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PEER REVIEWED

Optimizing Medical Records Collection in Clinical Research: Lessons Learned from Two Pediatric Cohort Studies

Marina Albuquerque de Souza Dantas, MD; Lacey B. Robinson, MD; Elie Mitri; Catalina Gallegos; Ashley F. Sullivan, MS, MPH; Carlos A. Camargo Jr, MD, DrPH

Medical records are a valuable source of data for clinical research, and the ongoing shift to electronic medical records (EMRs) allows for increased access to important data sources.{1} In 1996, privacy rules were established through the Health Insurance Portability and Accountability Act (HIPAA) to safeguard medical information and protect patients' privacy.{2} The HIPAA Privacy Rule is frequently misinterpreted by healthcare providers, contributing to difficulties in medical records collection and complicating research execution.{3} A national survey of clinical scientists in the U.S. showed that the HIPAA Privacy Rule was perceived to add uncertainty, cost, and delay to the conduct of health-related research.{4}

To date, little has been published on strategies for medical records collection in clinical research, which may discourage investigators from conducting robust studies relying on medical records, such as large multicenter studies. Therefore, a better understanding of the applicability of the HIPAA Privacy Rule, along with possible solutions to commonly encountered problems in records collection, would be of substantial benefit to clinical researchers.

To address this scientific gap, we describe our experience of collecting medical records in two multicenter pediatric cohorts, known as the 35th Multicenter Airway Research Collaboration (MARC-35), a prospective cohort study of severe bronchiolitis and risk of recurrent wheezing and asthma, and the 43rd Multicenter Airway Research Collaboration (MARC-43), a study of the airway microbiome asthma phenotypes in healthy infants. We have faced several challenges in medical records collection, but with experience, we have overcome many problems and improved our processes to obtain a high level of completeness of medical records. These experiences encouraged us to share the lessons we have learned for the benefit of future studies.

The MARC-35 and MARC-43 Cohorts

MARC-35 and MARC-43 are multicenter cohort studies following children from early infancy to approximately age 6 years for multiple outcomes, including clinician-diagnosed asthma. From 2011 to 2014, 1,016 infants (age < 1 year) were enrolled in MARC-35 in 17 U.S. hospitals (enrollment sites) during an inpatient hospitalization for bronchiolitis. In 2013 and 2017, a total of 720 healthy infants were enrolled in MARC-43 in five U.S. hospitals.{5,6}

Study procedures in these two parallel cohorts include serial telephone interviews with the legal guardians every six months, in-person physical exams every few years, and complete medical records review from birth to study completion at age 6 years or older. Complete medical records review includes physician review of records from all primary care providers (e.g., pediatrician) and specialists (e.g., pulmonologist, allergist), along with all urgent care visits, emergency department visits, and hospitalizations. All study activities are coordinated by the Emergency Medicine Network (EMNet) at Massachusetts General Hospital.

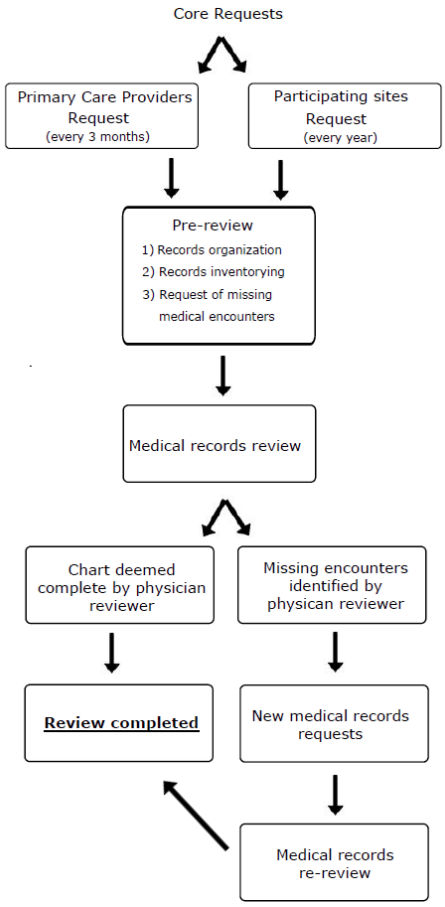
Informed consent and HIPAA-compliant authorization forms for records release were obtained at enrollment, authorizing the EMNet Coordinating Center to obtain all records for participants from birth until study completion. Per the HIPAA Privacy Rule, authorization forms may be valid until an

established date (e.g., until the end of the research study) or never expire. We decided to use a form that was valid until one year after completion of participant follow-up.

Medical Records Collection

We used a systematic approach for medical records requests and inventory (see Figure 1). Core medical records include records from the participating enrollment sites and the children's primary care providers (PCPs). Requests for these core records are made regularly on a predefined schedule. In November of each year, due to the existence of a Data Use Agreement, the EMNet Coordinating Center requests all medical records on file for the previous year from each participating enrollment site, including all visits to site-affiliated facilities within a shared EMR system.

Figure 1: A Systematic Approach to Medical Records Requests and Inventory



PCP information is confirmed and updated every six months by serial telephone interviews with legal guardians and stored in REDCap,{7} a HIPAA-compliant, web-based data capture tool. Time points for

PCP requests were predefined at ages 1, 3, 5, and 6 years. Every three months, we query which participants meet these specified age timepoints and send medical records requests to the PCPs they saw in the interval of interest. The requests are submitted twice by mail to PCPs, and any non-responders are then contacted by telephone.

After the core medical records are received, EMNet coordinators conduct a pre-review of the records by age section (e.g., 0–0.9 years, 1–2.9 years, and so forth). Pre-review includes checking medical records for consistency (e.g., ensuring available records match healthcare encounters reported by legal guardians) and identifying missing or incomplete records. Information regarding completeness of each age range, dates of submission, and details about problems with collection are recorded in Microsoft Access, a database management system.

During pre-review, medical records not obtained from PCPs through the initial core request (approximately 15–20%) are re-requested and followed up until the missing medical records are obtained. Urgent care visits, emergency department visits, specialist visits, and hospitalizations not obtained through participating enrollment sites are also requested at this time. The medical record is deemed complete when we have no chronological gaps and all well-child checks and sick visits are present for a given age section.

When complete, the medical records are assigned for review by trained physicians who extract relevant data portions and enter them in REDCap. If the physician reviewer identifies any remaining missing medical records, medical records requests are sent to the identified facilities.

Challenges

We encountered multiple challenges during the process of medical records collection (see Table 1). We will discuss our most common and difficult challenges and share our solutions.

Table 1: Medical Records Collection: Challenges and Solutions

CHALLENGES	SUGGESTED SOLUTIONS
DELIVERY OF MEDICAL RECORDS REQUEST TO THE CORRECT PROVIDER	Maintain periodic contact with participants after enrollment to update information about past and current healthcare providers. Maintain a database with contact information for all participants' PCPs, including preferred method of contact.* Ensure knowledge of records allocation rules in the case of facility closure.
LACK OF RESPONSE TO MEDICAL RECORDS REQUESTS	Perform systematic follow-up after submission with telephone calls. Track submission of requests and all subsequent contacts in an EMR tracking system.** Use Data Use Agreements to make large bulk requests when possible.
DECLINED AUTHORIZATION FORMS FOR RECORDS RELEASE	Use multiple checkpoints to ensure accuracy of authorization forms at time of completion. Adapt authorization forms to follow state-specific requirements. Avoid making authorization forms provider-specific and instead use broad authorization from many care providers. Set authorization form date of expiration after outcome of interest to allow additional time for medical records collection. Contact participants periodically to obtain a new authorization form if needed. Use an electronic system for authorization form signature.

*We use REDCap for this purpose. **We use Microsoft Access for this purpose.

Delivery of Medical Records Requests to the Correct Provider

During the many years of follow-up, children's PCPs frequently change, and facilities relocate or undergo closure, complicating delivery of medical records requests to the correct provider. Often, updated PCP information is provided by legal guardians, but at other times we only suspect PCP changes have happened due to gaps in the received medical records.

The HIPAA Privacy Rule forbids providers to release any protected health information by phone, including the name of other providers, and prevents facilities from sending records of others, thus hindering medical records collection in cohort studies that do not have longitudinal contact with participants. The serial telephone interviews with legal guardians included in both cohorts enable us to obtain updated contact information for PCPs in a timely and efficient manner. This process is aided by recording of alternate contacts for all legal guardians, increasing our ability to complete the serial telephone interviews.

However, in some cases, we are unable to obtain updated PCP contact information from the legal guardian (e.g., participant lost to follow-up) and then rely on information in the available medical records. For example, PCP names may be recorded on hospital discharge summaries or immunization records.

After the PCPs and other healthcare providers are identified, the submission of medical records requests is complicated by other factors, including inaccuracies in the contact information for PCPs or other healthcare providers received from legal guardians. To decrease errors, when the correct contact number and address of any healthcare provider are identified, we update REDCap and Microsoft Access with this verified information. Additional notes are entered, including best mode of communication (e.g., telephone vs. fax).

Although uncommon, some healthcare facilities undergo closure. Many factors influence the transfer of medical records upon closure, such as state and/or federal laws, Medicare and/or Medicaid requirements, recommendations from state licensing boards and professional societies, and the general circumstances of closure.{8} Therefore, medical records may end up with another healthcare provider, the state Department of Health, in commercial storage, or even destroyed if no transfer is possible.

When a closed facility hasn't released a public note listing the new custodian of its medical records, we contact the Department of Health for the state for further information. A summarized list of each state's requirements for medical records disposition after facility closure can be found via the American Health Information Management Association website.{9}

Lack of Response to Medical Records Requests

Even upon identification of the correct healthcare providers and their contact information, medical records request submissions frequently do not result in transfer of requested records to the research facility. In many cases, there is no direct communication on the status of requested records. The initial request to PCPs, submitted by mail, usually obtains a response rate of approximately 50%, with rates for a second mailing of requests typically increasing to 70%, and with the final requests by telephone, the response rate rises to at least 80%.

During the medical records pre-review, additional medical records requests to newly identified PCPs or other healthcare facilities are submitted first by fax, and then by telephone call if no response is received. After two attempts, the overall response rates for these groups is > 95%.

To increase the response rate for initial medical records requests to PCPs, we have established a systematic telephone follow-up system, in which EMNet coordinators call facilities that did not respond to the initial requests once per week to identify potential issues. All activities are registered in Microsoft Access, giving an overview of what has already been performed and what is due, and enabling monitoring

of the status of submitted and pending requests in an organized system that can be accessed by all key personnel.

Through the use of Data Use Agreements with enrollment sites, yearly bulk medical records requests can be completed for all study participants at each enrollment site. Records from sites and all affiliated healthcare facilities are then sent directly to the EMNet Coordinating Center for review, with a uniform response rate of 100%. This process increases efficiency, as there is a decrease in the overall number of individual requests.

Declined Authorization Forms for Medical Records Release

Even when medical records requests are received by healthcare providers, many authorization forms are declined, often due to different interpretations of the adequacy of the form. We use strictly HIPAA-compliant forms, but to decrease rates of declined forms we suggest attention to state-specific requirements, allowance of multiple providers to release records, and an expiration date after study completion.

Despite emphasis on the importance of accurate completion of the authorization form, we found that many returned forms have blank fields or incorrect dates which invalidate them. To decrease these errors, we performed additional training and established multiple checkpoints during the completion of the form, improving their completeness and validity.

Several facilities require use of a specific authorization form or report more strict state laws than the HIPAA Privacy Rule. Examples of these stricter rules include protections for specific conditions such as sexually transmitted disease, substance abuse and psychiatric conditions.{10,11} In these cases, we create new forms that account for these specific rules; these must be approved by the respective enrollment sites' institutional review boards and then signed by legal guardians. This process significantly delays collection of medical records.

In our experience, many legal guardians only include the participant's current PCP on the authorization form, and thus a new form has to be obtained to request information for any other providers. This is problematic because participants frequently switch PCPs or obtain care from multiple healthcare providers (e.g., from specialists, in urgent care settings, or various hospitals). One strategy we employed to minimize the need for separate forms for each medical provider is to authorize "all providers" at "all healthcare facilities" to release records. Stating a class of providers (e.g., all primary care providers or all providers) in the authorization form is allowed by the HIPAA Privacy Rule.{2}

Another common source of rejection of authorization forms is tied to the form's expiration date. In our experience, many facilities are unfamiliar with the fact that the HIPAA Privacy Rule allows the form to expire at the end of the research study or to never expire, thus facilities often refuse to provide medical records for service after the date of the signature on the form. This obstacle is problematic for prospective cohort studies, in which the form is usually signed at enrollment and meant to be valid for many years (e.g., until the end of the planned study period).

When facilities decline authorization forms because of signature dates, we discuss the applicability of HIPAA Privacy Rules directly with the facilities' medical records department staff by telephone. When necessary, we fax the federal HIPAA Privacy Rule to the facility, highlighting the specific paragraphs related to the flexible expiration date of the authorization form for research use. If the form was still declined, we would then contact the legal guardian and ask him/her to complete a new form.

Due to these reasons for rejecting an authorization form, it is not rare to need to obtain a new form outside a prespecified study visit. Initially, when a new form was required, we contacted the legal guardian and requested completion of a new form to be returned by mail. However, using this system we had very low rates of returned forms. We thus implemented a HIPAA-compliant electronic system (Ingram Micro Adobe Sign) to obtain a signature on the form, which has proven to be extremely helpful, as the rates of completed forms have increased. Our ability to contact subjects periodically during the study period is instrumental in our success in receiving updated forms when needed.

Conclusion

Medical records collection is a time-consuming activity that may become the rate-limiting point of any study without careful logistical planning. In the MARC-35 and MARC-43 multicenter studies, we faced many problems with records collection—from successful delivery of medical records requests to providers to declined authorization forms—but were able to develop and implement many successful solutions.

Some studies are solely based on medical record review, but in our experience the ability to periodically contact legal guardians has been vital to our success. This longitudinal follow-up allows us to update providers' information and obtain new authorization forms when required. Through use of electronic databases (REDCap and Microsoft Access), the information given by legal guardians is complemented by our experience contacting each provider, increasing the chances of successfully reaching these providers

in the future. In the unlikely event that a healthcare facility closes, we recommend contacting the state's Department of Health to locate the medical records.

Before requests are submitted, it is crucial to have a medical record tracking system such as Microsoft Access in place, as it will provide an up-to-date view of which records are ready for review and which need to be requested. This tracking system provides the basis for systematic follow-up of already submitted medical records requests—an important strategy to achieve a satisfactory response rate. Similar systems for medical record completeness documentation have been previously applied with success.{12} For multicenter studies, having a Data Use Agreement with participating enrollment sites decreased the number of individual requests and increased the rate of medical record collection.

Finally, much focus has to be devoted to the components of the authorization form, since they are the main source of medical records requests rejection. From the beginning of a multicenter study design, investigators should make sure the authorization forms contain state-specific elements, are not provider-specific, and expire after the outcome of interest, allowing time for medical record collection. Despite these precautions, authorization forms may still be declined, and thus we recommend having the ability to contact legal guardians to obtain a new form.

References

1. Smailes P. 2017. The ethics of research access to electronic medical record data. *Clin Res* 31(3):18–9. https://acrpnet.org/2017/06/01/data-tech-connect-ethics-research-access-electronic-medical-record-data/

2. National Institutes of Health, U.S. Department of Health and Human Services. 2004. Protecting Personal Information in Research: Understanding the HIPAA Privacy Rules. https://privacyruleandresearch.nih.gov/pdf/HIPAA_Booklet_4-14-2003.pdf

3. Nass S, Levit L, Gostin L. 2009. Beyond the HIPAA Privacy Rule: Enhancing Privacy, Improving Health Through Research (Institute of Medicine). www.nap.edu/catalog/12458.html

4. Ness R. 2007. Influence of the HIPAA Privacy Rule on health research. *JAMA* 298(18):2164.

5. Hasegawa K, Stewart C, Celedón J, Mansbach J, Tierney C, Camargo CA Jr. 2018. Serum 25-hydroxyvitamin D, metabolome, and bronchiolitis severity among infants—a multicenter cohort study. *Ped Allergy Imm* 29(4):441–5.

6. Hasegawa K, Linnemann R, Avadhanula V, Mansbach J, Piedra P, Gern J, Camargo CA Jr. 2015. Detection of respiratory syncytial virus and rhinovirus in healthy infants. *BioMED Cent Res Notes* 8(1):1–5.

7. Harris P, Taylor R, Thielke R, Payne J, Gonzalez N, Conde J. 2009. Research Electronic Data Capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Informatics* 42(2):377–81.

8. American Health Information Management Association. 2011. Protecting Patient Information After a Facility Closure (2011 Update). https://library.ahima.org/doc?oid=105074#.XNL5i-VKhpg

9. American Health Information Management Association. 2011. Protecting Patient Information After a Facility Closure (Appendix C: States with Laws, Regulations, or Guidelines Pertaining to Facility Closure). http://bok.ahima.org/doc?oid=105007#.XNL5TOVKhpg

10. Oklahoma State Department of Health. 2014. Oklahoma Standard Authorization to Use or Share Protected Health Information (PHI). https://bit.ly/2FEXVVH

11. Electronic Frontier Foundation. The Law and Medical Privacy. https://www.eff.org/issues/law-and-medical-privacy

12. Gareen I, Sicks J, Adams A, Moline D, Coffman-Kadish N. 2013. Identifying and collecting pertinent medical records for centralized abstraction in a multi-center randomized clinical trial: the model used by the American College of Radiology Arm of the National Lung Screening Trial. *Contemp Clin Trials* 34(1):36–44.

Marina Albuquerque de Souza Dantas, MD, (marinaalbuquerquede.dantas@nicklaushealth.org) is a Resident in Pediatrics at Nicklaus Children's Hospital in Miami, Fla., and a former Research Fellow in the Department of Emergency Medicine at Massachusetts General Hospital in Boston, Mass.

Lacey B. Robinson, MD, is a Research Fellow in the Division of Rheumatology, Allergy, and Immunology at Massachusetts General Hospital and an Instructor in Medicine at Harvard Medical School.

Elie Mitri is a Senior Clinical Research Coordinator at the Emergency Medicine Network at Massachusetts General Hospital.

Catalina Gallegos is a Senior Clinical Research Coordinator at the Emergency Medicine Network at Massachusetts General Hospital.

Ashley F. Sullivan, MS, MPH, is Director of the Emergency Medicine Network Coordinating Center at Massachusetts General Hospital.

Carlos A. Camargo Jr, MD, DrPH, is Division Chief of the Emergency Medicine Network at Massachusetts General Hospital, Professor of Emergency Medicine and Medicine at Harvard Medical School, and Professor of Epidemiology at Harvard T.H. Chan School of Public Health.

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The Data of Subject-Reported Adverse Events

Robert Jeanfreau, MD, CPI

Attributes of the thorough documentation of research data, endorsed worldwide by the U.S. Food and Drug Administration (FDA), the International Council for Harmonization (ICH), and the World Health Organization (WHO), are embodied in the ALCOA acronym, first used by an FDA Bioresearch Monitoring staff member.{1} "A" stands for accurate; "L" for legible; "C" for contemporaneous; "O" for original; and "A" for attributable. In 2010, the European Medicines Agency (EMA) added four additional attributes: **C**omplete, **C**onsistent, **E**nduring, and **A**vailable, thereby creating the more cumbersome acronym, ALCOACCEA.

The importance of thorough documentation is perhaps best appreciated by a closer inspection of the underlying rationale. As described in the following sections, there are three major, albeit related, reasons why adverse events (AEs), like all research data, should be thoroughly and consistently documented.

The Evaluation of Severity and Causality

First, a complete description of an AE is critical for the principal investigator's (PI's) evaluation of an AE's relatedness, or causality, and severity to the investigational product (IP). A one-word description is useless in this regard.

Even in those situations in which a very brief description might appear to be adequate to determine causality, a careful description is still necessary. Let's take as an example a study involving an IP to control atrial fibrillation. During the study, a subject is involved in a motor vehicle crash and reports that event to the coordinator. The subject denies any injury and provides no further description.

If no additional information is solicited, the PI may conclude that there was no AE and that the crash could not have been related to the IP. However, upon careful questioning, the subject thinks that he may have fallen asleep at the wheel. The subject is instructed to come to the site for an evaluation that reveals that the subject is having episodes of intermittent, complete heart block, which likely caused the subject to briefly lose consciousness.

Similarly, the PI cannot determine severity without an adequate description of the AE and its effect on the subject. Furthermore, based upon a good description of the AE, coupled with a thorough knowledge of the IP (including the mechanism of action, the half-life, and other information from the Investigator's Brochure), along with background information on the subject's medical history and any available laboratory studies, the PI may be able to formulate a differential diagnosis which then serves as a defensible basis for determining causality.

The Statistics of AEs

Secondly, this information serves as the starting point for the future statistical evaluation of a drug's safety profile.

The pursuit of medication safety is a complicated and a never-ending process that encompasses the entire lifespan of a drug. Understandably, the younger the drug, the more intensive the scrutiny. The greatest number of safeguards are in place for experimental drugs in their infancy, since safety information on risks and benefits is at its nadir.

Although the specific process will vary depending upon the stage of the drug's lifecycle, statistics plays an indispensable role at every step. Statistics require solid data, and critical to every phase is the reliable

garnering of data which first begins with the collection of AEs at the research site level. The entire subsequent process of safety evaluation could be flawed if the initial data are inconsistent or incomplete.

One cannot help but wonder if various problems encountered in pharmacovigilance, at least in part, could be traced back to the inadequate description of AEs obtained during clinical studies. According to one source, “In an attempt to solve this problem, many systems have been developed for a structured and harmonized assessment of causality. None of these systems, however, have been shown to produce a precise and reliable quantitative estimation of relationship likelihood. Nevertheless, causality assessment has become a common routine procedure in pharmacovigilance.”{2}

Although the description of AEs is an essential component of source documentation, the far-reaching importance of completeness in the description of AEs and the subsequent causality assessment are not only underappreciated, but also being questioned outright. An article from 2017 suggests that the PI process of determining causality is so subjective that the practice should be abandoned. According to the authors, their analyses demonstrate that assigning causality to AEs “is a complex and difficult process that produces unreliable and subjective data. In randomized double-blind placebo-controlled trials where data are available to objectively assess relatedness of AE to treatment, attribution assignment should be eliminated.”{3}

The determination of causality would then become purely a statistical exercise utilizing double-blind placebo-controlled studies. This view is supported in the FDA’s Clinical Investigator Course of 2018. One slide states: “Individual assessment (is) unlikely to help determine attribution for common AEs, i.e. headache, nausea, MI in elderly. Such AEs require aggregate analyses using a population approach (risk or rate with study drug vs. control).”{4}

Subject Safety

Even if causality assessment of AEs by PIs is abandoned in the future, there remains a third, compelling reason for the thorough description of AEs. A complete description is necessary for the PI to ensure the totality of a subject’s safety.

The PI’s responsibility extends beyond ensuring that the potential risks attributable to the IP are minimized. In the ICH’s Good Clinical Practice (GCP) guideline, ICH-GCP 4.3.2 states: “During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory

values**,** related to the trial. The investigator/institution should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware."

To determine if a patient-reported AE is indicative of a significant health threat, the PI must have an adequate description of the AE. Let's take, as an example, a subject having a headache. Causes of headaches are legion, and range from the relatively innocuous tension headache to the potentially life-threatening headache of a sentinel bleed.

Although the PI may feel that the IP is not causing the subject's symptom, the PI's involvement does not end there. If the subject's description is suggestive of a sentinel bleed, the PI must act. As one source observes, "Patients with subarachnoid hemorrhage (SAH) frequently describe the occurrence of an underestimated or even ignored severe headache in the days or weeks preceding the bleeding. If recognized early, this warning headache might lead to specific investigations and, if indicated, a surgical approach might avoid a dramatic hemorrhagic event."{5}

The Current Practice

Despite the clear importance of the proper collection of AEs, there are a number of challenges to its implementation, including the skill and time required.

Coordinators at research sites collect the vast majority of the data on subject-reported AEs and then present the information to the PI for evaluation of severity and causality. Interviewing subjects to obtain a complete description of an AE requires a complex skill set. Not only must the coordinator know which questions to ask for any given symptom, but also how to ask them and in what order. The result is lack of uniformity in how AEs are documented.

Bias, which can be nearly impossible to detect during an interview, can be bi-directional and requires considerable skill to avoid.

Admittedly, there has been an increasing emphasis on education and certification for coordinators. Moreover, many coordinators are nurses with the requisite skills. Nonetheless, the need for reproducible uniformity remains a concern. The amount and quality of information regarding AEs can vary widely within an organization's sites and may even vary within a single site.

Another roadblock is the amount of time required for this process. The duties of coordinators are broad and increasing. The thorough collection of information for an AE can be a time-consuming process for a

coordinator who is already overburdened with other duties. The frequent result is that the coordinator attempts to collect the information as quickly as possible. This pressured approach sometimes results in incomplete data. The frequency with which the PI, when presented with inadequate data, requests additional necessary information underscores the inefficiency of the current method.

A Different Approach

A potential solution is the use of well-crafted, electronic, self-administered questionnaires for the most common AEs. The questionnaires are loaded onto tablets available to subjects in the waiting room before a scheduled visit. These same questionnaires could also be accessed as an app on the subject's phone for home use. The information is then presented as a summary for the PI's review.

Importantly, in collecting subject data, the questionnaire presents qualifier questions with appropriate descriptions that a subject can easily process. Questions are layered into symptom tiers which are further layered into specific inquiries. The system is interactive in that answers to a question can alter which questions are subsequently presented.

The information within the questions is parceled to avoid overwhelming the subjects. The questions are also sequenced in such a way to make the flow of information intuitive. The questions and the sequence of questions are also fashioned to minimize the introduction of bias.

These goals, in part, are accomplished through logic trees and by presenting subjects with rational follow-up questions. The information is then processed in the background and sent to the PI in a narrative format, as can be seen in a sample questionnaire available online for a subject's reported symptom of fever.

Advantages

This system offers a number of other advantages over the current approach.

First, because the template could be utilized across a wide spectrum of clinical trials, this type of approach presents a much-needed standard for the uniform collection of data for AEs. There is a long-standing, recognized need for the standardized characterization of AEs. In 2001, in an article addressing variability in the assessment of AEs, the authors conclude: "There was considerable variability in categorization of AEs in an exercise following training for AE data collection. Type of report, relatedness, and severity were found to have more variability in reporting than did action taken or outcome."{6}

The past nearly two decades since that article have brought little progress in resolving this issue. In a recent review article of the analysis and reporting of AEs in randomized controlled trials (RCTs), the authors present similar conclusions: “This review highlighted that the collection, reporting, and analysis of AE data in clinical trials is inconsistent and RCTs as a source of safety data are underused. Areas to improve include reducing information loss when analyzing at patient level and inappropriate practice of underpowered multiple hypothesis testing. Implementation of standard reporting practices could enable a more accurate synthesis of safety data and development of guidance for statistical methodology to assess causality of AEs could facilitate better statistical practice.”{7}

A second advantage is that the system will save time for research staff, resulting in decreased sponsor costs. The technology, as used in electronic diaries for patient-reported outcomes, is readily available. Data security is ensured by not entering any identifiable subject information and by using vendors with a secure data exchange.

Lastly, such a platform offers a key component for the evolution of virtual clinical trials, which hold the promise of decreased trial costs, greater access to volunteers, and improved data quality.

For use on a wider scale, the questions could be approved by a panel of experts in the respective fields, with input from those in pharmacovigilance as well.

Conclusion

Laboring in an environment where there is no standard for approaching causality, the PI has no option but to rely on his or her own subjective approach. The first step in formalizing the approach to determining relatedness is to systematize the description of AEs.

Presently, the responsibility for the safety of current subjects and future patients rests squarely on the shoulders of the PI. A uniform system for collecting data will hopefully advance the industry’s search for safety.

References

1. Source Documentation. 2011. FCR - FDA Good Clinical Practice (GCP) Q&A. http://firstclinical.com/fda-gcp/?show=2011%2FRE+source+documentation

2. Naidu RP. 2013. Causality assessment: a brief insight into practices in pharmaceutical industry. *Persp Clin Res* 4(4):233–6. doi:10.4103/2229-3485.120173 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3835968/
3. Le-Rademacher J, Hillman SL, Meyers J, Loprinzi CL, Limburg PJ, Mandrekar SJ. 2017. Statistical controversies in clinical research: value of adverse events relatedness to study treatment: analyses of data from randomized double-blind placebo-controlled clinical trials. *Ann Oncol* 28(6):1183–90. doi:10.1093/annonc/mdx043 https://www.ncbi.nlm.nih.gov/pubmed/28184420
4. Yasinskaya Y. 2012. Safety Assessment in Clinical Trials and Beyond (U.S. Food and Drug Administration). https://www.fda.gov/downloads/Drugs/NewsEvents/UCM440805.pdf
5. Falco FAD. 2004. Sentinel headache. *Neuro Sci* 25(S3). doi:10.1007/s10072-004-0289-1 https://www.ncbi.nlm.nih.gov/pubmed/15549540
6. Raisch D, Troutman W, Sather M, Fudala P. 2001. Variability in the assessment of adverse events in a multicenter clinical trial. *Clin Theraps* 23(12):2011–20. doi.org/10.1016/S0149-2918(01)80153-3 https://www.sciencedirect.com/science/article/abs/pii/S0149291801801533
7. Phillips R, Hazell l, Sauzet O, Cornelius V. 2019. Analysis and reporting of adverse events in randomised controlled trials: a review. *BMJ Open* 9(2). https://bmjopen.bmj.com/content/9/2/e024537

Robert Jeanfreau, MD, CPI, (robertjeanfreau@medpharmics.com) is a Board Certified Internist affiliated with multiple hospitals and serves as the President and Medical Director of Medpharmics in Metairie, La.

[*Editor's Note: A coauthor on this article—not listed here—never responded to ACRP's request for a Statement of Independence from Commercial Influence.*]

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HOME STUDY

Rising Expectations in Research: Are You Sinking or Swimming?

Article One—Optimizing Medical Records Collection in Clinical Research: Lessons Learned from Two Pediatric Cohort Studies

LEARNING OBJECTIVE

After reading this article, the participant will be able to explain how the HIPAA Privacy Rule affects medical records collection and describe a systematic approach for records requests and inventory.

DISCLOSURE

Marina Albuquerque de Souza Dantas, MD; Lacey B. Robinson, MD; Elie Mitri; Catalina Gallegos; Ashley F. Sullivan, MS, MPH; Carlos A. Camargo Jr, MD, DrPH: *Nothing to disclose*

1. Complete medical records review for the MARC-35 and MARC-43 cohort studies included information from which of the following sources?

A. Patients' insurers and next of kin
B. Legally authorized representatives and study sponsors
C. Primary care providers and hospitalizations
D. Control groups and pharmacist providers

2. The study team utilized HIPAA-compliant authorization forms. How long were these forms valid for?

A. A year beyond the close of participant follow-up.
B. The form had no set expiration date.
C. Until the date set for the end of the research study.
D. The day each participant turned 18.

3. What agreement does the study's coordinating center have in place to facilitate medical records requests from enrollment sites annually?

A. Protected Health Information Agreement
B. REDCap Data Agreement
C. HIPAA Privacy Agreement
D. Data Use Agreement

4. In pre-review, how many initially requested medical records are typically not obtained from the primary care physicians contacted?

A. 10% to 15%
B. 15% to 20%
C. 20% to 25%
D. 25% to 30%

5. Per the HIPAA Privacy Rule, providers cannot release protected health information by what means?

A. Phone
B. E-mail
C. Postal service
D. In person

6. According to the authors, what total response rate is typically achieved following final requests for medical records?

A. Approximately 50%
B. About 70%
C. At least 80%
D. Nearly 100%

7. Which of the following do the authors suggest as tactics for decreasing rates of declined medical records request forms?

1. Setting expiration date after study completion.
2. Allowing multiple providers to release records.
3. Offering modest payments for delivered records.
4. Paying attention to state-specific requirements.

A. 1, 2, and 3 only
B. 1, 2, and 4 only
C. 1, 3, and 4 only
D. 2, 3, and 4 only

8. The authors suggest language about which of the following to minimize the need for separate forms for each medical provider?

A. Penalizing providers and healthcare facilities that decline to release records.
B. Offering providers and healthcare facilities rewards for releasing records.
C. Opening details about the cooperation of providers and facilities to the public.
D. Authorizing all providers at all healthcare facilities to release records.

9. The authors cite unfamiliarity with the HIPAA Privacy Rule for which of the following situations?

A. Facilities demanding payment for the release of requested medical records.
B. Facilities refusing to release medical records without FDA authorization.
C. Facilities not understanding when or if a medical request form expires.
D. Facilities only releasing medical records in face-to-face meetings with lawyers.

10. What do the authors recommend in the event that a healthcare facility from which medical records are being sought closes?

A. Contacting the Department of Health in the appropriate state.
B. Filing a grievance with the U.S. Food and Drug Administration.
C. Hiring private investigators to track down the necessary records.
D. Expecting patients or their legally authorized representatives to locate the records.

Article Two—The Data of Subject-Reported Adverse Events

LEARNING OBJECTIVE

After reading this article, the participant should be able to outline the importance of, and a potential new approach to, collecting data on subject-reported adverse events in terms of evaluating severity and causality to an investigational product, evaluating a drug's safety profile, and ensuring subject safety.

DISCLOSURE

Robert Jeanfreau, MD, CPI: *Nothing to disclose*

11. What do the three C's in the ALCOACCEA acronym stand for?

A. Consequential, capable, competent
B. Contemporaneous, complete, consistent
C. Controversial, contextual, cooperative
D. Collaborative, clinical, conservative

12. What is important to the principal investigator's (PI's) evaluation of how an adverse event (AE) is related to the investigational product?

A. A complete description of the AE.
B. A list of acceptable AEs from the sponsor.
C. A sworn statement from the patient.
D. A judgement from the FDA.

13. What timespan is covered in terms of tracking medication safety?

A. R&D phases prior to drug's launch.
B. Initial marketing and first two years of drug sales.
C. The entire lifespan of a drug.
D. Post-marketing phase up to 10 years.

14. What is the FDA's view on determining causality of common AEs?

A. Individual assessment is unlikely to help.
B. Only certified PIs can determine this.
C. Sponsors have final validation of causality.
D. Patients alone can make this judgement.

15. What importance to the PI does a complete AE description have?

A. Necessary for complete records in ClinicalTrials.gov.
B. Necessary for convincing sponsors that a problem exists.
C. Necessary for ensuring protection from patient lawsuits.
D. Necessary for ensuring totality of subject's safety.

16. Who collects most of the data on subject-reported AEs at study sites?

A. The PI
B. Coordinators
C. Monitors
D. Data managers

17. What is the danger of a rushed and overburdened approach to collecting AE information?

A. May result in patient removal from study.
B. May result in legal action by sponsor.
C. May result in injury to the patient.
D. May result in incomplete data.

18. What does the author suggest as a potential solution to the challenge of collecting data on the most common subject-reported AEs?

A. Developing a registry for PIs to enter the reports.
B. Creating a new staff position for collecting the data.
C. Using a questionnaire self-administered by subjects.
D. Ceasing collection of the data by study coordinators.

19. What does lack of standardized characterization of AEs lead to?

A. Variability in categorization of AEs.
B. Financial penalties for poor reporting.
C. High subject drop-out levels from studies.
D. Sponsors declining to use sites for future studies.

20. According to the author, standardized reporting practices for AEs could enable which of the following?

1. Cost savings on associated technology.
2. More accurate synthesis of safety data.
3. Saved time for research staff.
4. Evolution of virtual clinical trials.

A. 1, 2, and 3 only
B. 1, 2, and 4 only
C. 1, 3, and 4 only
D. 2, 3, and 4 only