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Periodic Safety Reports of Clinical Trials

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ABSTRACT

Safety data is an important part of clinical trials. Periodic safety reporting helps in understanding the safety risk of all investigational products. These reports inform regulators on evolving safety profile of an investigational drug and apprise them of actions to address any safety concerns. Some of the key safety reports are Investigator's Brochure (IB), Development Safety Update Report (DSUR), Periodic Safety Update Report (PSUR).

The DSUR is intended as a common standard for periodic reporting on products under development among the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) regions. DSUR is submitted annually. The main objective of a DSUR is to present a comprehensive, thoughtful annual review and evaluation of pertinent safety information collected. An IB is a collection of clinical data about the investigational product that is the focus of the study. A new IB is usually initiated for new products in preparation for Investigational New Drug submission. IB is also updated annually to assess the safety risk to trial participants. The PSUR is a comprehensive safety report that provides a periodic assessment of the safety profile of a marketed medicinal product. It covers the post-authorization phase and is submitted to regulatory authorities at semiannual or annual intervals according to regulatory requirements.

This paper focusses on workflow in producing reports for DSUR, IB and PSUR from a statistical programming perspective. Insights on different types of output used in producing DSUR, IB and PSUR. Special case situations on how to handle newer studies or closed studies, Medical Dictionary for Regulatory Activities (MedDRA) up-version effects and Adverse Events of Interests are discussed.

INTRODUCTION

FDA's E2F Development Safety Update Report is a guidance document on DSUR. The objective of DSUR is to report comprehensive safety information pertinent to a drug under investigation, whether or not it is marketed. DSUR should concisely provide information to regulators about the monitoring and evolving safety profile of the investigational drug. Safety information from all ongoing clinical trials that a sponsor is conducting or has completed during the reporting period in included. In order to promote comprehensive analysis and presenting the safety profile of investigational drug, a sponsor should prepare DSUR with data pertinent to all indications and all participant population under all studies with the investigational drug. Development International Birth Date usually referred to DIBD is used to determine the annual period for DSUR. Month and date of the DIBD is the start of the annual period for DSUR. Data cutoff point for DSUR, PSUR and IB is the last day of the one-year reporting period.

International Conference of Harmonization (ICH) ICH E2C(R1) guideline of November 1996, was a guidance document on PSUR. This established the PSUR as a harmonized format for post marketing periodic safety reports for approved drugs and biologic products, and described the format, content, and timing of PSUR submissions. Further addendums were made and a new guidance document E2C(R2) was created to replace the PSUR with the Periodic Benefit-Risk Evaluation Report (PBRER) for post marketing periodic safety reporting, and describes the recommended format, content, and timing of PBRER submissions.

Some ICH countries and regions accept submission of a PSUR to fulfill national and regional requirements for periodic reporting on the safety of approved drugs. Although the focus of the DSUR is on investigational drugs, there can be overlap between the content of the DSUR and PSUR, and some repetition is expected. Both the DSUR and PSUR should be comprehensive and stand alone as they focus on different subject matter and have differing periodicities and recipients.

The IB (Investigator's Brochure) is a comprehensive document that provides investigators with data and information about the drug under study giving them a better understanding of potential safety concerns in order to minimize risk to participants in the clinical trial. Precautions and/or special monitoring needed is also provided. ICH E6(R2) Good Clinical Practice Section 7 gives guidance for the content of the Investigator's Brochure. The IB is provided by the product's manufacturer and is updated during the drug development process. Adverse events occurring during the clinical trial(s) of the investigational drug are described within the IB. Statistical output in support of the IB will be discussed.

The ICH E2A and ICH E6(R2) Good Clinical Practice guidance documents are the foundation for what is expected in Reference Safety Information (RSI) in clinical trials. These mainly focus on patient safety, proper monitoring, and detailed reporting of adverse events. The primary purpose of RSI is to serve as the basis for expectedness assessments of 'suspected' serious adverse reactions ('suspected' SARs) by the sponsor for expedited reporting of suspected unexpected serious adverse reactions (SUSARs) and annual safety reporting to the Food and Drug Administration (FDA).

The purpose of this paper is to describe the standard workflow of the analysis and report plan for generating the standard outputs that support the preparation of the DSUR, PSUR and IB. The statistical programming team produces a standard set of tables and listing based on the ICH E2F and E2C(R2) guidance documents with input from Pharmacovigilance (PVE) safety scientists and statisticians.

STANDARD OUTPUTS SUPPORTING PERIODIC REPORTS AND WORKFLOW

The full title of each required summary table and listing is provided below. These standard supporting outputs are generated for each indication of the investigational drug should there be more than one. Titles are customized for a specific investigational drug and any indications that are being investigated.

Title	**Required for**
Cumulative Participant Exposure to *{Investigational Drug}* by study and all studies combined.	DSUR, PSUR
Cumulative Participant Exposure to *{Investigational Drug}* by Combination of Sex & Age.	DSUR, PSUR
Cumulative Participant Exposure to *{Investigational Drug}* by Race.	DSUR, PSUR
Summary of **Fatal** Adverse Events Leading to Premature **Discontinuation of Study** (Reporting Period: DDMONYEAR to DDMONYEAR - **yearly**) for Safety Analysis set population.	DSUR
Summary of Adverse Events Leading to Premature **Discontinuation of Study Drug** (Reporting Period: DDMONYEAR to DDMONYEAR - **yearly**) for Safety Analysis set population.	DSUR
Listing of **Fatal** Adverse Events Leading to **Premature Discontinuation of Study** (Reporting Period: DDMONYEAR to DDMONYEAR - **yearly**) for Safety Analysis set population.	DSUR
Listing of Adverse Events Leading to **Premature Discontinuation of Study Drug** (Reporting Period: DDMONYEAR to DDMONYEAR - **yearly**) for Safety Analysis set population.	DSUR
Summary/Listing of Death (Cumulative until the Yearly data cut – Separated by study)	IB
Adverse Event Overview/Summary by worst grade/Summary of Adverse events of Special Interest/Fatal Adverse Events listing/Adverse Events listing (Cumulative until the Yearly data cut – Separated by study)	IB
Demographics/Baseline Characteristics/Disposition/ Summary (Cumulative until the Yearly data cut – Separated by study)	IB
Reference Safety Information: Participant Incidence of Serious Treatment-Emergent Adverse Events (Cumulative until the Yearly data cut – All studies combined within the product)	IB/RSI

STANDARD WORKFLOW

This section describes the standard workflow from initial request to final delivery for the development of outputs supporting periodic safety reports.

- Pharmacovigilance team notifies the Biostatistician (or designee) of the reporting period and the list of studies to be included in the DSUR/PSUR/IB around six to eight weeks before the reporting period end date.

- Lead Biostatistician notifies the safety statistical programming team about the list of studies, shells of the outputs, specs of any derivations if required, and any other customized study information at least six to eight weeks before the data cutoff.
- Safety statistical programming lead notifies individual statistical programming study teams, clinical data management teams about the cutoff/ snapshot dates for the DSUR, PSUR and IB reporting periods.
- Using the pre-cutoff (dry run) data and prior to the snapshot safety statistical programming team will prepare the tables and listings programs and create the outputs.
- Outputs created by safety statistical programming team using the pre-cutoff data will be reviewed by biostatistics team. This is especially important for data reconciliation when a new study has been added to the periodic reports for the first time.
- On the day of cutoff/snapshot date, clinical data management team notifies the individual statistical programming study teams for the data readiness.
- Cutoff dates are applied to the raw data. Individual study statistical programming teams prepare the SDTM/ADaM datasets for the safety programming team.
- Using the snapshot data, safety programming team creates the outputs.
- Biostatisticians after reviewing the outputs and approving, will notify the Pharmacovigilance team about the availability of periodic report outputs.

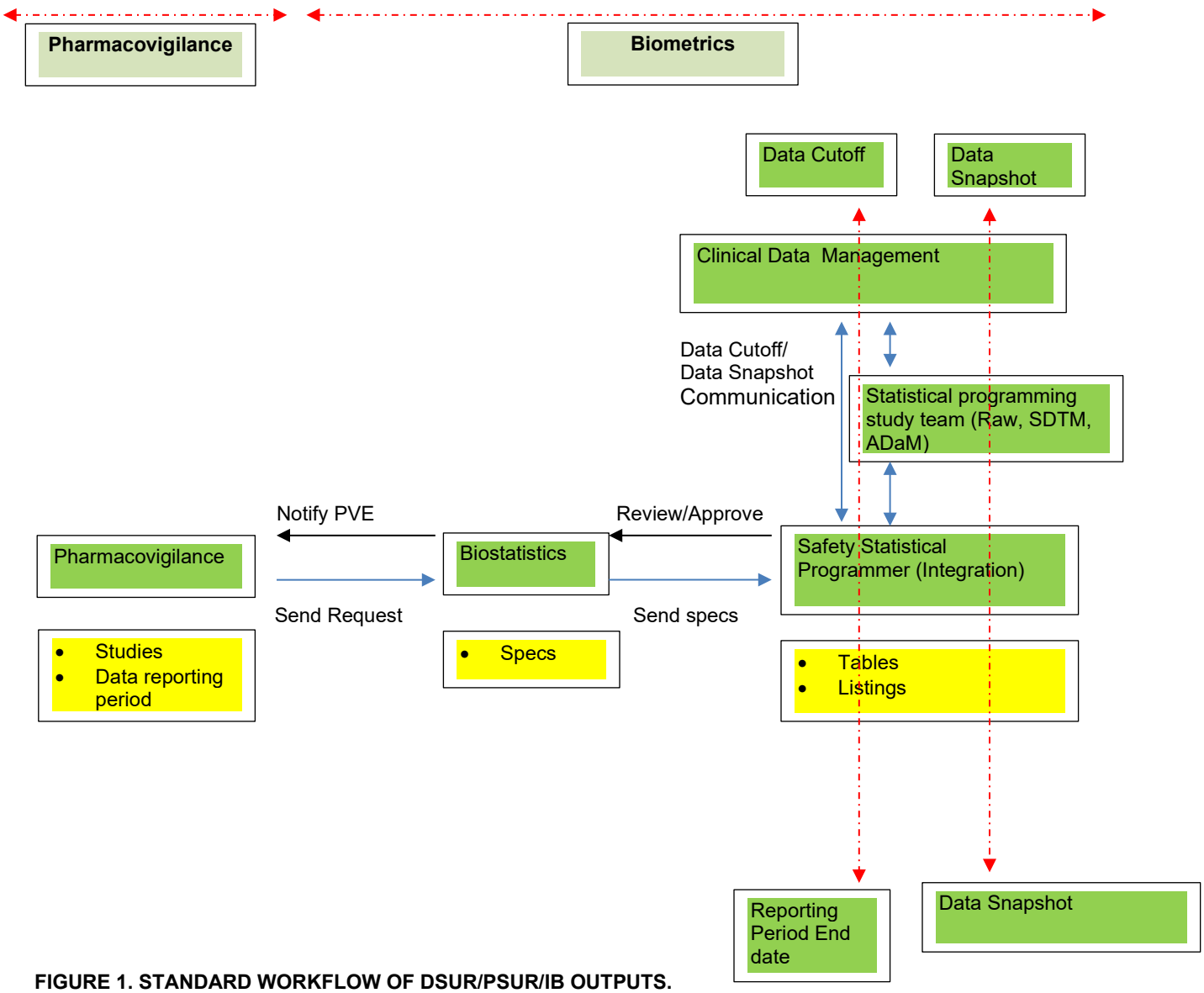

FIGURE 1. STANDARD WORKFLOW OF DSUR/PSUR/IB OUTPUTS.

INPUT DATA

For ongoing studies:

- Raw/SDTM/ADaM data extracted on the snapshot date are used to generate final analysis data files.
- If the reporting end date falls on a holiday or weekend, the snapshot date is the following business day. The analysis program aligns the cutoff date to the reporting end date.

For completed studies:

- For studies completed during the reporting period, the final ADaM datasets provided by the study team in the End of Study folder are the source data.
- For studies completed before the reporting period, the analysis datasets in the previous End of Study folders are the source data for periodic reports.
- Studies which are completed more than a year before the reporting period are not included in the IB outputs. However, cumulative exposure summaries will always continue to present the completed studies outside the reporting period.

REPORTING PERIOD

As DSURs are generally submitted to regulatory agencies annually, the reporting period of each DSUR is a one-year span (i.e., traced back approximately one year from the cutoff date). In some cases, a DSUR may be required for a period of less than one year (e.g., a DSUR for a shortened period may be required for the purposes of aligning the DSUR dates with the International Birth Date once a product is marketed). PSUR/PBRER are generally submitted to regulatory agencies every six months. The reporting period is identified in the headers of the applicable tables and listings. Cutoff dates generally fall on the Development International Birth Date of the product.

- DSUR/PSUR exposure summary are cumulative data since the start of the study.
- DSUR AE listing data is within the reporting period.
- IB listings/summary outputs are cumulative data since the start of the study.
- RSI outputs are cumulative data since the start of the study.

SHELLS SUPPORTING PERIODIC REPORTS

Table 1: Cumulative Participant Exposure to *{Investigational Drug}* by study and all studies combined.

For Blinded ongoing studies, the number of participants in each arm is estimated based on the study randomization scheme. For each study drug row (i.e., investigational drug, other, and placebo only), participants are counted once for each drug category. For example, if a participant was dosed with the investigational drug and one other study drug in a study, then the participant is counted once in the investigational drug category and once in the "Other" category. However, if a participant was dosed with two different non-investigational study drugs in a study, this participant is counted only once in the "Other" category.

Table PSUR-1. Cumulative Participant Exposure by Study of Investigational Drug (as of dd Month yyyy)

Study	Treatment	Number of Participants
All Studies Combined	All drugs including Investigational Drug	
	Non-Investigational drug 1	xxx
	Non-Investigational drug 2	xxx
	Participants Treated with Investigational Drug	xxx
	Other	xxx
	Total Unique Participants	xxx
Study 1	All drugs including Investigational Drug	
	Non-Investigational drug 1	xxx
	Non-Investigational drug 2	xxx
	Participants Treated with Investigational Drug	xxx
	Other	xxx
	Total Unique Participants	xxx
	.	
	.	
	.	

Note: Data from ongoing study (protocol ID) as of dd month yyyy.
Non-investigational drugs, excluding placebo, were presented as "Other".
If a participant was dosed with Investigational drug and non-investigational drugs, then the participant was counted once in the rows of "Participants treated with Investigational medicinal Product" and "Other" categories, and counted once in the row of "Total Unique Participants".

Data Source: xxxx, xxxx Program Name:xxxxxx Output Generated: YYYY-MM-DDThh:mm

Table 2: Cumulative Participant Exposure to *{Investigational Drug}* by Combination of Sex & Age.

Table PSUR-2. Cumulative Participant Exposure to Investigational Drug from Ongoing Clinical Trials by Age and Sex (as of dd Month yyyy)

Age (years)	Male (N=xx)	Female (N=xx)	Total (N=xx)
< 18	0	0	0
18 to 65	x	x	x
> 65	x	x	x
Total	x	x	x

Note: Data from ongoing study (Protocol ID) as of dd Month yyyy.
N = Participants treated with Investigational drug.

Data Source: xxxx, xxxx Program Name:xxxxxx Output Generated: YYYY-MM-DDThh:mm

Table 3: Cumulative Participant Exposure to *{Investigational Drug}* by Race.

Table PSUR-3. Cumulative Participant Exposure to Investigational Drug from Ongoing Clinical Trials by Racial Group (as of dd Month yyyy)

Racial Group	Number of Participants (N=xx)
AMERICAN INDIAN OR ALASKA NATIVE	x
BLACK OR AFRICAN AMERICAN	x
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	x
WHITE	x
ASIAN	x
OTHER	x
MISSING	x
TOTAL	xx

Note: Data from ongoing study (protocol ID) as of mm Month yyyy.
N = Participants treated with Study Drug.

Data Source: xxxx, xxxx Program Name:xxxxxx Output Generated: YYYY-MM-DDThh:mm

Table 4: Summary of **Fatal Adverse Events** Leading to **Premature Discontinuation of Study**, Summary of **Adverse Events** Leading to **Premature Discontinuation of Study Drug**.

If the action taken was captured for each study drug in the AE CRF, use the information, as captured, to determine which study drug led to premature discontinuation.

- If a participant received more than one study drug during the study, but only one study drug was prematurely discontinued due to an AE, the AE is counted only once under the study drug that was prematurely discontinued, but not under the other study drugs.
- If a participant received more than one study drug, including the investigational drug, during the study, but an action taken to each study drug for an AE that led to "study drug discontinuation prematurely" was not captured separately, but captured as a whole (i.e., only one check box available on the CRF), then this AE is counted once for "Investigational Drug" and once for the "Other" columns as the AE leading to study drug discontinuation.

Table DSUR- 1. Summary of Fatal Adverse Events Leading to Premature Discontinuation of Study (Reporting Period: dd Month yyyy to dd Month yyyy)
Table DSUR- 2. Summary of Adverse Events Leading to Premature Discontinuation of Study Drug (Reporting Period: dd Month yyyy to dd Month yyyy) (Safety Analysis Set)

System Organ Class Preferred Term	Investigational Product	Other	Total Unique
Number of participants experiencing any AE leading to premature discontinuation of study drug	xx	xx	xx
SOC 1	xx	xx	xx
PT Term 1	xx	xx	xx
PT Term 2	xx	xx	xx
PT Term 3			
... ...			
SOC 2	xx	xx	xx
PT Term 1	xx	xx	xx
PT Term 2	xx	xx	xx
PT Term 3	xx	xx	xx
... ...			

Note: Data from ongoing studies as of dd Month yyyy.
Non investigational drugs, excluding placebo, were grouped, and presented in "Other". AEs were counted under the study drug that was prematurely discontinued due to the AE; if association to the premature discontinuation was not identified, then AEs were counted once in each study drug applicable.
Multiple AEs were counted only once per participant for each system organ class and preferred term.
a Total Unique = the total number of unique participants who prematurely discontinued study drug during the reporting period.

Data Source: xxxx, xxxx Program Name:xxxxxx Output Generated: YYYY-MM-DDThh:mm

Table 5: Reference Safety Information: Participant Incidence of Serious Treatment-Emergent Adverse Events
(Cumulative until the Yearly data cut – All studies combined within the product)

Table 2C_1. Reference Safety Information: Participant Incidence of Serious Treatment-Emergent Adverse Events Related to IMP by System Organ Class and Preferred Term (Safety Analysis Set, N = xxx)
Table 2C_2. Reference Safety Information: Participant Incidence of Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Analysis Set, N = xxx)

Template: T_AE_SOC_PT

MedDRA System Organ Class Preferred Term, n (%)	Any Grade	Worst Grade ≥ 3	Worst Grade 1	Worst Grade 2	Worst Grade 3	Worst Grade 4	Worst Grade 5
SOC1	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
PT Term 1	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
PT Term 2	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
... ...	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
SOC2	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
PT Term 1	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
PT Term 2	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
... ...	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)

Data cutoff date = DDMMMYYYY.
Table summarizes serious, related TEAEs (prior to retreatment period of IMP if applicable) in the safety analysis set. TEAEs are defined as AEs onset during or after first IMP infusion.

Data Source: xxxx, xxxx Program Name:xxxxxx Output Generated: YYYY-MM-DDThh:mm

MEDICAL DICTIONARY FOR REGULATORY ACTIVITIES (MEDDRA) UP-VERSION AND ADVERSE EVENTS OF INTEREST

Up-versioning occurs when a new version of MedDRA is released, and adverse event terms (AEs) are recoded using the new version. Updated MedDRA versions are released twice a year, once on March 1st and then again on September 1st. It is recommended to up-version AE coding for active studies within two months of the release. Ongoing studies can be up-versioned in the database. However, closed studies up-version in the database is not feasible. If the closed studies are included in the periodic reports, these are required to be up-versioned to current MedDRA versions outside the database. AEs would need to be programmatically recoded outside of the database system.

Periodic safety reports such as IB may include summaries of AEI (Adverse Events of Interest). Examples of these are infections, cytopenia's (neutropenia, thrombocytopenia, anemia) and autoimmune disorders. Using MedDRA standard queries and/or customized queries, search term files are created and used by the statistical programmer to create AEI lookup tables. The lookup table is specific to an AEI and contains preferred terms associated with the AEI. Subsequently, during analysis dataset creation and/or output generation, AE data can be merged with the lookup table to flag and select the data associated with an AEI.

THREE DIFFERENT SCENARIOS ON HOW TO HANDLE MEDDRA UP-VERSION.

There can be three scenarios to handle the MedDRA up-version.

Snapshot dates fall outside the two months MedDRA up-version period: In this situation AE data can be up-versioned in the Database. Snapshot data will have the most recent version of MedDRA. This scenario doesn't pose much challenge while data extraction.

> **Example:** MedDRA up-version of AE occurs in database within 2 months after March 1st release. Snapshot date exists after May1st.

Snapshot dates fall within the two months MedDRA up-version period: If the periodic reports are going out to regulatory agencies after the two months period. It is required to up-version the data in database and use the most recent version in the periodic reports.

> **Example:** Snapshot date lies during 2nd week of April. Since the snapshot date lies within the two months period and reports most likely being delivered to regulatory agencies after May 1st, it is required to up-version the data in database.

MedDRA up-version for closed studies within the reporting period: If the study ends during the reporting period of the periodic reports, Up-versioning of MedDRA in the database might not be possible. We have to set up a process to up-version using MedDRA dictionary and coding team.

> **Example:** Study closed (locked) in July. Second version of the MedDRA release in September. Snapshot date for periodic report in November. We have to update the MedDRA outside the database to have the closed study data in most recent version.

CONCLUSION

This paper helps as a reference to statistical programming team on how to set up DSUR, PSUR, IB/RSI infrastructure. This paper also explains how to handle the MedDRA up-versions based on the different scenarios of reporting period and study status. How to make use of adverse events of interest lookup datasets for adverse event summaries is also discussed.

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