Whitepaper

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The Case for Better Health History Records

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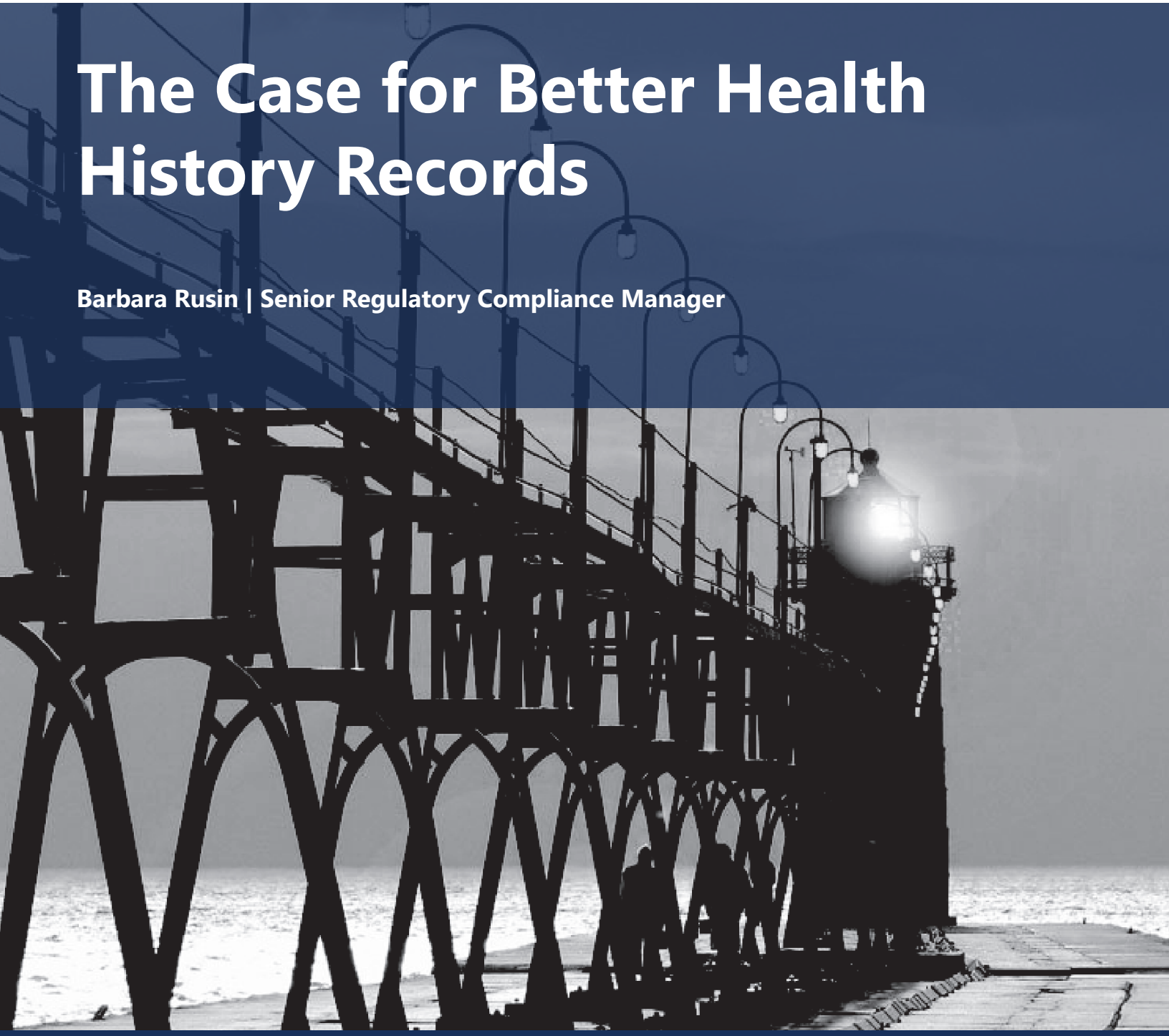

Part 1: Regulatory Requirements

One of the most consistent and most common findings following a regulatory agency clinical site inspection is enrollment of ineligible subjects. Indeed, this is the 2nd most common observation against clinical sites by the FDA over the course of the last three (3) years, and is among the Critical Observations from MHRA (MHRA, 2016). Importantly, unlike most other issues for which multiple examples are required prior to being considered an observation, enrollment of a single ineligible subject results in an observation for the clinical site, and enrollment of more than one (1) such subject can lead to official regulatory agency action independent of other findings.

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Outside of the clinical site's inspectional outcomes, study sponsors and clinical research organizations (CROs) may also be negatively impacted when ineligible subjects are enrolled. This White Paper aims to educate clinical investigators, CROs, and sponsors alike in regard to pertinent regulations, and will also present the possible outcomes of enrollment of ineligible subjects relative to all stakeholders. Finally, a case will be made for how much medical history should be collected, directions will be provided for how it should be reviewed, and I will discuss some of the barriers to collection of health history record and potential ways to overcome them.

Regulatory Guidance to Follow

Ineligibility is often not clear to the investigational site, monitor, or sponsor prior to audit or inspection. A common way at looking at this matter on their part is to consider it a deviation from the protocol. However, this is not acceptable from a regulatory point of view. The reasons behind the enrollment of ineligible subjects can vary from sloppiness, to a change in a medication, to failure to identify an unmet medical need, and go all the way up to fraud. Yet, the most common contributing factor in the last several years has been a failure to collect and/or review adequate medical histories prior to enrollment or randomization. This failure may be due to increased commercial pressure to meet rapid enrollment goals among others.

From a regulatory perspective, it is critical to collect adequate case histories on all potential study subjects. Focusing on the markets from which approvals are most often sought for new or generic drugs (Europe, US and Japan), the following list is pertinent, detailing specific guidelines laid out by regulatory authorities: see *Table 1. Regulatory Authority Guidelines*.

In practice, these requirements break down to two simple concepts: don't deviate from the study protocol by enrolling ineligible subjects, and request and maintain all records which prove eligibility.

What Happens When You Don't Adhere to These Principles?

One of the pitfalls of enrolling an ineligible subject is the potential for compromising subject

safety. For instance, a subject with an unknown contraindication may be more likely to experience an adverse or serious adverse event; and that event may be more difficult to treat without an accurate medical history. Additionally, there may not be a potential benefit for subjects who do not meet eligibility criteria such as having had a disease state for a specified period of time, having a specific form of a disease, or having failed specific previous therapies.

This alteration of the risk-benefit ratio for the individual can translate to the patient population at large. If enough subjects in a study or related studies are ineligible, but it is not known at the time of statistical analysis, the safety profile and side effects/adverse events will not necessarily be accurate. In essence, the trial will not have been controlled and the scientific validity of the study itself will be called into question. This then negates the potential value of the medication for the population it was intended for.

Statistical Analyses can be Affected

The power of any study can suffer with increasing subject ineligibility in terms of statistical analysis. Studies are developed with these parameters in mind, allowing for removal of a specified percentage of subjects without affecting the ability to analyze data. However, if too many sites fail to perform adequate medical history reviews and they enroll ineligible subjects, this threshold can be overcome rather quickly.

The exclusion of subjects for whom end point analysis is not possible, such as withdrawals or removals, may intensify situations like this. This can further decrease the number of evaluable subjects.

Table 1. Regulatory Authority Guidelines.

Regulatory Authority Guidelines	
ICH E6 (R2) Section 4.5.1:	"The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies) and which was given approval/favourable opinion by the IRB/IEC."
ICH E6 (R2) Section 4.5.1:	"The investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval/favourable opinion from the IRB/IEC of an amendment, except where necessary to eliminate and immediate hazard(s) to trial subjects..."
ICH E6 (R2) Section 4.9.0:	"The investigator should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects."
21 CFR Part 312.60:	"An investigator is responsible for ensuring that an investigation is conducted according to... the investigational plan."
21 CFR Part 312.60:	"An investigator is responsible for... protecting the rights, safety, and welfare of subjects under the investigator's care."
21 CFR Part 312.62(b), case histories:	"An investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigation drug or employed as a control in the investigation."
Ministerial Ordinance on Good Clinical Practice (J-GCP) for Drugs Article 44, Selection of Subjects:	"The investigators etc. shall select prospective subjects, taking into account the following principles: (1) The prospective subject's health condition, symptoms, age, ability to give consent, etc. shall be carefully considered, in line with the objective of the clinical trial, from ethical and scientific viewpoints."

Intent-To-Treat (ITT) analysis can also be negatively impacted if the number of subjects who are ineligible is too high, in the cases of not having the disease under study. In such instances, all of the ineligible subjects should be excluded from this type of analysis. In many situations, this is the only analysis considered vital for regulatory approval further impacting the validity of the study.

Beware of Potential Citations

For many clinical sites, there are very real regulatory risks associated with the enrollment and randomization of ineligible subjects.
The FDA – like most regulatory bodies – issues citations if a pattern of errors is identified. This is commonly referenced as a "rule of three," in that three or more examples of the same error type are considered adequate to justify a citation if there is an identifiably negative impact.

The two exceptions to this rule of thumb include:

1. The failure to adequately consent a subject or the enrollment of an ineligible subject, with a single identified example being enough to warrant an observation/citation in either instance, and

2. Enrollment of multiple ineligible subjects, or the combination of enrollment of a single ineligible subject with other serious observations, can make official action a near certainty for the clinical site.

In one of my experiences with the FDA, 50 percent of subjects enrolled at a site were identified as ineligible due to a lack of adequate review of medical histories. The outcome in this case was a warning letter to the clinical investigator, and the refusal of the medical institution to allow the investigator to do further research. The facilitate continuation of the long-term observation of study subjects in the affected studies and thus complete the studies as required, the sponsor was forced to obtain special permission from the FDA, and the medical institution provided special oversight of the clinical investigator during this period.

More recently, approximately 60 percent of the clinical sites reviewed by MMS investigators have enrolled at least one ineligible subject due to lack of request for and/or review of subject medical histories. In these cases, at a minimum, the individual subjects have had to be removed from all planned efficacy and/or safety analyses. In some instances, it has been recommended that the entire clinical site be removed from all analyses due to additional data integrity or subject safety issues. For the sponsor, the ability to submit a marketing application or an abbreviated new drug application (NDA) was therefore compromised in some instances.

Part 2: How Much Medical History is Necessary and How Should it be Reviewed?

How then do you ensure you have adequate information to support eligibility?

Most studies that I have reviewed in the last two years or more have enrolled subjects based solely on verbal medical histories and completed general medical history forms, without support from medical records.

It is not clear when this change to subject-only reporting of medical histories occurred, but it appears to have happened slowly over the last decade, and it is certainly becoming more the norm in the pharmaceutical industry. Although the subject-provided history may seem like enough, it most definitely is not—for a few reasons.

Verbal History is Not Enough

First and foremost, people are notoriously bad

personal historians when it comes to medically-related issues, even given good memory and mental health status. Indeed, at more than 50 percent of the clinical sites that I have personally audited in the last year in which someone was found to be ineligible, the review of written medical records and the subsequent resolution of conflicting information has shown that verbal histories were incorrect.

Even more subjects were found ineligible when sites followed my advice and requested historical medical records to support subject-provided histories, then re-reviewed eligibility status.

Second, verbal histories are, of course, very dependent on the memory and understanding of the person supplying it. Age, stress level, complicated medical histories, and familiarity with medical terminology can all play a part in reducing recall. Subjects may have unrecognized memory disorders; may have failed multiple treatment regimens, which could have lasted months or years; could have multiple medical conditions; or may have a disease with a complex etiology.

Third, financial motives can never be dismissed, particularly for studies in which there is recruitment of "healthy volunteers."

Finally, subjects may just not know everything that has been documented by their physician(s) as long-term or potential health issues. A patient's doctor, for instance, may be worried about their high blood pressure, which has been above normal for months or years. If a patient has not been medicated for it yet, they may not consider themselves to have hypertension, although they technically do.

Tips for Gathering the Proper Medical Records

To ensure that subjects meet eligibility criteria and do not face unknown risks by participating in a clinical trial, all necessary written medical records should be gathered to support each inclusion and exclusion criteria. As such, the study team should know the potential subject's primary care physician's contact information, along with that of as many specialists, hospitals, diagnostic centers, or clinics where the person has been examined and/or treated as is possible to collect.

Requested records should cover at least a six (6) month period, dependent on inclusion and exclusion criteria requirements (i.e., the subject may be required to have had a condition for at least a year). For all potential subjects, each set of records used to substantiate eligibility should

Quick Tips

1. Gather all necessary written medical records to support each inclusion and exclusion criteria.
2. Requested records should cover at least a six (6) month period
3. For all potential subjects, each set of records used **should include:** a summary of the most recent history and the patient's historical condition(s), a physical, and the most recent clinical laboratory and diagnostic test results.

include, at minimum, a summary of the most recent history and physical, a summary of the patient's historical condition(s), and the most recent clinical laboratory and diagnostic test results. If such summaries are not available, records covering the missing information (fuller histories, recent clinical lab results, etc.) should be requested.

The period covered should be proportionately lengthened, however, if the disease under study has a longer etiology and/or prior treatments are required to have been received or not received (i.e., radiation therapy, specific immunotherapy, etc.). If the individual subject has a condition which was diagnosed/treated for longer than 6 months and which could affect their eligibility or safety, the included period should be extended for this situation as well.

If the volume of records is not prohibitive, it is a best practice to gather complete medical histories related to all inclusion and exclusion criteria, as well as all comorbidities.

Concomitant Medications and Other Risks

In addition to reviewing the collected records for inclusion and exclusion criteria, and comorbidities, notes should be taken of concomitant medications, as they can provide clues to medical conditions that were neither verbally reported by the potential study subject nor explicitly listed in the medical records received.

To ensure accuracy, the list in the medical record(s) should also be compared to any list of medications that the study volunteer provided. Notably, if the subject is not adherent to prescribed therapies, it can be an indicator of potential subject compliance issues during the study.

The requested records should also be reviewed for any conditions which may complicate the study therapy, or are determined by the study investigator to potentially pose additional risks to the study subject, even though they were not listed in the exclusion criteria. These potential complicating factors can be comorbidities, historically adverse events while on specific treatments, or even participation in other clinical trials too recently.

Importantly, as all studies are reviewed by regulatory health authorities, like the FDA, and investigational review boards/ethics committees to ensure that risks and potential benefits are balanced, this last aspect of the medical history review should not be discounted. Certainly, protocol developers cannot foresee all potential risks that a patient population may face when there is a treatment under study. Since conditions outside the inclusion and exclusion criteria may be important to maintaining the approved risk-benefit balance when looking at an individual patient, the onus is on the investigator, as a physician, to ensure that his/her patient population is adequately screened and protected from undue risk.

Preventing risk to your patient can only be done with a full understanding and thoughtful review of each individual's medical history in as complete a form as possible. Always keep in mind that failing to prevent the participation of a subject who is ineligible or poses other additional risks while on the clinical study not only affects clinical site subject management, but it also increases the workload related to pharmacovigilance and safety reporting teams, and can confound study results during statistical analysis.

Resolving Conflicts in Medical Records

Even when you have all of the medical records, and are diligently reviewing them, histories may not always be clear cut, and may not match what the patient has reported. So, what is to be done when medical records conflict?

The simple answer is that the review proceeds just as it would for any new patient to a primary care practice. Historical and current treatments should be used to provide support for a diagnosis, and current physical examinations and clinical testing should be used in support as well. In addition, historical diagnostic studies should be requested if this has not already happened, and/or new diagnostic tests may need to be ordered.

All records should be reviewed to determine sources. If one record only relied on the patient's own reporting (i.e., verbal or completed intake form), while another relied on exams and tests, the personal reporting should be ruled out.

As additional support, the general/primary care physician or even specialists can be asked to provide written input, resolution and/or historical perspective via a letter. And, when there is a lack of diagnostic evidence (i.e., no documented history of an exclusionary condition, no treatment in use), it is then that a verbal or written confirmation by the patient or their legally-authorized representative is most appropriately utilized as documented support.

In all cases where a conflict has had to be resolved, the records reviewed, the methods used for the review, and the final decision on diagnosis(es) needs to be documented by the investigator in a note to file, memorandum, medical record, or source worksheet.

Part 3: Identifying Barriers to Access

Obstacles in Accessing Medical Records

Given the multiplicity of electronic document formats, the cost of attaining records, and many other factors, procurement can be a daunting task. In defining the barriers to access to historical medical records, it is important to first recognize that some potential study subjects will come with no obstacles to medical history availability, while other may present a combination of issues which must be tackled. Having flexibility in dealing with each situation is a must, and should be based upon clear identification of each issue at play. The most common barriers found during audits include:

- Subject refusal to provide permission for access;
- Charges implemented by record holders;
- Incomplete records;
- Document retention periods and locations;
- Education of staff members in charge of records release;
- Formatting of provided records, and;
- Time to procurement.

Although many of these barriers are self-explanatory, some deserve clarification as to how they appear and how they affect clinical research.

In the age of electronic medical records (EMRs), patient portals, and healthcare insurance web sites with medical claims information available at the touch of the button, it seems a little incongruous that many patients and physicians still struggle to get historical medical records. One of the bigger factors for patients seeking records is cost, which can vary widely between health care providers, and may even be passed on to requesting physician offices.

Charging Patients for Records

In the United States, under the Health Insurance Portability and Accountability Act (HIPAA) of 1996, patients can be charged for records. Although the US Department of Health and Human Services recommends a charge of only

$6.50 for an entire record, requires that charges be "reasonable", and has provided new regulations forbidding page-by-page fees, many healthcare providers charge well in excess of the recommended amount – sometimes into the hundreds of dollars.

These charges, which can be prohibitive for many patients, are considered to be the "administrative" costs of collecting, collating, copying, and otherwise handling medical records, many of which may still be in paper format.

In contrast, under GDPR, providers cannot routinely charge for records. However, if they have already been provided once, administrative or communication fees can be applied.

In Canada, on the other hand, regulations around charges for and availability of medical records vary due to differing territorial and provincial privacy laws, which should be consulted to determine allowed charges that patients may face.

Putting Pen to Paper

A common hurdle, whether you're a patient or a health care provider, is the ability to get a complete medical record. Several factors contribute to this issue, including the fact that some records are handwritten on paper while others are electronic, there is often a lack of integration of test results and documents from other facilities or providers, physician retirement or death results in record ownership and storage changes, and there can even be a refusal of some health care providers to supply complete medical records.

As the medical care industry in the US has been forced to begin using EMRs, the dependency on paper medical records has fallen sharply and will continue to do so, but this has not entirely been alleviated and records more than 5-10 years old may well be paper or on a disparate system.

The same is also true globally as many countries are investing heavily in electronic systems, while remote areas and poor regions continue to rely on pen and paper. Getting these paper records from one medical provider to another can prove daunting, depending upon the size of the records and copying or transmission capabilities. Since patients may be treated at multiple facilities, just finding out who to ask for records can complicate matters significantly, as most providers do not integrate records from specialists, laboratories, diagnostic centers, or hospitals directly into their own files to create a single repository for each patient.

Although some large health care systems do integrate records, they are also often only the records from providers and affiliates within their own system, and are usually only the electronic documents. The potential outcome, then, is study staff spending hours requesting and gathering the records needed, and putting them into a single format for clinical research.

Hospitals not Releasing Full Records

All this assumes that other medical providers will share complete medical records. While HIPAA guarantees access to complete medical records with some exceptions (i.e., mental health records, substance abuse treatment, etc.), a Yale study performed in 2018 clearly showed that only 53% of US-based hospitals "provided patients the

option to acquire the entire medical record." Physician offices, pharmacies, medical clinics, and health insurers, all of whom fall under the auspices of HIPAA and from whom records may be needed, should not be expected to fare much better.

Under GDPR, the outlook is improved, as health care providers are required to share the entire medical record with few exceptions (i.e., if the record discloses information harmful to a third party, is privileged, or is under court order) unless they can offer a reasonable explanation for not doing so. Even then, if the patient does not agree with the reasoning, she has the right to bring the issue to the Information Commissioner's Office (ICO) for review. Thus, under GDPR, health care providers may be expected to only refuse handover of exceptionally old records which are truly difficult to gather.

Third-Party Sharing of Medical Histories

Finally, the clinical researcher faces an additional barrier of staff at other healthcare provider facilities not recognizing that medical records can be provided to a third-party patient representative, or even other physicians.

Moreover, if they do provide the records, it is not always assured that the document format will be acceptable, as photocopies or faxes may be unreadable or the electronic program used to create the records may be incompatible with other systems.

Indeed, EMR compatibility has been a major obstacle since before 2013; and even given the recent move to create compatible electronic communication systems, the transfer of patient data across software systems can be accompanied with steep software developer charges that only large healthcare systems can absorb.

Importantly, both HIPAA and GDPR require that the patient receive medical records in their chosen format, but in the US this requirement is often not well-heeded. In Europe, GDPR is not old enough to provide full insight as to whether the provision will be adequately met in the near term as many providers are still in the educational stages of awareness.

Add to all of this the fact that HIPAA allows 30 days for fulfillment of a records request, and GDPR allows 30 days for an answer as to whether the request will be met, and it's obvious that collecting medical records at all can become a headache.

Going back to the previous installments of this series, it should be clear that there are serious risks involved if medical records are not adequately gathered and reviewed for study subject eligibility. These risks from the site, contract research organization (CRO), and sponsor level should not be taken lightly.

Part 4: Overcoming Barriers to Medical Records Access

Educating Patients is Paramount

One of the first problems that clinical investigators may face when attempting to attain medical records is patient refusal to either provide them, or allow them to be collected. At the outset of such a refusal, any potential study subject should educated as to how important medical histories are to research studies.

Some of the key reasons for requiring medical histories have been presented in Parts 1 and 2 of this series, and these reasons should be shared with your patient. If it is a concern, patients should also be informed that they have a right to request and receive their medical records (themselves or provided directly to you), even if they owe the practitioner or firm a debt at the

time of the request. The debt does not have to be paid as a condition of the records release under US, European Union, or Canadian law in addition to the laws of a majority of other regions and countries.

If a non-custodial parent can grant consent to clinical trial participation on behalf of a child under local or country-specific regulations, they should be aware that they also have medical records access rights – unless a court has ordered otherwise. Non-custodial parents should also be made aware of this right if they cannot grant consent to clinical trial participation, but the custodial parent has done so.

When a patient still will not agree to allow medical records to be shared with you, they should not be included in the clinical trial as their eligibility cannot be objectively confirmed.

Long-Term Patients and Provider Partnerships

Of course, patient permissions for medical record access may not be an issue if the patient has attended your practice for some time. Having information on record about, and an established connection with, their primary care physician, general practitioner, and/or treating specialists provides a clear opportunity to contact other providers to gather additional medical records and history as needed.

On the same token, enrolling subjects who have been treated within the same healthcare network allows access to many, if not all, of the necessary historical medical records. With medical records so readily available in these situations, consideration should be given to enrolling such patient populations only.

Additionally, professional relationships with other practitioners can also be taken under account when determining what patients to consider for clinical trials. In cases of established professional relationships with area clinics, general physicians, or even the specialists who treat the disease under study, it is possible to leverage these relationships to receive complete medical histories when the patient provides medical release permission.

If Patients Must Secure the Medical Record…

When you have to ask a patient to secure medical records, giving them the knowledge and confidence they need to complete the task becomes very important.

If the patient is concerned about charges that they may incur, they should be educated about their rights to their own medical records. Patients can be provided a copy of their rights under HIPAA, a copy of the Department of Health and Human Services (DHHS) 2016 guidelines, or their rights under GDPR, all of which limit charges to patients in different ways.

To further navigate HIPAA, they can also be directed to the GetMyHealthData website, which is patient-focused and friendly.

In Canada, patients should be provided information garnered from their Province regarding Healthcare Information privacy, as many of these territorial regulations also provide caps on or additional requirements regarding

charges. In other countries, patients should be directed to local websites or provided physical printed copies of their rights as appropriate.

Additionally, any of these websites, printed information, or both can be used for reference when the patient has a concern about third party access (i.e., someone picking up the medical records for them).

If a patient encounters difficulty with a given practitioner or firm, having a printed pamphlet of their rights may be useful to subsequently present to the refusing entity. To go a step further, consider providing patients with a model medical records release form to take to the necessary office or treatment facility. In this way, if the facility does not have their own process or form, this hurdle may be more easily overcome. Under HIPAA in the US, a written request from the patient is not required if the records are to be used for the purpose of "treatment" of the patient. However, some states require a signed release for records and the patient should be prepared to sign for them.

In the case of mental health records, access may require additional permissions from the patient.

In such cases, the patient should be educated that they will have to specifically allow the release of the mental health records, and that those records may not be given directly to them, but be mailed to your office. If this is the case, the patient should be assured that mental health records are treated differently not only to protect them, but to ensure that records are not misinterpreted as they may not contain a diagnosis but, instead, impressions which are considered more subjective but are the norm for the mental health area.

Format of Records

One of the more considerable hurdles faced by many clinical investigators is receiving electronic records in a readable format.

Under HIPAA and GDPR, records must be provided to patients in the format they choose, whether it be paper or specific electronic file format. You may, thus, consider having the patient advocate for the format you require. In addition, the method of record sharing can be directed by the patient (i.e., CD, fax, in person, in an email, or via patient portal from which print-outs can be made). Under GDPR, it should be noted, if the patient makes a record request electronically, the holder of the medical record is allowed to assume that electronic provision is acceptable (i.e., requests made via email may be responded to by emailing the records to the patient).

Given that medical records have been migrating from being paper-based in most of the world, to being electronic, it should be expected that older records will be provided as paper or as scanned copies maintained electronically. If very old medical records are requested, it should also be expected that they may not be available without considerable effort from the holder if they have not been scanned and electronically housed. In such cases, under GDPR, the holder is not obligated to provide the requested records.

Time to Receipt of Records

When you have requested historical medical records, but they are not yet available and you are nearing the end of the screening period, there are still actions you can take.

Even if it is not written in the protocol, you can contact the study sponsor and request to re-screen a potential subject. If re-screening is allowed, ensure that your IRB/IEC is aware of the change to the protocol and acknowledges/approves the decision. Maintain all sponsor approvals for re-screening in the trial records in such a case.

In addition, you may request that the screening period be extended for your particular patient. Again, IRB/IEC review and acknowledgment/approval of such a pre-planned deviation from protocol is necessary and documentation of sponsor approval must be maintained with the trial records.

Lack of Availability or Full Information

Even using all of the above suggestions, clinical investigators can find that they are still unable to get the medical records they need to support eligibility determinations. In such instances, the patient's general practitioner should be contacted and asked to confirm inclusion criteria, and rule out exclusion criteria. They should also be informed of the risks of trial participation so they can share any conditions that may put the patient at greater than expected risk. As they may be expected to know the patient well, the general practitioner may also be asked if they would expect the patient to be compliant with the trial if it demands completion of records (i.e., diaries), requires a great number of office visits, or requires participation in an extended follow-up period.

If a specialist has been consulted by the patient for a condition relevant to the clinical trial (i.e., for the disease under study, for exclusionary conditions, etc.), they should also be asked to confirm inclusion criteria are met, exclusion criteria are not met. As with the general practitioner, documentation from the specialist should be maintained in the subject records.

Worth the Effort

Although considerable effort may be required to get historical medical records, this effort must be balanced against the risks of not getting them and enrolling an ineligible or high-risk subject. As pointed out at the beginning of this White Paper, there can be serious repercussions in such cases, up to and including investigator debarment, requirements to repeat analyses, or the requirement to repeat an entire study. Given these potential negative impacts, each clinical investigator should take the time to develop best practices for obtaining medical records, both to ensure a successful clinical trial and your own success as an investigator. Using some of the suggestions in this series, every clinical investigator should be able to begin this process.

About the Author

Barbara A. Rusin is Regulatory Compliance Manager at MMS, providing technical oversight and direction to a global regulatory team, spread across four continents. Prior to MMS, Barbara was a Bioresearch Monitoring Investigator and Biologics Specialist with the Food and Drug Administration's (FDA) Detroit District office.

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