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Life After Drug Approval… What Programmers Need to Know About REMS

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ABSTRACT

While most of the spotlight in the drug development process focuses on clinical trials and the effort to get drugs approved, the U.S. Food and Drug Administration (FDA) is turning to Risk Evaluation and Mitigation Strategy (REMS) as a way to approve drugs they may have safety concerns about while closely monitoring those potential safety issues once the drug is approved. A REMS often involves drugs that have a high risk for specific adverse events, and the FDA requires manufacturers to put a program in place to mitigate those risks. REMS are a growing sector of the market, and will only continue to grow in the future. Therefore, it is increasingly valuable to know the "ins and outs" of how to approach programming with REMS data, as it is very different from clinical trial programming. This paper explores the basic concepts of a REMS from a programming perspective: from a high level explanation of what a REMS is to the main differences programmers will see between clinical trials and REMS. We will discuss what types of data are typically included in REMS, what data issues to expect, general table structures and reported statistics, and how to effectively report data from an ongoing/changing database throughout the life of a REMS.

INTRODUCTION

Risk Evaluation and Mitigation Strategies (REMS) are becoming increasingly common in the pharmaceutical market, and their increased complexity has resulted in more involvement by programmers who are often "borrowed" from the pool of statistical programmers who support clinical trials. To ensure successful support of REMS, programmers coming from the clinical trial sphere need to understand how the data and requirements to analyze a REMS are significantly different from clinical trials. From the challenges of figuring out where relevant data is stored to analyzing an ongoing database that is never totally "clean", it is critical for programmers to understand how the data and the role they play in analyzing it differs for REMS.

This paper explores the basic concepts of a REMS from a programming perspective, including the main differences between clinical trials and REMS – the different types of data collected, potential challenges to analyzing data collected in the "real world," typical statistics that are reported in tables, how to handle various reporting periods and how data can change from year to year.

WHAT IS A REMS?

DEFINITION OVERVIEW

A REMS is a "drug safety program that the [FDA] can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks. REMS are designed to reinforce medication use behaviors and actions that support the safe use of that medication" (Risk Evaluation and Mitigation Strategies | REMS | FDA). REMS are effectively a commitment by manufacturers to take additional steps beyond the safety information included on all medication labels to ensure that their products are used safely.

A REMS is not intended to mitigate all possible adverse events, but rather to mitigate specific adverse events that may have shown higher risk to patients in clinical trials. How these risks are mitigated can take one of several forms, or a combination. In some cases, a Medication Guide is required to be provided to patients to inform them of specific risks and how to avoid potential serious side effects. In others, a Communication Plan is required to actively inform various stakeholders (i.e., patients, prescribers, pharmacists) of the specific risks involved with a treatment and specific ways to actively monitor for and/or mitigate those risks. And finally, a REMS could include additional requirements that

stakeholders perform to ensure the safe use of the product. These requirements, collectively referred to as Elements to Assure Safe Use (ETASU), can include requiring that pharmacies be certified before dispensing, that prescribers be trained before prescribing, that patients demonstrate they meet safe use conditions (such as blood pressure below a specified threshold), as well as other conditions. Rather than deny approval of much-needed treatments, the FDA can require a REMS to ensure the benefits of the drug continue to outweigh the risks while giving patients safe access to products with known risks.

While conditions similar to REMS existed previously, the Food and Drug Administration Amendments Act of 2007 gave FDA the authority to *require* a REMS from manufacturers. Since then, there have been over 250 products approved with some level of REMS requirements. This paper will focus on REMS that include ETASU, as these are the programs that include more complex reporting requirements that often require programming support.

REMS DOCUMENT

A proposed REMS document is typically submitted with a New Drug Application (NDA) when early feedback from FDA indicates that a REMS may be required. Once reviewed and approved by FDA, the REMS is a public-facing document that is attached to the approvable letter after FDA completes review of an NDA. The FDA posts a list of all current REMS on its website (see Approved Risk Evaluation and Mitigation Strategies (REMS) (fda.gov)). In addition to specifying exactly what risks the REMS is intended to mitigate and the method(s) to accomplish those mitigation goals, the REMS document includes copies of the medication guide, educational materials that will be provided to stakeholders, enrollment forms, and any other forms required for REMS data collection. For programmers, this document is the source for the REMS equivalent of CRFs.

REMS SUPPORTING DOCUMENT

In contrast to the public REMS document, the REMS Supporting Document is a confidential document between manufacturers and FDA. The Supporting Document provides specific details about the elements of the REMS, how the manufacturer will implement the components of the program to meet REMS goals, and what metrics the manufacturer will report back to the FDA to demonstrate how well the REMS is meeting those goals. For REMS, this Supporting Document is the equivalent of a clinical trial protocol.

REMS ASSESSMENTS

A key concept with REMS is that they require manufacturers to report back to FDA at specified intervals on how well the REMS is meeting its risk mitigation goals. Part of that includes reporting on how closely the stakeholders are fulfilling their obligations to the REMS (e.g., if prescribers are passing knowledge tests and/or if they are reviewing the medication guide with patients prior to prescribing to patients). A REMS Assessment Report (AR) is the equivalent of the Clinical Trial Report but is required at specific intervals throughout the life of the REMS; ARs are effectively a series of very thorough Interim Analysis reports.

ASSESSMENT SCHEDULE

The frequency at which ARs are required to be submitted to FDA is detailed in the REMS Supporting Document but is typically required at 6 months after initial product approval, 12 months after approval, and then annually thereafter.

One key difference between Clinical Trials and REMS is that the AR submission date is not an internal goal for the manufacturer that can shift if required; once a submission date for the AR is determined, it cannot be changed without FDA approval. If the REMS AR is submitted late, the FDA can take actions to enforce compliance including fining the manufacturer. The frequency of AR submissions can change over time, or FDA can release a manufacturer from its REMS obligations if the risks that the REMS was designed for are no longer a concern.

REMS PROGRAM METRICS

Based on the extent of REMS requirements, there are a number of ways in which FDA can require data collection and reporting. REMS that include ETASU also include an Implementation System to collect information on the required elements. This typically includes enrollment or certification of various stakeholders in the REMS. Enrollment of patients may include their demographic characteristics and geographic location, while certification of prescribers may include their medical specialty and degree. In addition, information regarding product shipment and/or dispensing from distributors and/or pharmacies is another data element that is used for reporting a variety of metrics, from volume of product being distributed to number of enrolled patients who are actively receiving treatment.

While many of the metrics required by FDA may look similar across REMS programs, each is tailored specifically to the drug being monitored. Therefore, an enrollment summary table may have the same components (number enrolled and number actively being treated) but the requirements for enrollment, additional information collected and definition of "active" could vary widely.

Beyond general operational metrics, REMS with ETASU often collect information specific to the serious adverse events they are designed to mitigate. For example, if serious liver damage is the risk that the REMS is designed to mitigate, there may be a requirement for patients to have liver laboratory tests drawn every month to ensure it is safe for them to continue receiving treatment. The REMS may require the prescriber to report the results of specific laboratory tests to the REMS on a Patient Status Form or Patient Monitoring Form. As the risks that each REMS is designed to mitigate can vary as widely as the indications the products are intended to treat, the type of information collected about the adverse events as well as the timing for when it is collected can vary extensively across different REMS as well.

REMS DATABASE AND DATA TYPES

REMS that include ETASU with Implementation Systems have a variety of different types of data that are unique to REMS. Because more complex data algorithms are often required to accurately summarize REMS metrics, it is almost always beneficial to create analysis data sets, since these complex derivations are easier to trace and validate in an analysis data set. On rare occasions it is less complicated to use original data sets directly in generating tables.

Note that while the data collected as part of REMS is used to support an AR that is submitted to FDA, unlike for Clinical Trials, other than a very few rare exceptions the data itself (original or analysis) is *not* submitted to FDA. As a result, Clinical Data Interchange Standards Consortium (CDISC) standards are not required for REMS data. While the data does not lend itself to most Clinical Trial data standards, general guidelines for SAS® Version 5 transport file compatibility, as well as good data design and documentation practices are strongly recommended.

REMS DATA "CUTS"

As noted previously, REMS data is part of an ongoing database that is "cut" at specific pre-defined times to provide information for ARs, usually due to FDA at 6 months after initial product approval, then at 12 months, and then annually thereafter. Regardless of the interval when the AR is due to FDA, the REMS database must be cut within 60 calendar days of the date the AR is due to FDA. For example, if the AR is due to FDA on July 20th, the REMS database must be cut no sooner than May 21st.

Given that a REMS database is part of a "live" risk mitigation program that cannot be "shut down" for reporting purposes, this means that data is added continually, and previously added data can be updated. As a result, the database extracts for use in support of ARs must be done at set cutoff points that include date *and* time. For example, if the data cut date is May 21st there could be a significant difference in the content of the database at 9 AM vs. 9 PM that day. Because of this, database extracts are often scheduled to occur at a time well after most users would no longer be in the system, typically 11:59 PM on the end day of the reporting interval. This ensures that the data that is reported captures the snapshot of data as it was at the exact time of the required data cut.

REMS data can come from a variety of sources, such as the Implementation System database, distributors, specialty pharmacies, other vendors or other internal documents. While the REMS database

can be cut at a specified date and time, it is important to understand how data provided by other sources is reported. It is common to have a 1- or 2-day lag in when a pharmacy or other data provider reports their shipment or dispensing information. This is usually not a problem except when it occurs around the time of a data cut. Shipment dates and other applicable dates may have occurred during the reporting interval (prior to the data cut), but the data was not received until after the data cut. Any data that is received after the data cut, even if the actual activity dates occur prior to the data cut, would need to be reported in the next reporting interval. This lag in data reporting between sources can lead to discrepancies between reported metrics based on different sources. This is one example of the data challenges with REMS, which is discussed more later in this paper.

REPORTING PERIODS

Tables for the current data cut usually report at minimum the Current Reporting Period and the Cumulative Period (also sometimes called Program to Date). The Cumulative Period includes data from all of the previous reporting periods plus the Current Reporting Period, so it includes all of the data in the database. Sometimes a REMS will also require each table to report a separate column for the Previous Reporting Period, or, each reporting period individually beginning from the first REMS Assessment Report. Table 1 below shows an example of how reporting periods may be displayed in table column headers.

Table 1: Example of How to Display Reporting Periods in Table Column Headers

Previous Reporting Period 01JAN2019 to 30JUN2019	Current Reporting Period 01JUL2019 to 30JUN2020	Cumulative 01JAN2019 to 30JUN2020

TYPES OF DATA

The biggest difference between Clinical Trials and REMS is the types of data collected. While there are a few areas of overlap (e.g., patient age and sex), most data collected are unique to REMS. Some examples of data that may be included in a REMS database are noted below:

- Prescriber Certification or Enrollment Status (e.g., Certified, Inactive, De-certified)
- Pharmacy Certification Status (e.g., Certified, Non-certified, De-certified)
- Patient Enrollment Status (e.g., Enrolled, Active, Inactive, Discontinued)
- Wholesaler / Distributor Enrollment Status (e.g., Enrolled, Active, Inactive, De-enrolled)
- Patient Demographic Information (e.g., Age, Sex, Race, Geographic Region)
- Prescriber Demographic Information (e.g., Degree, Medical Specialty, Geographic Region)
- Pharmacy Demographic Information (e.g., Pharmacy Type, Geographic Region)
- Contacts with the REMS Coordinating Center and Frequently Asked Questions (e.g., who called or emailed and why)
- Patient Status Forms / Patient Monitoring Forms (e.g., blood pressure pre- and post-treatment, laboratory test results, specific adverse event details)
- Knowledge Assessments (e.g., Prescriber, Pharmacist, etc.)
- Patient Shipments, Wholesaler/Distributor shipments (e.g., shipment date, recipient ID, quantity shipped)

Metrics on many of the items above are stratified by others. For example, shipment data is often reported stratified both by patient and prescriber characteristics. It is important to understand what these data represent, and how they are interconnected.

Certification or Enrollment Data

Prescribers, pharmacies, wholesalers/distributors and patients are key stakeholders that are either certified or enrolled in the REMS. Not all REMS have all of these stakeholder types, but many do. “Certified” is a term that is associated with prescribers and pharmacies, while “Enrolled” is typically associated with patients and wholesalers/distributors. Prescribers and pharmacies often need to meet certain requirements to be considered as Certified within the REMS, such as successfully completing a Knowledge Assessment questionnaire that tests their knowledge about the drug in question, such as prescribing information and other elements to assure the drug is prescribed and dosed in a safe manner.

Sometimes a stakeholder who was previously Certified will become De-certified, if they fail to meet the REMS requirements, or, become Inactive if they are no longer prescribing or dispensing the product. Likewise, patients can also change statuses from Enrolled and Active (Active usually means the patient is both enrolled and receiving treatment), to Inactive for a variety of reasons. The potential for changing statuses is something that needs to be considered carefully when designing and programming summary tables, as a stakeholder may be active in one reporting period but inactive in the next.

Table 2 below shows a typical Prescriber Certification table with reporting period columns which summarize the number of prescribers who became “Newly Certified” in each period, as well as how many were “Active” within the period. Note that the Cumulative number of Certified prescribers is equal to the sum of the newly certified in each period. On the contrary, the Cumulative number of Active prescribers does not have to equal the sum of active in each period, because a prescriber may be “active” in more than one period but only counted once in Cumulative.

Table 2: REMS Prescriber Certification

	Previous Reporting Period 20JAN2020 to 21MAY2020		Current Reporting Period 22MAY2020 to 21NOV2020			Cumulative 20JAN2020 to 21NOV2020	
	Newly Certified	Active[a]	Newly Certified	Newly Certified and Active[b]	Active[a]	Certified	Active[a]
Prescribers, n							
Total[c]	100	40	50	20	80	150	75
Geographic Region,[d] n (%)							
Northeast	25 (25.0)	10 (25.0)	11 (22.0)	4 (20.0)	21 (26.3)	36 (24.0)	19 (25.3)
Midwest	25 (25.0)	7 (17.5)	12 (24.0)	4 (20.0)	24 (30.0)	37 (24.7)	17 (22.7)
South	20 (20.0)	10 (25.0)	15 (30.0)	6 (30.0)	20 (25.0)	35 (23.3)	18 (24.0)
West	30 (30.0)	13 (32.5)	11 (22.0)	5 (25.0)	14 (17.5)	41 (27.3)	21 (28.0)
Other	0	0	1 (2.0)	1 (5.0)	1 (1.3)	1 (0.7)	1 (1.3)

[a] Prescribers who have treated at least one patient with NEWDRUG during the reporting period indicated.
[b] Includes only newly certified prescribers who have treated at least one patient with NEWDRUG during the current reporting period.
[c] Used as the denominator for percentages.
[d] U.S. Census Bureau, last revised April 1, 2010, Geography Division. Northeast includes CT, MA, ME, NH, NJ, NY, PA, RI, and VT. Midwest includes IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, SD, and WI. South includes AL, AR, DC, DE, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, and WV. West includes AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA, and WY. Other includes Puerto Rico.

Patient Status Forms / Patient Monitoring Forms

Some REMS require Patient Status Forms (PSFs) or Patient Monitoring Forms (PMFs) at set intervals while a patient is actively taking the product. Such forms document a patient’s status or condition and

sometimes require additional patient lab tests, vital signs assessments, and other patient monitoring activities. For example, a PSF may be required each time the patient is dosed, or at set intervals after the patient receives their first shipment, or at any kind of time cadence depending on the specific requirements of the REMS.

Though PSFs are expected at set intervals, many times they are received more or less frequently than required. The challenge with this comes when reporting the total number of expected, received and outstanding PSFs, and how to define these 3 frequently required REMS metrics. One solution is to assign a series of "expected dates", based on the cadence in which forms are expected. In other words, the table summarizes expected *dates*, and not expected *forms*. For example, if a PSF is first expected at the time of a patient's first shipment and every 3 months thereafter, then the first expected date would be equal to the first shipment date, the 2nd expected date would be 3 calendar months after, and so on. Any form that is received within an allowed window of each expected date makes that expected date count as either "received" or "outstanding", based on when the form was received within the allowed window. For example, if a form was received after the 2nd expected date and prior to the 3rd expected date, but it was within the allotted "grace period" (i.e. +10 days, +30 days, etc.), then it would count as "received". Otherwise, if the form was due within an allowed window of the expected date but still not received as of the data cut date, then it would count as "outstanding", and if it was not yet due as of the data cut date then it would count as "not due". If multiple forms are received within an expected window, the respective expected date is only counted once as having been received, outstanding, or not due. Furthermore, using this method, the total number expected should equal the sum of the number received, outstanding and not due.

Table 3 below shows a Patient Status Form table that summarizes the number of Expected, Received and Outstanding forms.

Table 3: Disposition of REMS Patient Status Forms

	6-Month Reporting Period 20JAN2019 to 21MAY2019	**12-Month Reporting Period 22MAY2019 to 21NOV2019**	**24-Month Reporting Period 22NOV2019 to 21NOV2020**	**Cumulative 20JAN2019 to 21NOV2020**
Active patients, n				
Total	70	105	203	210[a]
***Patient Status Forms*, n (%)**				
Expected	70	95	122	287
Received[b]	63 (90.0)	79 (83.2)	105 (86.1)	247 (86.1)
Outstanding as of 21NOV2020[b]	7 (10.0)	16 (16.8)	12 (9.8)	35 (12.2)
Not received within 90 calendar days for the first 18 months of treatment[c]	5 (71.4)	14 (87.5)	11 (91.7)	30 (85.7)
Not received within 120 calendar days after 18 months of treatment[c]	2 (28.6)	2 (12.5)	1 (8.3)	5 (14.3)
Not due as of 21NOV2020[b]	0	0	5 (4.1)	5 (2.4)

	6-Month Reporting Period 20JAN2019 to 21MAY2019	12-Month Reporting Period 22MAY2019 to 21NOV2019	24-Month Reporting Period 22NOV2019 to 21NOV2020	Cumulative 20JAN2019 to 21NOV2020
Patient Status Form received for a patient who has not completed enrollment	2	4	4	10

[a] Number of patients who have ever received at least one outpatient dispense of NEWDRUG. Patients are only counted once regardless of the number of dispenses in each reporting period.
[b] Number of expected forms used as the denominator for percentages.
[c] Number of outstanding forms used as the denominator for percentages.

Contacts with the REMS Coordinating Center and Frequently Asked Questions

A common metric that is required for reporting is the number of contacts with the REMS Coordinating Center by stakeholder type (patient, prescriber, etc.), including the reasons for contact and/or Frequently Asked Questions (FAQs). Contacts generally include all calls, mail, emails and faxes sent to (inbound) or from (outbound) the REMS Coordinating Center. Any given contact can have more than one action associated with it (inbound call, follow-up email, etc.). For example, if a Prescriber calls in asking a question, and the Coordinating Center later follows up on that question by sending an email, this interaction would count twice in the summary table as two separate actions associated with a single contact.

It is a general practice to generate at least 2 types of tables for the Call Center metrics:

1. All contacts by stakeholder, counting follow-up actions associated with each initial contact separately
2. Reasons for initial contact by each stakeholder

Table 4 below shows an example of a table that summarizes the reasons for initial contact by stakeholder.

Table 4: Reasons for Initial Contact with the REMS Coordinating Center

	Cumulative 20JAN2020 to 21NOV2020					
Reason for Contact	**Patient/ Caregiver N=xxx n (%)**	**Prescriber N=xxx n (%)**	**Pharmacy N=xxx n (%)**	**Wholesaler/ Distributor N=xxx n (%)**	**Other[a] N=xxx n (%)**	**Total[b] N=xxx n (%)**
Adverse Event	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Enrollment Question	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Medical Information Request	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PSF - Missing Information	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Prescription / Refill Inquiry	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
REMS Program Information	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Verification of Certification	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Reason for Contact	Cumulative 20JAN2020 to 21NOV2020					
	Patient/ Caregiver N=xxx n (%)	Prescriber N=xxx n (%)	Pharmacy N=xxx n (%)	Wholesaler/ Distributor N=xxx n (%)	Other[a] N=xxx n (%)	Total[b] N=xxx n (%)

[a] Includes all other stakeholders not otherwise classified, such as contact with unidentified callers.
[b] Reflects the aggregate number of reasons for initial contacts.
Note: Contacts included communication via email, fax, telephone call, or mail.
PSF = *Patient Status Form*

Shipment Data

Most REMS involve shipment data, specifically product shipments sent to patients. This data usually contains a large volume of records with one record per patient per shipment, as well as a large volume of variables (50 or more) such as patient ID, prescriber ID, total quantity, daily dose, days' supply, prescription number, prescription authorization date, transaction ID, shipment date, etc. Because this is a continually growing database as records are added throughout the life of the REMS, it is highly recommended to use efficient programming techniques to streamline the data processing in any SAS programs that involve shipment data, in order to minimize run time.

Another challenge with shipment data is that there are often incorrect entries by the specialty pharmacy or other vendor. Sometimes the data issues require updates from the specialty pharmacies after the database cut, but that need to be incorporated with the rest of the data as it was from the time of the database cut. More often there are duplicate shipment records that need to be verified and removed if found to be true duplicates.

Shipment data is usually used to determine if a patient, prescriber or pharmacy was "Active", meaning that either the patient received a shipment, the prescriber prescribed the drug to a patient or the pharmacy dispensed the drug.

Some REMS may also include wholesaler/distributor shipment data, which contain information about the shipments distributed by a wholesaler/distributor to a pharmacy. This is usually summarized separately in a wholesaler/distributor shipment table but is also used to determine if the wholesaler/distributor is "Active", or actively distributing product.

REPORT SUMMARY TABLES

REMS tables are typically not as complex as clinical trials in terms of the types of statistics that are reported. However, the complexity of programming a REMS lies in understanding the operational data, how to pull it together and present it in an accurate and meaningful way. It is not usually obvious from looking at a REMS table what data goes into it, what subsets to use, and how calculations are performed. Tables are often a complex merging of different data sets and subsets, and this requires you to put on your "Analyst" hat and not just your "Programmer" hat!

TYPICAL STATISTICS

The extent of statistics reported are usually simple counts and percentages, the occasional descriptive statistics (mean, standard deviation, minimum and maximum) and rarely p-values. Because of this, statisticians are often not required to generate mock Tables, Listings and Figures (TLFs). Instead of a Statistical Analysis Plan (SAP), it is recommended that the lead programmer work with the REMS Project Manager to create something similar to a SAP which displays all TLF mocks, in addition to the logic details for how each table metric should be summarized. This document will help you think through exactly what should be displayed in each table to meet the requirements of the REMS metrics, and will help answer questions that may come "after the fact" when medical writers begin writing the AR using the final tables. Ideally, these mocks would be reviewed and approved by the broader project team before programming begins, but the logic details are always subject to change once actual programming occurs.

OUTPUT FORMATTING

While statistical analysis tends to be simple, due to the short, fixed timeline from database cut to submission of the final AR, tables need to be programmed based on the AR Style Guide so tables can be dropped into the report with minimal changes by the medical writer. There is no time for selective copy and paste of tables, let alone manual creation of tables. As a result, much more attention to detail must be made to ensure the final table "cosmetics" (e.g., font type, font size, footnote spacing) meet document requirements.

COMMON CHALLENGES

REAL WORLD DATA

Data collected in Clinical Trials is transcribed from real world patient charts to a database specifically designed to analyze that data. In addition, sites reporting data in clinical trials are obligated to answer queries that ensure accurate reporting of that data. In contrast, data collected for a REMS is done in a way that minimizes burden for stakeholders as much as possible while still gathering the required information. REMS data is routinely reviewed on an individual case basis, so reviewing or analyzing data in aggregate is not necessarily the primary concern. As a result, data can be collected in ways that can provide a particular challenge for analysis. For example, blood pressure is a two-part measurement with systolic and diastolic values. In clinical trials, this information would typically be captured in two numeric fields – one with systolic and one with diastolic values. In a REMS, blood pressure may be captured in a single character field with the two values separated by a slash (e.g., "120/80"). While this character field is easy enough to parse, it does not allow for range checks to confirm that the entered values are each within an acceptable range, so data could end up as "12/80" in the final REMS data.

When working with REMS data, it is important to understand how the data is collected and what key data is required. There is not a full query resolution process for REMS – in many cases, the data that you receive is all that can be collected, even if it is obviously incorrect. In these situations, the programmer needs to work with the broader project team to determine how best to analyze the data available.

WHY DOES CUMULATIVE NOT EQUAL LAST YEAR'S CUMULATIVE + THIS YEAR'S CURRENT?

This is a very common question, as it almost always happens, both from internal reviewers and from clients when they see the tables. The question is: Why does this year's Cumulative not equal the sum of last year's Cumulative plus this year's Current Reporting Period? This will inherently happen because of the way the REMS database is collected and maintained. It is a running database, and sometimes items are "corrected" or changed or added "after the fact"… so something that was not displayed in tables for a previous data cut may show up in the next data cut, but will only display as part of the Cumulative column (because it is older data). Because this happens so frequently, it is recommended to add a global footnote in the table mocks explaining that this can happen and why. But regardless, programmers should be prepared to get questions asking specifically which IDs are causing these differences.

VERY LARGE SAS DATA SETS

Some REMS SAS data sets are inherently large, namely shipment data and REMS Coordinating Center contacts, especially as the length of the REMS goes on and the data only becomes larger and larger. As a result, it is very important to use SAS code that processes data efficiently or programs could run for hours. One suggestion with REMS is to pull in the SAS data set once with the applicable subsets, keep only the necessary variables, and have as few data steps as possible to save running time.

PROGRAMMING CLINICAL TRIALS VS. REMS

Programming clinical trials and REMS are very different in many aspects. Table 5 below shows a side-by-side comparison of some of the differences discussed above.

Table 5: Comparison of the Main Differences Between Clinical Trials and REMS

Clinical Trials	REMS
Protocol	Supporting Document
Case Report Forms / standardized database documentation	Form screen shots (where applicable) / sparse database documentation in a variety of formats
Main contact: Statistician	Main contact: Project Manager
End-of-text style output	In-text style output
Data is collected specifically for data analysis and is “clean”	Data is collected to reduce burden on stakeholders and is often “messy”
Datasets are typically small	Datasets are often very large (>1 GB)
Datasets are always submitted to FDA following CDISC guidelines	Datasets are rarely submitted to FDA, following general submission rules
Tend to have mostly straight-forward datasets with complex tables	Tend to have mostly simple tables with *very* complex data handling rules

While there are clear differences between Clinical Trials and REMS, many of the same programming and analytical skills are needed for both types of projects. While some skills may be needed more in one type of project than the other, the key to successfully programming in REMS is the willingness to ask a *lot* of questions. Programmers need to understand what data is collected and how, as well as what the goal is for reporting metrics to FDA. This typically involves a lot more interaction between the programmer and the broader project team, and a willingness to “own” technical documentation describing what was done to generate analysis datasets and tables.

It is critical for programmers to keep in mind one more key difference between Clinical Trials and REMS. Clinical Trials are “one and done” – the data is collected, the database is locked, tables are produced, a report is written and the entire project is finished. REMS are usually ongoing for years, with reports that are submitted at regular intervals over the lifetime of that REMS. It is even more critical for REMS programs to be well documented, be structured so others can follow logic, be free of extraneous notes and warnings, and to process data as efficiently as possible so that the programs are maintainable over time.

CONCLUSION

As shown above, there are a number of key differences between Clinical Trials and REMS. Awareness of these differences, a willingness to learn what makes them unique and ability to work closely with the broader project team can result in interesting new challenges for programmers and ensure that high-quality metrics tables are provided to FDA.

REFERENCES

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