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Evolution and Implementation of the CDISC Study Data Tabulation Model (SDTM)

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ABSTRACT

The CDISC (Clinical Data Interchange Standards Consortium) SDTM is a standard for submitting data tabulations to the FDA in support of marketing applications. In July of 2004, this standard became Study Data Specification (1) referenced in the eCTD Guidance (2). In December of 2006, the FDA announced their intention to make the SDTM required by regulation (3). This paper/presentation will provide an overview of the SDTM and the associated Implementation Guides, commonly referred to as the SDTMIG (SDTM Implementation Guide) and SEND (Standard for the Exchange of Nonclinical Data). Included will be the evolution of the standard, the current status of the SDTM, strategic reasons for considering implementing the SDTM, and how the SDTM is used in the FDA review environment, including an overview of the tools used by the FDA to review SDTM data.

INTRODUCTION

CDISC BACKGROUND

From its inception in 1997, CDISC has recognized the need for the establishment of standard data models to improve the process of electronic acquisition and exchange of clinical trials information for the benefit of all medical and pharmaceutical stakeholders. This is reflected in the mission statement: *"CDISC is an open, multidisciplinary, non-profit organization committed to the development of worldwide industry standards to support the electronic acquisition, exchange, submission and archiving of clinical trials data and metadata for medical and biopharmaceutical product development. The mission of CDISC is to develop and support global, platform-independent data standards that enable information system interoperability to improve medical research and related areas of healthcare."*

CDISC has four major standards: the Lab Model (LAB) for the transfer of lab data from vendors to sponsors; the Operational Data Model (ODM) for the transfer of clinical trial data and metadata, including administrative data and audit trail; the Analysis Data Model (AdaM) for analysis datasets; and the SDTM for data tabulations. The LAB and ODM models are designed for the transfer of data from vendors and CROs to sponsors, while the ADaM and SDTM models apply to the submission of data to the FDA.

CRTs

Case Report Tabulations originated in FDA regulation of the late 1980's. Originally intended to allow sponsors to submit data tabulations to the FDA instead of copies of every subject CRF. Recently, as documented in the FDA Study Data Specification (1), which is referenced in the eCTD Guidance (2), the definition has expanded to include data listings, patient profiles, data tabulations, and analysis datasets.

EVOLUTION OF THE SDTM

The SDTM originated as the Submission Data Model (SDM), developed by the CDISC Submission Data Standards (SDS) Team. The SDS Team is comprised of approximately thirty volunteers from industry. Team meetings have also been regularly attended by three key FDA observers representing the Office of Business Process Support, Statistics, and Medical Review. Team members come from a cross-section of industry, including most major pharmaceutical companies, numerous small to mid-level pharmaceutical companies, CROs, and service providers. The SDS Team collaborates regularly through biweekly teleconferences, quarterly face-to-face meetings, and literally thousands of regular email communications, all in an effort to support the CDISC mission, to "…improve medical research and related areas of healthcare."

The concept that developed into the Study Data Tabulation Model (SDTM) v1.0 / Submission Data Standards (SDS) v3.1 was initially presented to the SDS Team by FDA liaisons in October, 2002. Prior to that time, the SDS Team had developed the Submission Data Domain Models Version 1.0 (v1, 2001), and Version 2.0 (v2, early 2002), and was just about to publish v2.1. All of these versions focused on safety domains. While the v1 and v2 data concepts had been well received by industry, it was recognized there were a couple of major shortcomings. The revolutionary concept that the FDA proposed, termed Version 3.0

by the Team, addressed those major shortcomings by 1) providing a standard for all clinical trial data, not just safety data, and 2) providing a standard based on data modeling principles, rather than data management / operational database principles. This concept provided a consistent approach for modeling all clinical trial data across three primary data types (Events, Interventions, and Findings), allowing standard review tools to be developed.

The preliminary draft version of the SDTM concept was published in June of 2003 as the Submission Data Domain Models Version 3.0, or better known as SDS v3.0. The first version intended for implementation was published as two documents in June of 2004: the SDTM v1.0 (the model), and the SDTMIG v3.1 (the implementation guide). During the period from June 2003 to June 2004, there were a number of enhancements leading to the final approved version, many the result of a joint FDA/industry pilot to test SDS v3.0, and two public review/comment periods. Version 1.1 of the SDTM was published in April of 2005, followed by Version 3.1.1 of the SDTMIG four months later.

REGULATORY EVENTS RELATED TO THE SDTM

Shortly after the publication of the first production versions of the SDTM and the SDTMIG in June and July, respectively of 2004, the FDA recognized the SDTM as an approved method for submitting the data-tabulation component of Case Report Tabulations (CRTs) in the then-draft eCTD guidance. Health and Human Services (HHS) announced in the December, 2004 regulatory agenda (3) that the agency was moving towards requiring the submission of clinical trial data in a standard format.

In its 2004 Critical Path Report, the FDA presented its diagnosis of one of the scientific challenges underlying the medical product 'pipeline problem'. The report then laid out a path forward, beginning with extensive outreach and consultation with public and private stakeholders. Stakeholders confirmed our diagnosis and provided examples of scientific investments that could revolutionize medical product development. In January of 2005, Dr. Janet Woodcock, acting Director of CDER, met with the CDISC Board of Directors (BOD) to review the FDA's Critical Path Initiative. She clearly stated that industry adoption of the SDTM for submission of data for all clinical trials in marketing applications was a significant component of the FDA's Critical Path Initiative, and asked the CDISC BOD for recommendations on how CDISC and the FDA could enhance their collaboration to promote quicker industry adoption of the SDTM.

On February 1, 2005, the FDA conducted a public meeting to review the status of industry adoption of the SDTM. Multiple FDA liaisons reviewed the importance of the SDTM and its value to both industry and FDA. They also confirmed that sponsors submitting data in the SDTM would not be required to submit data listings and patient profiles. FDA review tools will automatically produce data listings and patient profiles from properly formatted SDTM datasets. Additionally, FDA agreed to provide advance training to reviewers on the SDTM, and the review tools, when sponsors notify FDA in advance that they are submitting in the SDTM format. The FDA has recognized that ensuring this training occurs is a necessary component of SDTM implementation in industry.

In March 2006, the agency the FDA released The Critical Path Opportunities List (4) based on feedback from stakeholders and the special insights of FDA's product reviewers. Item 44 on that list is entitled Development of Data Standards, and it mentions the SDTM in the following text:

> "CDISC is paving the way by developing its Study Data Tabulation Model for describing observations in drug trials. That model could someday encompass observations needed for other types of trials. Health Level 7 and CDISC are working to create standards that can be used for the exchange, management, and integration of electronic healthcare information to increase the effectiveness and efficiency of healthcare delivery."

Within the past year, two major announcements have further indicated the FDA's commitment to the SDTM. On September 29, 2006, the FDA announced the withdrawal of the three Electronic Submission Guidances for eNDA, eANDA, and eAnnual Reports (5). This notice designates eCTD as "preferred format for electronic submissions" and notes that beginning January 1, 2008, any electronic submission going to CDER must be eCTD. On December 11, 2006, announced that there would be Notice of Proposed Rulemaking in March of 2007 (6). The rule would mandate that data must be submitted and provided in an electronic format that the FDA can process, review, and archive. It would also mandate the use of standardized data structures, terminology, and code sets according to the CDISC SDTM guidance, and is expected to mention a two-year transition period for implementation.

The consistent message from the FDA at recent meetings such as the Annual DIA Meeting and the CDISC Interchange has been to submit data in SDTM format.

LONG-TERM BENEFITS OF USING THE SDTM

The FDA has been developing the Janus data warehouse as the repository to store all submitted clinical-trials data. Janus will provide a stable foundation for FDA's growing list of standard review tools, developed through Cooperative Research and Development Agreements (CRADAs) between the Agency and various vendors. The tools have been developed to utilize the SDTM, rather than vice versa. Most of these tools create tabular and/or graphical views of the SDTM data via canned reports, although custom reports can be run as well. The tools routinely bring demographics and treatment data into all views of subject data, utilizing the fixed relational database structure of Janus (upon which much of the SDTM is based). Many tools also provide built-in hyperlinks that allow drilling down from group summaries to individual-subject data, and to navigate from

graphs to tables. Some allow for various "what-if" scenarios, such as allowing the elimination of outlying values from the calculation of means.

The regulatory status of the SDTM not withstanding, it is to a sponsor's advantage to move toward implementation of the SDTM for submission datasets. Once FDA reviewers become accustomed to being able to easily navigate through submitted data using the dedicated tools, being unable to do so for subsequent submissions may lead to inefficiencies in the review process.

SDTM BASICS

The current CDISC Submission Data Standard consists of two documents: the Study Data Tabulation Model Version 1.1, published in April 2005, and the Study Data Tabulation Model Implementation Guide: Human Clinical Trials Version 3.1.1, published in August 2005. The first describes the model, while the second provides guidance on model implementation, including domain models and examples with real data for commonly submitted datasets, a set of assumptions to aid in interpretation of the intended implementation, more detailed descriptions of the Trial Design Model (TDM) tables, and a more detailed discussion on representing relationships within and across submission datasets. The SDTM is built around several key concepts. These are described in the following paragraphs.

Domains
Domains are groups of related observations. These observations are grouped by topic in datasets. Datasets and domains are usually the same, but some domains contain two classes of observations and have to be split into two datasets.

Observations
Observations can be described by a series of named variables. Each variable, which normally corresponds to a column in a dataset, can be classified according to its role. Most variables in a domain begin with a prescribed prefix.

Example: In Study ABC001, Subject 1234-0001 had a heart rate of 100 bpm on Study Day 6. This would be represented in a dataset as follows:

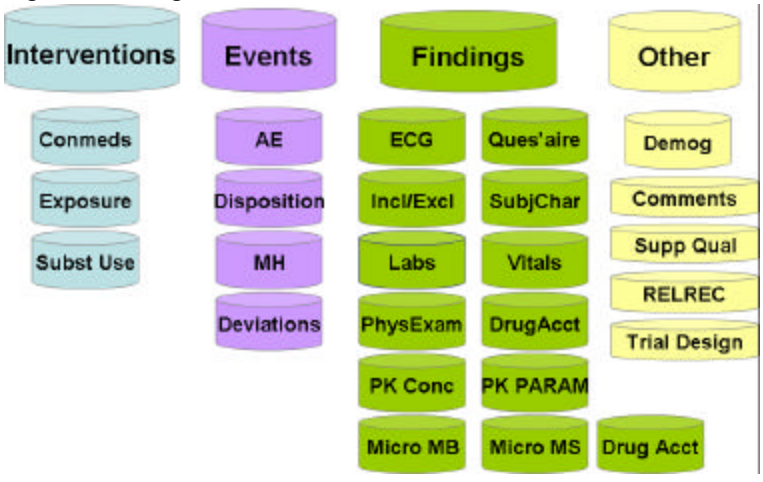
STUDYID	USUBJID	VSDY	VSTESTCD	VSORRES	VSORRESU
ABC001	1234-0001	6	HR	100	bpm

Observation Classes
An observation can be classified as one of three major types: Interventions, Events, or Findings. They can be described as follows:

- **Interventions:** investigational treatments, therapeutic treatments, and surgical procedures administered to the subject or animal. One record per constant dosing/treatment interval.
- **Events:** occurrences or incidents independent of planned study evaluations occurring during the trial (e.g., adverse events) or prior to the trial (e.g., medical history). One record per event.
- **Findings:** observations resulting from planned evaluations (e.g. lab tests, ECGs, microscopic findings). One record per finding result or measurement.

Each observation class has a defined set of standard variables. These standard variables, along with Identifiers and Timing Variables, both of which can be used in all observation classes, are the building blocks for constructing SDTM domains. Variables other than the standard ones for each class must be represented in a SUPPQUAL dataset (to be discussed later). Figure 1 shows the observation classes for the domains modeled in the SDTMIG.

Figure 1. Fitting V3.1.2 Domains into Observation Classes



Variable Roles

Every variable has been assigned a Role that describes the type of information conveyed by each variable within an observation. These Roles are defined in the SDTM:

- **Topic Variable** - Identifies the focus of the observation. There is only one per dataset.
- **Identifier Variables** - Identify the study, the subject, the domain, and sequence number of the observation.
- **Timing Variables** - Describe the start and end of the observation, and/or when it was collected.
- **Qualifier Variables** - Describe the attributes and results of the observation. These can be further subdivided into Grouping, Result, Synonym, Record, and Variable Qualifiers.

Variable Metadata

Each dataset or table is accompanied by metadata definitions that provide information about the variables used in the dataset. Included are the SAS label, the {data) type, controlled terms or format, the origin (e.g., CRF, derived), and the role (as described above).

Additional Datasets and Tables that Need To Be Submitted

In addition to data submitted in accordance with the three observation classes, there are a number of special-purpose datasets that are also part of the SDTM. Included are the Demographics dataset, the Comments dataset, the Supplemental Qualifiers dataset(s), the RELREC (Related Records) dataset, and seven TDM datasets. Supplemental Qualifiers may be submitted either as one SUPPQUAL dataset per study or as one SUPP-- dataset per domain, with the hyphens representing the two-letter domain code. The term SUPPQUAL used subsequently in this paper will be used to collectively refer to both options.

The Demographics dataset includes a set of standard variables that describe each subject in a clinical study. The Comments domain is a fixed domain that provides a solution for submitting free-text comments related to data in one or more domains or collected on a separate CRF page dedicated to comments. The Comments dataset is similar to the SUPPQUAL dataset but it allows for one comment to span multiple variables (COVAL-COVALn) in order to accommodate comments longer than 200 characters. It is flexible in that it permits comments to be related to a subject, to a CRF page or SDTM domain, or to specific parent records in a domain.

Relationship Tables

In order to understand the two primary relationship tables, SUPPQUAL and RELREC, it is necessary to understand that every record in the observation-class datasets has a unique set of keys consisting of STUDYID (Study ID), USUBJID (Unique Subject ID), DOMAIN (SDTM Domain), and the --SEQ (the two hyphens indicating the two-letter domain code) variable. The latter variable is sponsor defined, and unique within STUDYID, USUBJID, and DOMAIN. Knowing the values for these four columns allows precise identification of a single record within a submission. Both RELREC and SUPPQUAL use this same concept to identify a parent record to which either a non-standard variable (SUPPQUAL) or another independent (parent) record (RELREC) is related. These tables use STUDYID, USUBJID, RDOMAIN (Related Domain), and two other variables that point to the related record. These two variables are IDVAR and IDVARVAL, which describe the parent record's unique identifier variable and its value. Other variables aside from --SEQ, such as Grouping Qualifiers and Identifiers, can be used in IDVAR to express relationships other than one to one. An example would be using --GRPID (Grouping Identifier) to relate multiple ECG measurement records to a single SUPPQUAL attribution.

The Supplemental Qualifiers (SUPPQUAL) special-purpose dataset is used to submit values for variables not presently included in the general-observation-class models. In addition to the keys described in the previous paragraph, each SUPPQUAL record also includes the name of the Qualifier variable being added (QNAM), the label for the variable (QLABEL), the actual data value for each instance or record (QVAL), the origin (QORIG) of the value (e.g., whether it was collected via CRF, or derived), and the Evaluator (QEVAL, to specify the role of the individual who assigned the value, such as an Adjudication Committee or the sponsor).

Most sponsors will need to use a SUPPQUAL dataset to submit additional non-standard variables that cannot be represented in the three general observation classes. If the SUPPQUAL dataset becomes too large, a sponsor has the option of submitting a separate supplemental qualifier dataset for each submitted domain that has supplemental qualifiers. The naming convention for these is "supp" followed by the two-letter domain code (e.g., suppae.xpt for adverse events). Sponsors should realize that individual supp-- datasets will be required once XML becomes the recommended submission format for the SDTM.

Another common reason for using a SUPPQUAL dataset is to capture attributions. An attribution is typically an interpretation or subjective classification of one or more observations by a specific evaluator, such as a population flag that classifies a subject or their data according to their evaluability for efficacy analysis. Since it is possible that different attributions may be necessary in some cases, SUPPQUAL provides a mechanism for incorporating as many attributions as are necessary. For example, if two individuals provide a determination on whether an adverse event is treatment emergent (e.g., the investigator and an independent adjudicator) then separate QNAM values should be used for each set of information, perhaps AETRTEM and AETRTEM2. This is necessary to ensure that reviewers can join/merge/transpose the information back with the records in the original domain without risk of losing information.

The Related Records (RELREC) dataset is used to describe collected relationships between records in two (or more) datasets, such as an Event record and an Intervention record, or a Finding record and an Event record. One example would be the collection of an Adverse Event number on a Hospitalization or Lab page. RELEC should be not be used to determine associations after the fact (e.g., as part of the analysis process). Relationships are described by creating RELREC records for each of the related observation records, and then by assigning a unique character identifier value for the relationship. Each RELREC record contains same keys as SUPPQUAL to identify a record (using --SEQ in IDVAR) or group of records (using --GRPID in IDVAR). RELREC uses an additional, unique variable, RELID, the relationship identifier, which is the same for all related records. The value of RELID can be any constant value chosen by the sponsor.

The Trial Design Model (TDM)

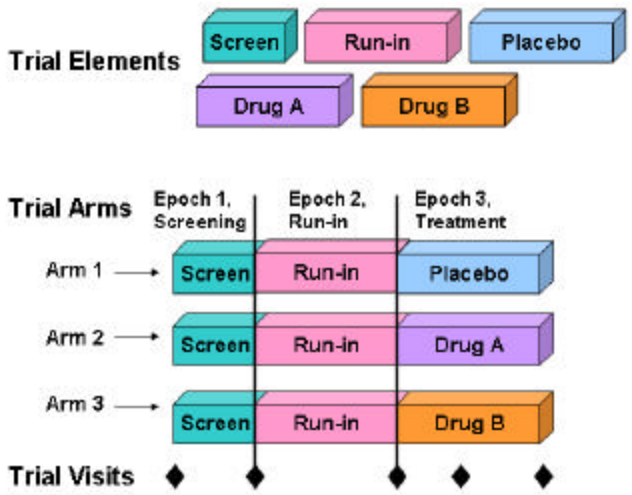
The TDM allows description of key aspects of the planned conduct of a clinical trial in a standardized way. These standardized descriptions will allow reviewers to:

- clearly and quickly grasp the design of a clinical trial
- compare the designs of different trials
- search a data warehouse for clinical trials with certain features
- compare planned and actual treatments and visits for subjects in a clinical trial

Modeling a clinical trial in this standardized way requires the explicit statement of certain decision rules that may not be addressed, or may remain vague or ambiguous, in the usual prose protocol document. Prospective modeling of the design of a clinical trial should lead to a clearer, better protocol. Retrospective modeling of the design of a clinical trial should ensure a clear description of how the trial was interpreted by the sponsor.

The TDM is built upon the concepts of Elements, Arms, Epochs, and Visits. They are shown in Figure 2, and can be described as follows:

Figure 2. Key Concepts of Trial Design



- An Element is the basic building block for a discrete treatment period (or constant-dosing interval) within a clinical trial. Planned Elements are described in the Trial Elements (TE) table, which includes a description of the treatment(s) are planned for subjects in that Element, rule for starting the Element, a rule for ending the Element, and a planned duration (if it's fixed and not conditional).
- An Arm is a planned sequence of Elements, and is usually equivalent to a treatment group. The Trial Arms (TA) table describes the sequence of elements within each Arm, as well as rules for branching and transitions. The Demographics domain contains the name of the Arm to which the subject was randomized.
- A Visit is defined as a clinical encounter that encompasses planned and unplanned trial interventions, procedures, and assessments that may be performed on a subject. Planned visits are described in the Trial Visits (TV) table. A Visit has a start and an end, each described with a rule. Different Arms can have different planned-visit schedules. A Visit need not be nested within a single Element. In other words, it may start in one Element and end in another.
- The term EPOCH is used to describe a period of time that cuts across Arms, and applies to the trial as a whole Epochs may contain the same number or a different number of Elements for each Arm. Epochs are defined in the TA table.

There are two subject-level tables that describe the actual element sequence (Subject Elements) and visit schedule (subject Visits). These tables include the actual dates for the start and end of each element or visit, and are flexible enough to handle both planned (and therefore in the TE and TV tables) or unplanned elements and/or visits.

The TDM also includes the Trial Inclusion/Exclusion (TI) and Trial Summary (TS) datasets. The TI table is used to describe the inclusion/exclusion criteria used to screen subjects. This is contrast to the IE domain, which contains the subject-specific exceptions to those criteria (i.e., criteria not met) for subjects included in the submission data. TS is used to submit trial-level summary information such as the blinding schema, drug indication, and trial objectives.

THE STANDARD FOR THE EXCHANGE OF NONCLINICAL DATA (SEND)

SEND is an implementation of the SDTM for nonclinical studies. The work on this standard began in July 2002, with an FDA pilot project announced in January of 2003. The pilot tested Version 1.0 for data from acute, subchronic, and carcinogenicity studies. Input from the pilot and efforts to more closely align this implementation with that for human clinical trials resulted in the Version 2.x standards, with current version being 2.3, posted in November 2005. As expected, some SEND domains are identical to those described in the SDTMIG for human clinical trials (e.g., ECG, Vital Signs); however, there are a number of domains specific to nonclinical research such as Microscopic findings, and Food and Water Consumption.

Because the majority of animal studies are parallel studies with single treatments or single combination treatments per group with very few deviations from what was planned, the initial versions of SEND did not include the TDM, instead using a the implementation-specific Group Characteristics domain. The need to address more complicated trial designs (e.g., Latin square) for safety-pharmacology studies has resulted in plans to add the TDM to future SEND versions.

A separate implementation guide is planned for reproductive toxicology studies because of the staggered timing of the phases of gestation and weaning within treatment groups, as well as the complex relationships that need to be maintained between mating partners and between parents and offspring, possibly through multiple generations.

WHAT DOES THE FUTURE LOOK LIKE?

We can expect to see a greater level of harmonization of standards within CDISC, as well as between CDISC standards and those of other standards-development organizations such as HL7 (Health Level 7). The areas to which existing standards can be applied will likely grow as well. To try to create an inclusive list of all the standards-development efforts would be a daunting, if not impossible task. Some of the major efforts are described below.

Efforts are well underway to harmonize the SDTM with other CDISC standards, and to harmonize CDISC standards with those of Health Level 7 (HL7) standards. Harmonization is being accomplished through work on the BRIDG (Biomedical Research Integrated Domain Group) model. BRIDG was developed to provide an overarching model that could readily be understood by domain experts and would provide the basis for semantic interoperability between these various standards. In this way, there could be interchange of data between clinical research, biomedical/clinical research, and patient healthcare. Work has been ongoing to model the SDTM to the BRIDG model.

Within the CDISC SDS Team, work will continue to develop new domains to serve as guides for implementing the SDTM in more therapeutic areas. In 2006, domains for Microbiology, Pharmacokinetics, Drug Accountability, and Protocol Deviations were posted for public comment and will appear in the next version of the SDTMIG due out later in 2007. Domains for pharmacogenomics, medical devices and, oncology studies are currently under development.

The TDM in the SDTM is being harmonized with the HL7 Protocol Representation (PR) Group. The Trial Design Subteam of the SDS Team and PR Group released Part 2 of the TDM for comment in late 2005. TDM Part 2 adds functionality to describe the scheduling of Trial Activities such as assessments, interventions, and administrative actions. The TD Subteam is currently revising Part 2 in light of the comments received, and a new release is planned for 2007. The Trial Design team is also working on UML (Universal Modeling Language) diagrams as part of the BRIDG Model.

The CDISC define.xml standard is now a Study Data Specification (1) referenced in the eCTD Guidance (2). It is a replacement for the traditional define.pdf, allowing much greater flexibility in the metadata describing the submitted data. The SDS-Team-based Metadata Subteam conducted a pilot project in 2006 and will be publishing an implementation guide for the submission of define.xml, which will also include recommendations for the annotation of CRFs.

The CDISC Controlled Terminology Team has been redesigned to work across all CDISC teams to develop standardized, controlled terminology across all the models. The CDISC ADaM team has developed a number of analysis-level standards, using the SDTM as the foundation. A sub-team formed with representatives from the ADaM and SDS Teams conducted a pilot project in 2006, and will be proposing 1) a best-practice approach for producing and submitting analysis datasets and/or analysis logic, and 2) a standard analysis models harmonized with the SDTM. A sub-team has also formed with representatives from the SDS and ODM teams to map the SDTM into ODM XML.

CONCLUSION

Since becoming the recommended standard for the submission of clinical and preclinical trial data to the FDA in marketing applications, the SDTM has begun to be used by sponsors for their upstream processing to support Clinical Study Reports and Integrated Summaries. This paper covers the basics and background of the SDTM. Material presented in our session will expand on information presented here and provide additional justifications and implementation examples.

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