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Deep Dive into IB and DSUR: A Compound Lead Programmer's Perspective

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ABSTRACT

During the clinical development of an investigational drug, it is crucial to regularly report safety information to assess the risk to trial subjects. Periodic reports, such as the Investigator's Brochure (IB) and Development Safety Update Report (DSUR), identify new or emerging safety issues during the trial. In order to ensure the successful delivery of periodic reports, statistical programmers must not just focus on the details of programming work, but more significantly, the essential management and coordination of various studies from a compound lead perspective. This article outlines the relevant regulatory requirements and emphasizes the collaborative efforts required among different departments within the company. It also identifies potential challenges and offers solutions that programmers may face in this process. The goal of this article is to provide valuable insights and knowledge to improve the efficiency and effectiveness of periodic report delivery processes.

INTRODUCTION

During the clinical development of a new drug or medical intervention, it is crucial to continually monitor and report safety information to ensure the well-being of study participants and the integrity of the trial data. This process helps to identify and address any potential risks or adverse events promptly, demonstrates compliance with regulatory requirements, and contributes to the overall success of the study. Two key components of reporting safety information during clinical development are the Investigator's Brochure (IB) and the Development Safety Update Report (DSUR). The IB provides essential information on the investigational product, including its pharmacological properties, mode of action, previous clinical experience, and known or potential risks and benefits. This document serves as a vital resource for investigators and study staff, guiding them on the safe and effective use of the investigational drug throughout the trial. On the other hand, the DSUR consolidates safety data from ongoing clinical trials to provide a comprehensive overview of the drug's safety profile. This periodic report includes information on adverse events, laboratory findings, and any emerging safety concerns, allowing regulatory authorities and sponsors to assess the overall safety of the investigational product and make informed decisions about its continued development. In summary, the collaborative efforts to compile and report safety information through IB and DSUR are essential for maintaining the safety of study participants, meeting regulatory requirements, and facilitating the successful completion of clinical development programs. These reports play a vital role in safeguarding the integrity and ethical conduct of clinical trials, ultimately contributing to the advancement of medical knowledge and the improvement of patient care.

In summary, DSUR provides a one-year snapshot of safety data for an asset, while IB captures cumulative data at a specific point in time. Typically, IB and DSUR align their cutoff and data extraction dates to avoid discrepancies in presenting similar data, reducing the workload on programming teams by allowing a single set of outputs to cover both documents. This article will therefore discuss IB and DSUR together.

REGULATORY REQUIREMENTS FOR PERIODIC REPORTS

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) has developed guidelines to harmonize the requirements for the reporting of safety information in clinical trials. These guidelines aim to promote the safety and efficacy of investigational products and ensure the protection of trial participants.

REGULATORY REQUIREMENTS FOR DSUR

According to the ICH Development Safety Update Report E2F, the primary aim of a DSUR is to present a comprehensive, thoughtful annual review and evaluation of pertinent safety information collected during the reporting period related to a drug under investigation, whether or not it is marketed.

This entails several key points. Firstly, a DSUR is an annual report, and regulatory bodies such as the FDA, EMA and CDE follow ICH guidelines but also maintain their own national requirements based on ICH E2F. DSURs should be submitted as long as dictated by national or regional laws or regulations. Upon cessation of annual report submission requirements in a particular country or region, the sponsor should specify that the final DSUR serves as the concluding annual report for the investigational drug in that jurisdiction. Additionally, sponsors should indicate the status of clinical trials elsewhere.

Secondly, although DSURs primarily focus on reported safety information, any data indicating inefficacy, or inefficacy relative to established therapy, for investigational drugs intended to address serious or life-threatening illnesses should be summarized in the overall safety assessment section, as it could present a significant risk to clinical trial subjects.

Thirdly, the reporting period encompasses a specific start and end date. The Development International Birth Date (DIBD), representing the first clinical trial authorization date globally, marks the commencement of the annual period for the DSUR. The data lock point (DLP) of the DSUR should coincide with the conclusion of the one-year reporting period. For administrative ease, at the sponsor's discretion, the data lock point of the DSUR can be set as the final day of the month preceding the month of the DIBD. Submission of the DSUR to all pertinent regulatory authorities should occur no later than 60 calendar days after the DSUR data lock point.

Fourthly, the objective of a DSUR should pertain to the drug under investigation. While DSURs primarily concentrate on investigational drugs, they may provide information on comparators only if relevant to the safety of trial subjects.

Finally, the scope of the DSUR encompasses pre-marketing and post-marketing studies, as well as all ongoing clinical trials and other studies conducted or completed by the sponsor during the review period.

The IB in effect at the start of the reporting period should serve as the reference safety information to determine whether the information received during the reporting period remains consistent with previous knowledge of the safety profile of the investigational drug. The DSUR should clearly indicate the version number and date of the IB used for this purpose. If the IB has been revised during the reporting period and not previously submitted to the relevant regulatory authority, the sponsor should provide a copy of the current version of the IB as an attachment to the DSUR.

REGULATORY REQUIREMENTS FOR IB

According to the ICH Integrated Addendum to ICH E6(R1). The Investigator's Brochure (IB) is a compilation of the clinical and nonclinical data on the investigational product(s) that are relevant to the study of the product(s) in human subjects. Its purpose is to provide the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol. The IB should be reviewed at least annually and revised as necessary in compliance with a sponsor's written procedures.

SPECIAL REQUIREMENTS OF REGULATORY AUTHORITIES IN DIFFERENT COUNTRIES

Regulatory agencies such as the FDA, EMA, and CDE have established guidelines for reporting safety information in clinical trials. These guidelines outline the requirements for submitting periodic reports such as the IB and the DSUR.

The FDA guidelines emphasize the importance of continuous monitoring of safety data throughout the course of a clinical trial. Sponsors are required to submit safety reports on an ongoing basis to ensure the protection of trial participants. The EMA guidelines also stress the need for timely reporting of safety information, with specific requirements for the content and format of safety reports.

Similarly, the CDE guidelines in China outline the key components that should be included in the IB and DSUR, such as detailed descriptions of the investigational product, safety data from clinical trials, and any

important updates or changes to the product. These components are essential for ensuring that regulators have a comprehensive understanding of the safety profile of the investigational product.

In terms of timing and frequency of reporting requirements, all three regulatory agencies have specified deadlines for submitting safety reports. For example, the IB is typically submitted before the initiation of a clinical trial to provide investigators with important safety information about the investigational product. The DSUR, on the other hand, is submitted periodically throughout the trial to provide updates on safety data and any emerging safety concerns.

Additionally, the new requirement proposed by CDE and EMA may impact our DSUR programming work. CDE requires the inclusion of List of subjects who dropped out of clinical trials in association with an adverse event during the reporting period and list of subjects who died during the reporting period. Therefore, we need to add two separate listings for patients from Chinese sites. According to the Clinical Trials Regulation (EU) No 536/2014 Questions & Answers Version 6.9, compliance with Article 43.3 necessitates that Serious Adverse Reactions (SARs) in the line listing be identified by case ID and study ID, excluding subject ID from the document. Similarly, when reporting lists of deceased subjects and subjects who withdrew from trials due to adverse events, the use of case ID and study ID should not enable the identification of individuals. It is advisable to use study ID, DSUR version, and patient numbering (starting from 001 in each listing) as alternatives to subject IDs in these contexts. (This reflects our company's recommended practice rather than a regulatory requirement.)

Overall, adherence to regulatory requirements for reporting safety information is crucial for maintaining the integrity of clinical trials and ensuring the safety of trial participants. By following the guidelines established by regulatory agencies such as the FDA, EMA, and CDE, sponsors can demonstrate their commitment to monitoring and reporting safety data in a timely and comprehensive manner.

COLLABORATION AMONG DEPARTMENTS

The development and submission of an IB and a DSUR involve the collaborative efforts of multiple departments within an organization. Each department has distinct responsibilities and timelines to ensure the accuracy, compliance, and timely delivery of these critical documents. Here's a brief overview of the responsibilities assigned to each department:

Given that the initial version of the IB is submitted before the first IND submission and programmers are not involved in the creation of the new IB, our article focuses solely on the process of IB updates, rather than its creation. This pertains to the 2nd IB and subsequent versions.

PROCESS AND RESPONSIBILITIES

Processes

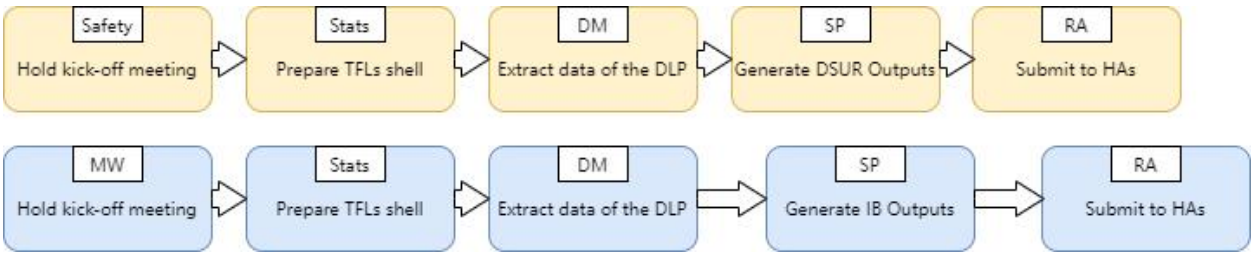

Figure 1. Processes for IB and DSUR

The flowchart above illustrates the processes for IB and DSUR in our company. This serves as a reference document outlining the distinct workflows, with DSUR processes marked in yellow and IB processes in blue. Given the similarities in scope between IB and DSUR, both utilize the same data lock point (DLP). This strategic alignment helps streamline data extraction and statistical programming efforts, contributing to efficiency across both processes.

Upon comparing IB and DSUR processes, several key observations emerge:

1. Ownership and responsibility: DSUR owned by the safety department. While IB owned by the medical department.

2.Timeline alignment on pre-DLP activities: Both IB and DSUR workflows initiate similar activities. Typically the KOM will be scheduled one month before the DLP, facilitating project coordination and planning.

3. Regulatory submission timelines: For DSUR, regulatory guidelines necessitate submission within 60 days post-DLP. While IB Submission generally occurs within 90 days post-DLP, allowing for a buffer to mitigate potential project conflicts post-DLP.

Responsibilities

DSUR	IB
The safety department is responsible for overseeing the development of the DSUR, manages various aspects including timelines, resource allocation, assignments, and ensuring final document quality. They also create and manage access to the folder, hold kick-off meetings, ensure timely delivery of the document, and arrange for translation of the DSUR.	The safety department contributes safety-related content to the IB updates
The medical writer is tasked with requesting necessary data, drafting and finalizing the DSUR, and verifying the plausibility of the required data. They initiate the draft document review, incorporate comments, and produce the final document, which is then routed for approval.	The medical monitor makes decisions regarding the clinical-related content for the IB with overall coordination of IB development, including timelines, resourcing, assignments, and final quality. The medical writer provides authoring support, general formatting.Initial authoring will be conducted over email. Medical Writer will provide the draft document and guidance for sections needing revision.
The data management (DM) team provides data of the data lock point (DLP), extracts data and ensures data cleanliness if required.	
The biostatistics (Stats) team drafts and coordinates the review of table, figure, and listing (TFL) shells, validating and delivering final TFLs.	
The statistical programming (SP) team generates TFLs based on the TFL shell structure within set timelines.	
The regulatory affairs (RA) team provides regional regulatory guidance, ensures compliance with regulatory guidelines and submits the final approved document to regulatory authorities.	
Other departments are tasked with updating pertinent content in the IB and DSUR. Specifically, the IB involves collaboration with preclinical departments, which is not directly related to programmers and thus will not be elaborated on here.	

Table 1. Responsibilities Regarding IB and DSUR

POTENTIAL CHALLENGES AND SOLUTIONS FACED BY PROGRAMMERS

This section explores various challenges commonly encountered by programmers, along with potential solutions. These insights are intended to spark reflection rather than prescribe a definitive approach. By sharing our experiences, we aim to encourage critical thinking and adaptive problem-solving among peers and industry stakeholders. Our proposed solutions, while effective in our environment, serve as starting points for discussion and innovation within the broader programming community.

SCOPE

DSUR	IB
The DSUR should provide safety information from all ongoing studies or completed during the review period including: ➢ Clinical trials conducted using an investigational drug whether with or without a marketing approval, i.e., human pharmacology, therapeutic exploratory and therapeutic confirmatory trials (Phase I – III); ➢ Clinical trials conducted using marketed drugs in approved indications, i.e., therapeutic use trials (Phase IV); ➢ Other therapeutic use of an investigational drug; and ➢ Comparability trials conducted to support changes in the manufacturing process of medicinal products. ➢ DSUR should not contain initial notification of any significant new safety issues, as these should have been communicated to regulatory authorities via expedited reporting	Safety Data In Scope ➢ Studies where ⩾ 10 patients have received study drug as of safety data cut off (DCO) Out of Scope ➢ Studies with FPI during the month before safety DCO ➢ Blinded studies ➢ Studies under Data whose release would compromise data integrity protection plan ➢ Investigator-initiated studies ➢ observational studies Efficacy Data In Scope ➢ Efficacy data that have been publicly presented/disclosed or published may be included in the IB as of the data cut off used at the last public presentation/disclosure ➢ If a molecule has received approval in any indication, the efficacy data from the drug label should be that which is included in the IB ➢ The decision as to the appropriate efficacy data to include (such as waterfall plots / sub-sets of efficacy data) should be decided between the Medical Monitor in consultation with (if appropriate) the DCTL for the molecule Out of Scope ➢ If data has been accepted for a conference or journal but not yet presented / published, it should not be included in the IB ➢ Data which has been or is about to be submitted for a filing is considered highly confidential and should not be included in the IB

Table 2. Scope of IB and DSUR

DATA SOURCE SELECTION STRATEGIES

Clinical studies typically involve the progression of data from raw data to SDTM and then to ADaM, or directly from raw data to ADaM. Regardless of the data source used, the ultimate aim is to generate TFLs from ADaM. However, each study presents unique challenges and considerations:

Data Sources

Data Source	Advantages	Disadvantages
Raw data	➢ Available in every study, reducing communication costs. ➢ Allows for direct ADaM generation,	➢ Lower standards may lead to data issues and missing data. ➢ Requires significant resources for

	facilitating unified logic control.	programming ADaM from raw data.
SDTM	➢ Maintains high standards. ➢ Facilitates unified logic control when used for ADaM generation.	➢ Not available in every study, resulting in higher communication costs. ➢ Studies without SDTM may require separate handling, increasing resource allocation.
ADaM	➢ Offers high derivability. ➢ Each study better understands its own situation when performing ADaM.	➢ Not available in every study, leading to increased communication costs. ➢ Lack of standardized derivations requires additional resources for verification.

Table 3. Comparison of Data Sources

Strategic Data Sourcing in Different Scenarios

When there are multiple studies within a compound, each study typically has different statuses—some contain only raw data, while others include SDTM or ADaM datasets. In such cases, it is advisable to use raw data directly to generate ADaM. Consistency in raw data within the same compound facilitates uniform derivation logic. Utilizing raw data avoids adding burden to individual study teams and reduces communication costs.

In the scenario where multiple studies belong to one compound, and studies from other compounds use this compound as part of a combination, it is recommended that within this compound, ADaM should be generated directly from raw data. For studies from other compounds supporting the submission of this compound, providing ADaM datasets directly is preferred. This approach reduces misunderstandings since colleagues from other compounds may not be familiar with the specific logic of this compound. Moreover, as their own compounds may require IB and DSUR in the future, using ADaM directly is advisable.

OTHER QUESTIONS

Consistency Issues

It is crucial to pay special attention to the derivation logic of key variables. It is advisable to maintain consistent textual documentation of discussion outcomes, supplemented by programming checks when necessary. Examples include variables such as AEACN and AEREL in ADAE and treatment related variables in ADSL, especially when the study drug is used in combination with other compounds.

Coding Problem

In the pooled safety tables, it's important to ensure that the MedDRA pooling tables are consistent. For the individual study tables in the IB, preferably aligned, but acknowledging feasibility challenges. The CTCAE versions do not need to be consistent, but each version used should be specified with version numbers and dates in the table footnotes.

CONCLUSION

The development and submission of IB and DSUR are crucial for ensuring clinical trial participant safety and investigational drug program success. These documents comply with stringent regulatory requirements and serve as vital resources in clinical development. IBs provide comprehensive safety information at specific times, while DSURs offer annual safety profile updates, aligning with global regulatory expectations. Production involves coordinated efforts across multiple departments, ensuring accurate, complete, and timely submissions. Statistical programmers face challenges in data standardization and consistency, requiring robust planning and communication. Choosing appropriate data sources is essential for reliable outputs, supporting data integrity across diverse clinical scenarios. Continuous process monitoring and improvement optimize report efficiency, enhancing clinical trial operations and regulatory compliance.

REFERENCES

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