative end-points, such as time to nth seizure or time to maximally tolerated dose in dose-finding studies. Simple interfaces on mobile devices may allow collection of more detailed information, such as duration of the postictal period, than is typically collected in paper-based diaries.

Diary-based studies also can be useful as descriptive "snapshots" of a population, as demonstrated in a report on the demographics, seizure types, seizure times of day and medication usage in a group of people with epilepsy [25]. Unsupervised or patient-driven diary-based observational studies have a few advantages over supervised trials, such as low cost, allowing participation and locus-of-control by the patient and testing in a "real-world" environment. Geographic data might inform public health initiatives in epilepsy by revealing trends in referral patterns, commonly used treatments, and quality of care. The type of information available is very different from that obtained by prospective controlled studies. Diary research is by nature retrospective. Diary completers are not likely to be representative of the general population of epilepsy patients. Diaries are, furthermore, subject to a "Heisenberg effect," by which the act of observing (self-observing in this instance) alters the data. After a change in therapy, users may be more likely to attend to a diary for a while and thereby record more seizures or side effects than before the treatment change and monitoring period. As noted above, care must be taken in the interpretation of intervals in which no seizures are reported, since it may be impossible to distinguish absence of seizures from non-compliance with diary maintenance. This can be

resolved using a "no seizures today" checkbox or electronic reminder system (*My Epilepsy Diary* has implemented such a checkbox). Differential attrition, in which patients with certain characteristics (e.g., low seizure frequency) are more likely to stop completing diaries, can cause significant bias in longitudinal studies. Observations from diary data must be considered in light of these possible biases, and key findings must be confirmed by other methods.

Strategies to improve validity of unsupervised diaries could include use of structured questionnaires to improve seizure classification, linking of diaries to electronic medical records or to physicians who can verify data, or restricting data analysis to patients who maintain a certain threshold of diary activity. Online diarists can be recruited to participate in "add-on" diaries for specific purposes, such as detailed quality-of-life inventories, adverse effect questionnaires, or information on comorbidities and concomitant medications.

8. View from industry

FDA approval of a new medication or high-risk therapeutic device requires at least one adequately controlled randomized clinical trial. The manufacturers of drugs and devices are very aware of the use of medical diaries for PROs that may provide key outcome data for pivotal trials. Advisors to industry will consider whether a diary has been validated against conventional standards and whether it provides accurate as well as precise information. A diary with missing or inaccurate information, especially if errors are distributed more in one treatment group, can invalidate a major clinical trial. Who makes and records information for a diary is important for a clinical trial, since patients may not be aware of all of their seizures. Potential biases introduced by the use of diaries (paper or electronic) must be considered and acknowledged during trial design.

Most industry-sponsored clinical trials of seizure therapies still base primary outcome on paper diaries. Paper diaries are favored due to familiarity, ease of use, low cost, and availability to every study subject and observer; further, this has become the industry standard, regardless of the drawbacks. Known negative features include poor control and validation of input, potential language translation problems, transcription expenses and the likelihood of obtaining extraneous data. Electronic diaries promise real-time transmission of data, time-stamping of entries, reminders to subjects, and potentially automatic interfaces to other devices, such as electronic pill boxes. Electronic diaries should enable more rapid study close-out activities at the end of a trial. Some factors that explain the limited use of electronic systems are limited patient access to computers, unfamiliarity with technology, increased time and cost for study start-up activities, possibility of loss or malfunction of the entry device and unclear regulatory acceptance. Diary devices might break during seizures or be stolen during postictal periods.

As noted above, the FDA has proposed validation requirements for collection of patient-reported outcomes [13]; no currently available diary meets these requirements. Neither FDA nor EMA has publically indicated a position on willingness to accept trials using such devices to be pivotal. Also, regulatory authorities typically would require a daily entry to ensure diary compliance, as they do with paper diaries.

Most pivotal trials require back-up primary source data, in addition to paper or electronic diaries. This source data typically is the medical chart. In case of a regulatory audit, the source data are compared to the diary data, looking for discrepancies. Therefore, a diary is extra work for the patient and the clinician and as such should present the least possible added burden.

9. Future directions

Predicting can be hazardous. In 1949, Popular Mechanics asserted that "Computers in the future may weigh no more than 1.5 tons." (Wikipedia). Speculation about the use of on-line information systems in medicine will likely be as wide of the mark as was the Popular Mechanics prediction. Two trends, however, are likely for the near future: links to biosensors and electronic diaries for clinical trials.

Biosensors can be linked to on-line diaries, in order to automatically collect information about seizures. Such tracking devices and links are available for blood pressure [30] and glucose monitoring [28]. Efforts are underway to link detection of seizure-like shaking by a watch with a built-in accelerometer [27] to *My Epilepsy Diary*. Such a link will allow automatic recognition, logging, time-stamping and recording of duration for tonic-clonic seizures. False-positive detections can be addressed by a cancel button.

Several devices exist for documentation of medication compliance, including the MedMinder Maya Electronic Pillbox, the Evalan RTMM Mobile Electronic Pillbox and Vitality Glowcaps. Patients can open pillboxes or bottle caps without taking the medication. A new device named "Raisin" embeds pills with a microchip that broadcasts information to a shoulder patch and ultimately a smartphone when the chip is digested in the stomach (http://www.dailymail.co.uk/sciencetech/article-1302814/NHS-launch-intelligent-pill-texts-you-forgotten-dose.html). We envision a time when medication compliance and seizure frequency will be automatically and accurately charted electronically, with no need for patient-reporting. The MedMinder and Evalan pillboxes have integrated with the *My Epilepsy Diary* potentially allowing integration of patient-reported data with pillbox-reported data.

Computerized and on-line diaries are likely to be used for clinical epilepsy trials; indeed, use is increasing. One study, entitled "Women with Epilepsy: Pregnancy Outcomes and Deliveries (WEPOD)" has utilized *My Epilepsy Diary* for tracking seizures, medications and side effects for their trial. A special module was written to allow tracking of activities related to fertility, as well as a special reminder system on the mobile platform to encourage entry of a complete data set. This exemplifies how custom changes can be made over a base of core functionality. So far, compliance and information collection are adequate for the needs of the study. A new clinical trial tool, accessible from any hand-held device with a web browser and utilizing the *SeizureTracker* format, is currently being used in a neurocognitive clinical trial in children with tuberous sclerosis complex to test the efficacy of an mTOR inhibitor. The *SeizureTracker* clinical trial tool will document seizure type, frequency, severity, triggers (including hormonal shift surrounding menstrual cycles) and other attributes of the seizures during the trial. Movement of future trial data collection to electronic and on-line formats seems likely.

10. Recommendations for clinical research

The diary subgroup attending the NINDS conference on epilepsy clinical trials offered several recommendations pertaining to seizure diaries for clinical research. These are listed below.

1. Develop studies to validate current and new uses of epilepsy diaries as clinical and research tools.
2. Develop a core of data sets useful for all epilepsy diary users, taking into account existing diaries and the NIH Common Data Element material.
3. Develop a method to have core common diary information and customizable special modules for individual projects.
4. Encourage automatic links of electronic diaries to biosensors, e.g., pillboxes or shake monitors.
5. Provide legal protection for the diary and develop a user and privacy policy.
6. Propose ways in which diaries can be used to improve compliance/adherence.
7. Make diaries simultaneously useful for clinical care, as well as for research.
8. Allow extension of diary use to children.
9. Develop principles for observational research from diaries.
10. Determine how different diaries can best share anonymous data.

11. Provide validation data to make electronic diary systems useful and FDA compliant for industry-sponsored clinical trials.
12. Availability of the electronic platform globally (using local languages and confirming with local regulations) as an infrastructure for international studies.

Disclosure of conflicts of interest

Dr. Fisher consults for Neuro-Vista, Cyberonics, ICVRx, Irody, SmartMonitor. Stanford University has received research support from Medtronic with Dr. Fisher as principle investigator. Dr. French serves as the president of The Epilepsy Study Consortium, a non-profit organization. NYU receives a fixed amount from the Epilepsy Study Consortium towards Dr. French's salary. The money is for work performed by Dr. French on behalf of The Epilepsy Study Consortium, for consulting and clinical trial related activities. Dr French receives no personal income for these activities. Dr. French and Bree DiVentura are affiliated with the Epilepsy Study Consortium. Within the past year, The Epilepsy Study Consortium received payments from: Cyberonics, Eisai Medical Research, Entra Pharmaceuticals, GlaxoSmithKline, Icagen, Inc., Johnson & Johnson, Marinus, Neurotherapeutics, NeuroVista Corporation, Ono Pharma USA, Inc., Lundbeck, Pfizer, Sepracor, Sunovion, SK Life Science, Supernus Pharmaceuticals, UCB Inc./Schwarz Pharma, Upsher Smith, Valeant, Vertex. Susan Herman received research support from Lundbeck, Inc. and UCB Pharma. Dr. Hixson has received research funding from UCB Pharma Inc., and provide consulting services for Lumetra Healthcare Solutions. Robert Moss has no disclosures, except authorship of *Seizure Tracker*. Brandy Fureman and Jennifer Vannest have no conflicts to declare. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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References

[1] Asaka Y, Takada S. Comparing sleep measures of infants derived from parental reports in sleep diaries and acceleration sensors. Acta Paediatr 2011;100:1158–63.
[2] Blanson Henkemans OA, van der Boog PJ, Lindenberg J, van der Mast CA, Neerincx MA, Zwetsloot-Schonk BJ. An online lifestyle diary with a persuasive computer assistant providing feedback on self-management. Technol Health Care 2009;17:253–67.
[3] Blum DE, Eskola J, Bortz JJ, Fisher RS. Patient awareness of seizures. Neurology 1996;47:260–4.
[4] Carlson C, Arnedo V, Cahill M, Devinsky O. Detecting nocturnal convulsions: efficacy of the MP5 monitor. Seizure 2009;18:225–7.
[5] Carney CE, Buysse DJ, Ancoli-Israel S, et al. The consensus sleep diary: standardizing prospective sleep self-monitoring. Sleep 2012;35:287–302.
[6] Conradsen I, Beniczky S, Wolf P, Terney D, Sams T, Sorensen HB. Multi-modal intelligent seizure acquisition (MISA) system—a new approach towards seizure detection based on full body motion measures. Conf Proc IEEE Eng Med Biol Soc 2009;2009:2591–5.
[7] Cornaggia CM, Beghi M, Moltrasio L, Beghi E. Accidents at work among people with epilepsy. Results of a European prospective cohort study. Seizure 2006;15:313–9.
[8] Cuppens K, Lagae L, Ceulemans B, Van Huffel S, Vanrumste B. Detection of nocturnal frontal lobe seizures in pediatric patients by means of accelerometers: a first study. Conf Proc IEEE Eng Med Biol Soc 2009;2009:6608–11.
[9] Dale O, Hagen KB. Despite technical problems personal digital assistants outperform pen and paper when collecting patient diary data. J Clin Epidemiol 2007;60:8–17.
[10] Dawes MG, Kaczorowski J, Swanson G, Hickey J, Karwalajtys T. The effect of a patient education booklet and BP 'tracker' on knowledge about hypertension. A randomized controlled trial. Fam Pract 2010;27:472–8.
[11] DuBois JM, Boylan LS, Shiyko M, Barr WB, Devinsky O. Seizure prediction and recall. Epilepsy Behav 2010;18:106–9.
[12] Elzawahry H, Do CS, Lin K, Benbadis SR. The diagnostic utility of the ictal cry. Epilepsy Behav 2010;18:306–7.
[13] FDA. Guidance for industry patient-reported outcome measures: use in medical product development to support labeling claims; 2009.
[14] Ferrari R, Russell AS. Effect of a symptom diary on symptom frequency and intensity in healthy subjects. J Rheumatol 2010;37:2387–9.
[15] Fisher RS. Tracking epilepsy with an electronic diary. Acta Paediatr 2010;99:516–8.
[16] Gaertner J, Elsner F, Pollmann-Dahmen K, Radbruch L, Sabatowski R. Electronic pain diary: a randomized crossover study. J Pain Symptom Manage 2004;28:259–67.
[17] Glueckauf RL, Girvin JP, Braun JR, Bochen JL. Consistency of seizure frequency estimates across time, methods, and observers. Health Psychol 1990;9:427–34.
[18] Gotman J. Automatic recognition of epileptic seizures in the EEG. Electroencephalogr Clin Neurophysiol 1982;54:530–40.
[19] Hall CB, Lipton RB, Tennen H, Haut SR. Early follow-up data from seizure diaries can be used to predict subsequent seizures in same cohort by borrowing strength across participants. Epilepsy Behav 2009;14:472–5.
[20] Heo K, Han SD, Lim SR, Kim MA, Lee BI. Patient awareness of complex partial seizures. Epilepsia 2006;47:1931–5.
[21] Hoppe C, Poepel A, Elger CE. Epilepsy: accuracy of patient seizure counts. Arch Neurol 2007;64:1595–9.
[22] Karayiannis NB, Xiong Y, Frost Jr JD, Wise MS, Hrachovy RA, Mizrahi EM. Automated detection of videotaped neonatal seizures based on motion tracking methods. J Clin Neurophysiol 2006;23:521–31.
[23] Kerling F, Mueller S, Pauli E, Stefan H. When do patients forget their seizures? An electroclinical study. Epilepsy Behav 2006;9:281–5.
[24] Kramer U, Kipervasser S, Shlitner A, Kuzniecky R. A novel portable seizure detection alarm system: preliminary results. J Clin Neurophysiol 2011;28:36–8.
[25] Le S, Shafer PO, Bartfeld E, Fisher RS. An online diary for tracking epilepsy. Epilepsy Behav 2011;22:705–9.
[26] Leutmezer F, Schernthaner C, Lurger S, Potzelberger K, Baumgartner C. Electrocardiographic changes at the onset of epileptic seizures. Epilepsia 2003;44:348–54.
[27] Lockman J, Fisher RS, Olson DM. Detection of seizure-like movements using a wrist accelerometer. Epilepsy Behav 2011;20:638–41.
[28] Mastrototaro J, Lee S. The integrated MiniMed Paradigm REAL-Time insulin pump and glucose monitoring system: implications for improved patient outcomes. Diabetes Technol Ther 2009;11(Suppl. 1):S37–43.
[29] Neugebauer R. Reliability of seizure diaries in adult epileptic patients. Neuroepidemiology 1989;8:228–33.
[30] Park MJ, Kim HS, Kim KS. Cellular phone and Internet-based individual intervention on blood pressure and obesity in obese patients with hypertension. Int J Med Inform 2009;78:704–10.
[31] Poochikian-Sarkissian S, Tai P, del Campo M, et al. Patient awareness of seizures as documented in the epilepsy monitoring unit. Can J Neurosci Nurs 2009;31:22–3.
[32] Rossi MC, Nicolucci A, Di Bartolo P, et al. Diabetes Interactive Diary: a new telemedicine system enabling flexible diet and insulin therapy while improving quality of life: an open-label, international, multicenter, randomized study. Diabetes Care 2010;33:109–15.
[33] Rothman M, Burke L, Erickson P, Leidy NK, Patrick DL, Petrie CD. Use of existing patient-reported outcome (PRO) instruments and their modification: the ISPOR good research practices for evaluating and documenting content validity for the use of existing instruments and their modification PRO task force report. Value Health 2009;12:1075–83.
[34] Schubart JR, Stuckey HL, Ganeshamoorthy A, Sciamanna CN. Chronic health conditions and Internet behavioral interventions: a review of factors to enhance user engagement. Comput Inform Nurs 2011;29:TC9–TC20.
[35] Stafford M, Gavriel S, Lloyd A. Patient-reported outcomes measurements in epilepsy. Expert Rev Pharmacoecon Outcomes Res 2007;7:373–84.
[36] Stokes J, Pogge D, Wecksell B, Zaccario M. Parent–child discrepancies in report of psychopathology: the contributions of response bias and parenting stress. J Pers Assess 2011;93:527–36.
[37] Stone AA, Shiffman S, Schwartz JE, Broderick JE, Hufford MR. Patient compliance with paper and electronic diaries. Control Clin Trials 2003;24:182–99.
[38] Tatum WO, Winters L, Gieron M, et al. Outpatient seizure identification: results of 502 patients using computer-assisted ambulatory EEG. J Clin Neurophysiol 2001;18:14–9.
[39] van Berge Henegouwen MT, van Driel HF, Kasteleijn-Nolst Trenite DG. A patient diary as a tool to improve medicine compliance. Pharm World Sci 1999;21:21–4.