Paper SA07

Development Safety Update Report (DSUR)/ Periodic Safety Update Report (PSUR)

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ABSTRACT

Development Safety Update Reports (DSUR) are annual safety reports that provide a review and evaluation of the safety data collected during the reporting period a compound is under investigation.

Periodic Safety Update Reports (PSUR) are a periodic safety report that provides a comprehensive safety report of a marketed compound.

DSURs and PSURs follow a similar process and are often confused as being the same thing. This paper will discuss what DSURs and PSURs are, why DSURs and PSURs required and how DSURs and PSURs are developed. The differences between the two reports should remove the confusion.

INTRODUCTION

DSURs and PSURs are reports that focus on all the safety data from all clinical trials during an annual or periodic review period. Using the data, sponsors, investigators, and regulatory agencies can ensure the safety of participants, identify any new risks or benefits, identify any changes to the benefits and risks assessments, provide ongoing safety monitoring, provide ongoing evaluations, identifies if any further clinical trials will be required and identify any action required to protect public health.

The goal of this paper is to explain what DSURs and PSURs are, why they DSURs and PSURs are required and how DSURs and PSURs are produced.

WHAT IS A DSUR?

Development Safety Update Reports (DSUR) are an annual review and evaluation of the safety data collected during the reporting period of any compound under investigation. The compounds development international birth date (DIBD) initiates the requirement for a DSUR. As soon as a compound is required to have a DSUR, they should be submitted annually and can continue post-marketing but should end when the marketing authorization is obtained.

The rules for trials to be included in the DSUR or PSUR are as follows:

- Any ongoing trial where at least one participant has signed informed consent prior to the data lock point (DLP) and has yet to have the clinical study report (CSR) approved.
- Any trial where the CSR approval date falls prior to the DLP and within the review cycle.

What this means is, that any trial where the CSR approval date fell prior to the review cycle is not required and any new trials yet to have informed consent prior to the DLP are not required to be included in the report.

The DSUR should provide details of any adverse events (AE), details of any serious adverse events (SAE), details of any deaths, details of withdrawals due to AE, details of safety concerns, a full benefits and risks assessments, details of any efficacy data, and any requested information from regulatory bodies.

The DSUR should be submitted within 60 days of the DLP.

WHAT IS A PSUR?

Periodic Safety Update Reports (PSUR) are a comprehensive review of safety data of a marketed compound during a defined interval. The defined interval can range from every six months to every five years. The compounds international birth date (IBD) initiates the requirement for a PSUR. As soon as a compound is required to have a PSUR, they should be submitted in line with their defined intervals. The interval for a PSUR can change through the cycle of a compound. The initial interval is usually the shortest interval, and with time tends to increase.

The data reported in the PSUR is remarkably like that of a DSUR. However, it also provides a broader assessment of safety data, utilising data collected from post-marketing sources, it also gives more regular updates of assessments of the benefits and risks assessments.

Regulatory authorities provide more guidelines for the content format and timelines of PSURs than they do for DSURs.

Like the DSUR, The PSUR should be submitted within 60 days of the DLP.

WHY ARE DSURS REQUIRED?

DSURs are required because:

- They are a valuable tool that helps to ensure the safety of participants taking part in clinical trials for the compound.
- They provide ongoing safety monitoring of the compound, identify any positive trends or potential issues.
- They provide ongoing evaluations, which can be used to determine if a compound should continue or not.
- Can help to identify positive trends or potential issues, which may lead to additional trials being required.
- Often a requirement from regulatory authorities during the development stages of a compound.

WHY ARE PSURS REQUIRED?

PSURs are required because:

- They can identify new risks for a compound at frequent intervals.
- They can identify any changes to the benefits and risks assessments at frequent intervals.
- They can identify any further investigations required on specific issues.
- They can identify any action required to protect public health.
- They are a regulatory requirement in most regions for a marketed compound.

DIFFERENCES AND SIMILARITIES BETWEEN THE DSUR AND THE PSUR?

Differences

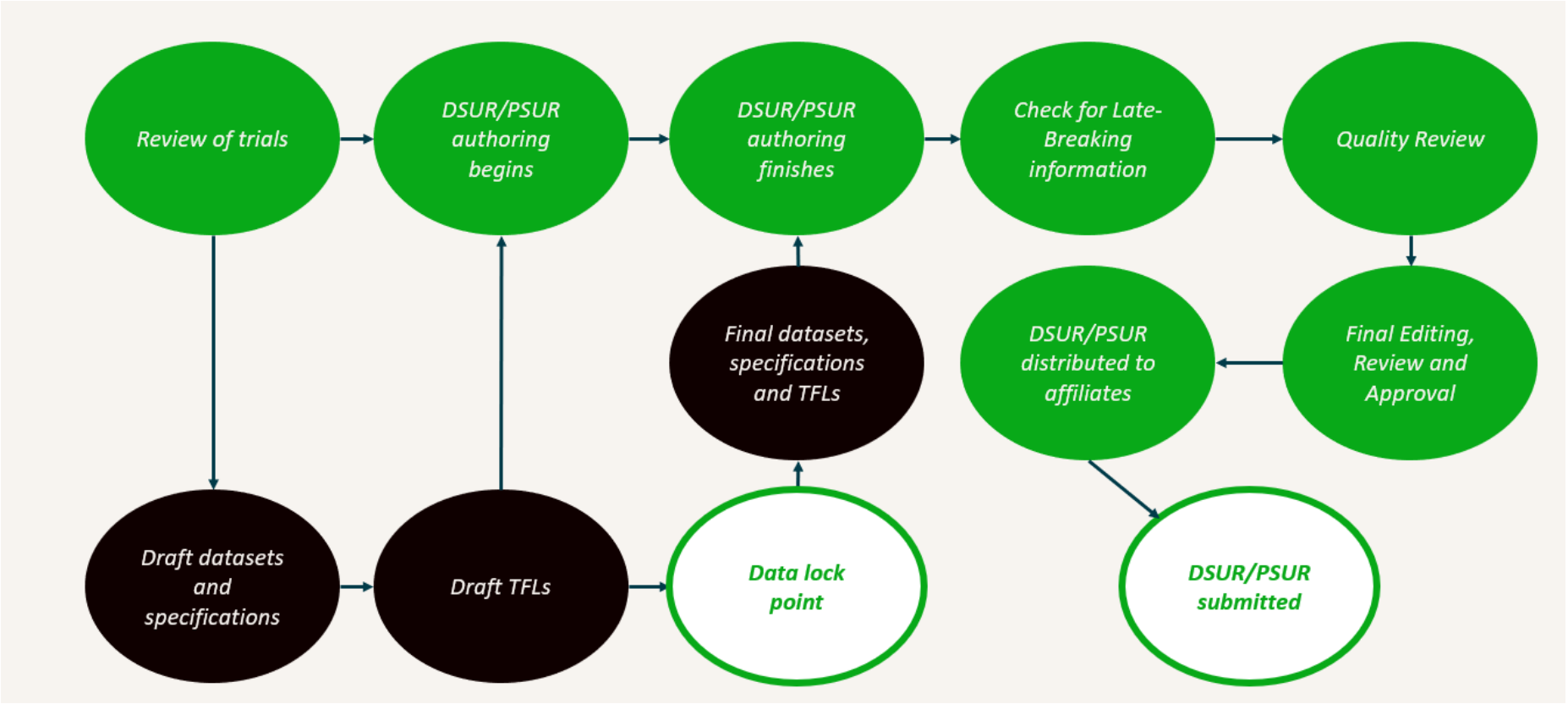
- The DSUR is initiated from the compound's development international birth date, whereas the PSUR is initiated from the compound's international birth date. This means that the DSUR process begins a lot earlier than the PSUR as it begins prior to the marketing of a compound, whereas a PSUR begins after the marketing of a compound has begun.
- The DSUR is submitted annually whereas the PSUR can be submitted at a defined interval, varying between 6 months and 5 years.
- The DSUR can include information on the efficacy of a compound, whereas a PSUR does not include this.
- The PSUR gives more detailed information than the DSUR, as it can use data from post-marketing sources.
- The PSUR can give more frequent data to update and change the risks and benefits assessments of a compound.
- The PSUR is required by most regulatory bodies than the DSUR.

Similarities

- The DSUR and PSUR both report data related to AEs, SAEs, AEs leading to discontinuation, Disposition, Demographics and Exposures of a compound.
- The DSUR and PSUR are both required to be submitted within 60 days of the DLP.
- The focus is primarily on participate and public health for both the DSUR and PSUR.
- The DSUR and PSUR can lead to the identification of specific areas that need further investigation.
- Whilst the PSUR is often done more frequently the DLP of the DSUR can be synchronized with the PSUR. E.g. if the PSUR was every 6 months, one of the two PSURs provided each year could have the same DLP as the DSUR.
    - If they are synchronized the sponsor can either choose to have one report or a separate report for the DSUR and PSUR.

HOW ARE DSURS AND PSURS DEVELOPED?

Process Flow



TFL = Tables, Figures and Listings.

Review of Trials

Approximately 55 days prior to the DLP the sponsor of the compound will have an internal kick off meeting for the DSUR or PSUR.

During this kick off meeting:

- The sponsor will confirm the date of the DLP for the reporting period, it is often the same day and month as the previous year.
- Every trial that is currently on the compound's portfolio will be reviewed. During this review, the sponsor is looking for:
    - The CSR approval date for any completed trials. Any trials with the CSR approval date within the current review cycle will be required. Any trials with the CSR approval date prior to the date of the previous cycle's DLP will be excluded.
    - Any ongoing trials that have had first participant visit (FPV) prior to the kick off meeting will be included.
    - The FPV for any trials yet to begin. If the FPV is scheduled to be greater than one week after the DLP will be excluded. Any trials with FPV between the kick off meeting and DLP will be flagged to review closer to the DLP.
- Every ongoing trial will also be reviewed to see what the blinding scheme is for the trial. Blinded trials are expected to be blinded unless they have locked prior to the DLP.
- The sponsor will review any requests by the regulatory bodies.
- The sponsor will review any areas of data they believe should be discussed.

Once the sponsor has completed their internal kick off meeting, they will reach out to their vendor and set up an external kick off meeting. Within this kick off meeting they will relay their conclusions from their internal kick off meeting. This will allow the vendor to be informed of the required trials, the blinding scheme for each trial, any areas of interest outside the standard requirements and trials to keep an eye on to see if they will be needed for the DSUR or PSUR. The TFLs required will be shared alongside approved TFL Shells.

Draft Datasets and Specifications

Following on from the external kick off meeting, the programming team will begin the process of creating the DSUR or PSUR datasets.

An individual dataset and related specification will be created for each trial that is required to be included. For each trial, the programmer will use the protocol, TFL shells, randomization (for unblinded or open label trials) and either the locked database extract or a recent database extract. Using all this information and SAS enterprise guide, the programmer will create a dataset that contains all the required data for the DSUR and PSUR.

A specification will be produced alongside the dataset with the following columns:

- Variable: This is the name of the variable. It should be no more than eight characters long.
- Label: This is the label of the variable. It should be no more than forty characters long.
- Type: This indicates if the variable is character or numeric.
- Format: This indicates if the data has any formats applied to it, e.g., DATE9. Which presents the data as DDMMMYYYY.
- Length: This indicates the length of the variable.
- Origin: This indicates if the data is presented directly from the database or if it has been derived.
- Method: This will provide the methodology of how any derived variable was created.

Each dataset contains treatment variables and estimated treatment variables. For unblinded trials, the treatment variables are used, and the estimated treatment variables are null. For blinded trials, the treatment variables are populated with 'BLINDED' and the estimated treatment variables contain a dummy randomisation of the treatments. This dummy randomisation follows the same model provided within the protocol of a trial.

Once a dataset and specification are produced for a trial it will have a full quality check performed by the programmer, this involves the programmer working through a list of specified checks to ensure the quality of the output. Then depending on the sponsor an independent programmer will either perform a peer review of the outputs or dual program them to double check they are correct.

Once the datasets and quality checks are completed for all trials these will be sent to the sponsor and medical writer (MW) as a draft version. The sponsor and MW will then provide feedback to the programming team and any updates or further requests for new data will be incorporated into the dataset.

The datasets and specifications will then be ready for use within the TFL production.

Draft TFLs

The TFL production will begin once the datasets and TFL shells are available. For each sponsor there is a standard set of TFL shells that conform to their expectations. This is usually be provided at the external kick off meeting but can be updated during the production phase of the DSUR or PSUR when new requests are made. As well as the TFL shells and datasets, the programmer will use the protocol and randomization (for unblinded or open label trials). Even though the randomisation was used for the datasets, it is also used for the TFLs to add in an extra confirmation check. Using all this information and SAS enterprise guide, the programmer will create the required TFLs.

The TFLs are created at a compound level, which means all the individual trial datasets need to be integrated together. This is not an issue as the format of all trial datasets is consistent. The process for quality control of the TFLs is like the datasets. The programmer will check the outputs using a specified list of checks and then an independent programmer will either peer review or dual program to check the data and outputs.

Standard Listings produced are:

- Disposition
- Treatment-Emergent Adverse Events
- Serious Adverse Events
- Adverse Events Leading to Withdrawal
- Deaths

Standard Tables produced are:

- Summary of Disposition
- Summary of Demographics
- Summary of Exposures by Treatment and Dose Level
- Summary and Frequencies of Treatment-Emergent Adverse Events
- Summary of Serious Adverse Events

Additional TFLs can include:

- Adverse Events of Special Interest
- Summary of Weight by timepoint
- Summary and Listing of Immunogenicity
- Out of Range Lab Safety Data

Once the TFLs and quality checks are completed these are sent to the sponsor and MW as a draft version. The sponsor and MW will then provide feedback to the programming team and any updates or further requests for new TFLs will be incorporated into the TFLs.

Data Lock Point

The DLP is a selected date. This date starts the countdown to the submission date, which should be within 60 days of the DLP.

Once the DLP has occurred the programming team will check all the trials that were flagged as being potential risks of not having any participants with informed consent being signed. The programming team will confirm their findings with the sponsor and MW.

Final Datasets, Specifications and TFLs

Following the DLP and checking of trials the programming team will request extracts for all ongoing trials and then re-run all the datasets and TFLs. Quality checks will be performed and any changes to the data will be flagged and passed on to the sponsor and MW.

The final versions of the datasets and TFLs will then be delivered to the sponsor and MW for approval, once approved the programmers will await confirmation from the final editing, review and approval that no further work is needed.

DSUR and PSUR Authoring

Authoring of the DSUR or PSUR will commence shortly after the external kick off meeting, usually prior to the draft datasets and TFLs being sent for review. The MW and sponsor have access to the trial databases and receive extracts in the form of excel spreadsheets and are therefore to have a knowledge of what they are expecting to see in the datasets and the TFLs.

When the draft datasets and TFLs are provided the sponsor and MW will assess to see if there are any further areas that need to be explored. Any feedback will be passed on to the programming team and updated datasets and TFLs will be provided prior to the DLP to aide in the completing a draft version of the DSUR or PSUR.

The sponsor will then review the DSUR or PSUR and provide their feedback. Feedback will be incorporated prior to the DLP. However, the DSUR and PSUR is not usually sent back to the sponsor until after the DLP.

Following the DLP the MW will incorporate the final TFLs into the report and send this on to the sponsor for their approval.

The DSUR or PSUR should:

- include all the key safety data, which includes new or emerging safety information.
- include information on any AEs that occurred.
- include any changes to protocols.
- be clear and concise.
- include any additional information requested by the regulatory bodies.
- be submitted even if there has been no new safety information during the reporting period.
- include a risk-benefit assessment.
- include details of efficacy data. (DSUR only).

The DSUR and PSUR are typically only seen by those involved with the clinical trials, the sponsor, the investigators, and the regulatory agencies.

The format of DSUR and PSUR is governed by regulatory bodies, with the European Medicines Agency (EMA) heavily involved with the format of PSURs. The Guideline on good pharmacovigilance practices (GVP)[1] and Article 35 of the Commission Implementing Regulation (EU)[2] provide good detail on what is needed for the PSUR. In addition the EMA provides some useful documentation for the DSUR, the ICH guideline E2F on development safety update report – Step 3[3] and the ICH guideline E2F on development safety update report – Step 5[4]

Check for Late-Breaking Information

Once the report has been provided to the sponsor, both the sponsor and the MW will review everything and check there is no late-breaking information that has occurred since draft that needs including in the DSUR or PSUR. If there is any late-breaking information, then additional data within the datasets and additional TFLs may be requested.

Quality review

Once the report has been improved, and any late-breaking information included, the DSUR or PSUR are sent to the sponsor and vendors quality review teams. These quality review teams then check that the DSUR or PSUR comply with the regulatory bodies' expectations for the format of the report. All regulatory requests have been incorporated and that no blinded trial has been unblinded.

Any feedback that needs actioning is then given to the sponsor and MW.

Final Editing, Review and Approval

The final editing, review, and approval of the DSUR or PSUR will begin following the findings from the quality review team. If there are no findings, then the report will be finalised. If there are findings these will be incorporated into the DSUR or PSUR and then sent back to the sponsor and quality review teams for approval.

The final DSUR or PSUR will then be approved by the sponsor.

DSUR/PSUR Distributed to Affiliates

The sponsor will then distribute the DSUR or PSUR to the appropriate affiliates. The affiliates will review and confirm if the DSUR or PSUR comply with guidelines.

If the DSUR or PSUR do not comply with the guidelines then this will be fed back to the sponsor and the process will jump back to the appropriate place to incorporate the feedback. If the DSUR or PSUR are confirmed to comply the DSUR or PSUR can then be submitted.

DSUR/PSUR Submitted

Once given the go ahead to submit, the sponsor will ensure the DSUR or PSUR are submitted prior to the 60 day deadline.

CONCLUSION

DSURs and PSURs are a useful report that provide regular updates on safety data for a compound, be it in the development phase or following release to the market. The reports can lead to positive changes to a compound during it's life cycle by highlighting any positive or negative trends leading to further investigation. In reviewing the DSUR or PSURs sponsor can find unexpected outcomes of a compound, which could lead to further investigations and a different use of the compound.

One of the key principles of the reports is to ensure participant safety and protect public health. I think within our industry this must be seen as quite an important reason for the DSUR and PSURs to be produced.

Without DSURs and PSURs, issues presented by a compound may not be highlighted until it is far too late. A sponsor should see DSURs and PSURs as a great tool. They can use the data from them to make key decisions on a compound such as:

- Further trials being required to ensure the safety of a compound.
- Changing the target area of a compound.
- Positive impacts of a compound.
- If a compound should be cancelled.

It should now be clear what the difference between a DSUR and PSUR is and hopefully this paper should have given an idea of what a DSUR and PSUR are. Why a DSUR and PSUR are required. The work required to develop a DSUR and PSUR for a trial. The process from start to finish usually take 115 days.

REFERENCES

[1] Guideline on good pharmacovigilance practices (GVP): Guideline on good pharmacovigilance practices (GVP) Module VII – Periodic safety update report (Rev 1) (europa.eu).

[2] Article 35 of the Commission Implementing Regulation (EU): Commission Implementing Regulation (EU) No 520/2012 of 19 June 2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the CouncilText with EEA relevance (europa.eu)

[3] ICH guideline E2F on development safety update report – Step 3: E2F - Development Safety Update Report (europa.eu)

[4] ICH guideline E2F on development safety update report – Step 5: E2F Step 5 Note for guidance on development safety update report (europa.eu)

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