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ANALYTICAL REPORT

Aggregate Safety Assessment Planning for the Drug Development Life-Cycle

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Abstract

The Program Safety Analysis Plan (PSAP) was proposed previously as a tool to proactively plan for integrated analyses of product safety data. Building on the PSAP and taking into consideration the evolving regulatory landscape, the Drug Information Association–American Statistical Association (DIA–ASA) Interdisciplinary Safety Evaluation scientific working group herein proposes the Aggregate Safety Assessment Plan (ASAP) process. The ASAP evolves over a product's life-cycle and promotes interdisciplinary, systematic safety planning as well as ongoing data review and characterization of the emerging product safety profile. Objectives include alignment on the safety topics of interest, identification of safety knowledge gaps, planning for aggregate safety evaluation of the clinical trial data and preparing for safety communications. The ASAP seeks to tailor the analyses for a drug development program while standardizing the analyses across studies within the program. The document is intended to be modular and flexible in nature, depending on the program complexity, phase of development and existing sponsor processes. Implementation of the ASAP process will facilitate early safety signal detection, improve characterization of product risks, harmonize safety messaging, and inform program decision-making.

Keywords Product risks · Clinical trial · Data review

Introduction

The Council for International Organizations of Medical Sciences (CIOMS) VI report [1] has had a significant influence on the development of best practices related to ongoing safety monitoring and reporting from clinical trials. This paper has provided a foundation for aggregate review of

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Table 1 Glossary

Term	References	Meaning
Adverse Drug Reaction (ADR)	[46]	All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least reasonably possible
Aggregate Safety Assessment	[6]	In the context of this manuscript: Analyses of safety data based on a holistic look across all completed and ongoing clinical studies of a program. Often, this aggregate review is facilitated by programmatic integration, or pooling, of some or all of the clinical study data, but could also consist of a collective review of data from individual studies
Anticipated events	[6]	Events likely to happen in the target population, independent of drug exposure
Identified risk	[47]	An untoward occurrence for which there is adequate evidence of an association with the medicinal product of interest
Potential risk	[47]	An untoward occurrence for which there is some basis for suspicion of an association with the medicinal product of interest but where this association has not been confirmed. Examples given in ICH E2F include non-clinical safety concerns not yet observed in clinical studies, as well as events which are "known to be associated with other products of the same class."
Safety Topics of Interest	None	Identified risks, potential risks, and other safety events of special interest based on, for example, preclinical data, early clinical trial data, epidemiology of the patient population or traditional regulatory concerns (e.g. DILI)
SAC	[6]	Safety Assessment Committee: An unblinded committee with relevant expertise, external and/ or internal to the organization, but independent of the study team. The SAC is focused on decisions regarding IND safety reporting based on aggregate safety assessment
SUSAR	[46]	Suspected Unexpected Serious Adverse Reaction: While "SUSAR" is not used directly, all of the pieces ('unexpected', 'serious', 'adverse drug reaction') are defined in E2A. SUSARs are subject to expedited reporting rules
SMT	[1, 3]	Safety management team: a cross-functional team associated with a product's clinical development program and led by a safety physician. The SMT is focused on program-level assessments of the accumulating safety data

accumulating clinical trial safety data over the course of a product life-cycle to facilitate earlier safety signal detection. The subsequently published CIOMS VIII addresses signal detection in the post-approval setting [2]. Following the CIOMS VI publication in 2005 [1], the Safety Planning and Evaluation Reporting Team (SPERT) was established in 2006 by the Pharmaceutical Research and Manufacturers of America (PhRMA) with the aim of proposing a pharmaceutical industry standard for safety planning, data collection, evaluation and reporting. In 2009, SPERT issued a key publication [3], recommending implementation of a Program Safety Analysis Plan (PSAP). The PSAP was intended to be a living document constructed by a sponsor's multidisciplinary Safety Management Team (SMT) early in product development. The PSAP outlined proactive plans for routine aggregated analyses of clinical trial safety data to define the safety profile of the product and ensure standard approaches for data collection and analyses. The PSAP concept was an important first step toward focused planning for aggregate safety evaluations. However, since its introduction in 2009, global regulatory expectations for safety monitoring and reporting have evolved with clear expectations for ongoing quantitative and aggregate review of accumulating safety data [4].

In 2017, the Drug Information Association–American Statistical Association (DIA-ASA) Interdisciplinary Safety Evaluation scientific working group was formed [5]. This joint working group has representation across the pharmaceutical industry and across regions, and includes clinical and pharmacovigilance scientists, epidemiologists, and statisticians with expertise in safety evaluation. Building on the PSAP, the DIA-ASA working group herein proposes the concept of an Aggregate Safety Assessment Plan (ASAP) as an evolution of clinical trial safety planning. The ASAP facilitates proactive, cross-disciplinary strategic planning for the characterization of the emerging safety profile of a product (i.e. the "safety story"). The ASAP is an internal document developed by clinical trial sponsors. The ASAP is composed of modules aimed at ongoing aggregate safety evaluation, standardizing product-level assessments, identifying safety knowledge gaps and preparing for safety communications. 'Aggregate', in this context, refers to a holistic assessment of the totality of available data for a drug development program, including ongoing studies. Ideally, this

aggregate review is supported by programmatic integration, or pooling, of the clinical trial data but also could consist of a collective review of data from individual clinical studies.

This paper outlines the ASAP framework and provides details on the value proposition, proposed content, and approaches to overcoming challenges in the implementation. The initial ASAP should be created by the SMT early in the clinical development program, typically no later than the end of Phase 2A or completion of a proof of concept study. However, certain components of the ASAP, such as identification of the safety topics of interest, would be beneficial to develop in conjunction with the initiation of human studies. The ASAP should be updated throughout the lifecycle of the product based on the accumulating safety information.

While we anticipate that the ASAP framework will first be adopted in a regulatory context, the potential needs of health technology assessments also may be considered within this framework. Finally, it should be noted that the framework is applicable for medicines, vaccines, devices and combination products.

A glossary of terms is included in Table 1. Additionally, a sample template for the ASAP is provided as a guidance (see Supplement Materials).

The ASAP template is proposed as a tool whose structure is designed to achieve the following:

- A consistent approach to collection and analysis of safety data, including safety topics of interest, across the program
- Description of ongoing product-level clinical trial safety monitoring, including quantitative assessments
- Characterization of the emerging safety profile of the product ("safety story")
- Identification of important safety knowledge gaps
- Preparation for regulatory application filing, periodic reporting and other safety-related communications or responses to regulatory queries

To meet these objectives, an ASAP template with the following components is proposed:

- ASAP value proposition and governance
- Safety topics of interest and pooling strategies
- Data analysis approaches
- Analysis of key gaps and future data collection
- Ongoing aggregate safety evaluation (OASE)
- Communication of safety information

Acknowledging that various clinical trial sponsors may have other documents that focus on some of these components, the ASAP is intended to be modular in nature. However, the main aspects of aggregate safety data assessment reflected in the ASAP template should be addressed in some manner by sponsors, whether in the ASAP, another document, or a work instruction or standard operating procedure (SOP). Although the template presented (supplemental materials) contains all components of the ASAP as an example, sponsors may choose to populate selected sections of the template.

The current paper focuses on the general ASAP process and modular framework. Further, points to consider for each of the ASAP sections are discussed below, taking into account the recommendations of CIOMS VI [1]. More detailed guidance for specific situations encountered in various therapeutic areas is beyond the scope of the current paper. Also, while the current focus is on aggregate safety assessment during clinical development, clinical studies may continue for many years after the first marketing authorization of a product. In addition, while the analysis of post-marketing safety data is not specifically addressed, initial clinical trial data findings set the stage for post-marketing surveillance activities and safety studies conducted. Conversely, post-marketing safety findings may influence still ongoing clinical development programs of the product.

ASAP Section 1: ASAP Value Proposition and Governance

This section should state the purpose of the ASAP, describe the ASAP governance model and provide an overview of the relevant clinical databases. A glossary of terms used in the ASAP should be considered near the top of the document or in an appendix.

This section should either briefly describe at a high level how the different bodies involved in aggregate safety assessment (e.g. SMTs, Data Monitoring Committees (DMCs), and/or internal safety governance bodies) will interact or refer to relevant company SOPs. If applicable, the engagement of a Safety Assessment Committee (SAC) with members of relevant expertise who are independent of the study team may be noted here or described in a standalone appendix to the ASAP template. The SAC guides decisions about investigational new drug (IND) safety reporting based on program-level data [6]. A graphical example depicting potential interactions between the SMT, DMC and SAC can be found in the ASAP template (Supplemental Materials). If employed, the roles and responsibilities of the SAC (which may or may not be assumed by a DMC) should be clearly delineated in a separate written charter.

A detailed description of the ASAP "value proposition" could be included in ASAP training, with a shorter purpose statement within the ASAP such as:

> The purpose of this Aggregate Safety Assessment Plan (ASAP) process is to coordinate an interdisciplinary,

cross-study review of the accumulating safety information from designated completed and ongoing studies of Product X. This systematic data review supports the identification of safety signals, the characterization of the evolving product safety profile, including safety topics of interest and alignment on important risks which may impact the benefit:risk profile of the product, and consistent and accurate safety messaging. Moreover, the ASAP process facilitates compliance with various national and international safety reporting rules, including the 2010 FDA IND safety reporting final rule that stipulates product relatedness be assessed by ongoing aggregate evaluations of the frequency of events in clinical trial programs.

Each iteration of the ASAP should have a version number and an approval date by agreed upon stakeholders. Change control could be included or described in a SOP. The ASAP typically will be co-authored by the safety physician and statistician, in collaboration with other cross-functional representatives, which should include, at a minimum, an epidemiologist and a clinical physician. The planned cadence of updates (e.g. annually, or after designated "trigger events") should be determined, and rules regarding for-cause updates specified. An appendix noting the nature of changes to the ASAP for each version update also should be considered for inclusion.

The development of the ASAP starts with a comprehensive evaluation of the available safety information. This information may be summarized at a high level in the ASAP (Section 2), or documents such as the Investigator's Brochure could be referenced. Information consulted in the development of the ASAP should be listed, such as: the target product profile, development risk management plan, benefit risk value tree, or any relevant safety related regulatory guidance or product specific feedback (e.g. requirement for numbers of patients exposed, particular data sets or safety analyses requested).

ASAP Section 2: Safety Topics of Interest and Pooling Strategies

Cross-functional alignment on the safety topics of interest and pooling strategies for studies included in the aggregate analyses is a critical first step in developing the ASAP. Safety topics of interest broadly include important identified and potential risks of the product as well as other safety topics of interest that require specialized data collection, monitoring or analyses (i.e. actions beyond "routine"). Safety topics of interest typically have the potential to impact the product's benefit:risk profile and could be related to clinical adverse events or changes in laboratory, vital signs or electrocardiogram (ECG) measurements, or other safety parameters being evaluated. The safety topics of interest may evolve over time as knowledge of the product, product class or patient population changes and should be incorporated into the planning of the Ongoing Aggregate Safety Evaluation (OASE) (Section 5).

At the outset of clinical development, safety topics of interest of a product generally arise from theoretical concerns based on the product's mechanism of action, preclinical findings or reported risks of products of the same class. Potential risks may emerge from early clinical trial data. For important potential risks, relevant clinical data should be generated during the development program to either: elevate to an important identified risk or refute the risk. Otherwise these events should remain as important potential risks in the future risk management plan and be further evaluated in the post-marketing setting, such as in a post-approval safety study.

Some safety topics of interest may originate from traditional regulatory concerns for all products (e.g. drug induced liver injury). For these events, there may not be any data indicating a signal or potential concern for the product. In addition, health authorities such as FDA and EMA have encouraged incorporating the patient perspective during drug development and associated evidence generation [7, 8]. Engagement with patient advocacy groups or individual patients through one-on-one interviews, focus groups, or survey instruments may identify safety topics of interest of higher importance to patients compared to regulatory authorities or healthcare providers. These patient safety concerns may involve events which generally do not require hospitalization but significantly impact quality of life or drug adherence.

Further, the epidemiology of the patient population under study should be researched for safety topics of interest. This evaluation should identify adverse events which have a higher likelihood of being observed in clinical trials due to disease associated comorbidities ("anticipated events") (e.g. myocardial infarction in osteoporosis trials) or commonly administered concomitant medications. These issues may confound product causality assessment of certain adverse events. For studies with unequal allocation randomization to experimental drug versus comparator, uncommon or rare events may only be observed on experimental drug. In addition, some clinical studies may lack a comparator arm (such as in long-term open label extension studies), leading all events to be reported on study drug.

Of importance, employing systematic data collection and analyses may help refute a role of the product in particular events. For example, targeted data collection or expert adjudication may allow assessment of whether an event meets a pre-specified event definition (e.g. major cardiovascular adverse events, MACE) or if specific risk factors other than product administration were present. Further, determining

reference background rates for anticipated events in the study population is critical, with vaccine trials presenting an instructive example [9, 10]. Background rates also facilitate indirect comparisons with competitor products that might be needed to support a health technology assessment.

In summary, methodical safety planning is needed to generate data to determine whether there is sufficient evidence to conclude a true causal relationship with the product as well as to further characterize any identified risks. Consequently, as part of the safety planning process, the following points should be considered:

1. Alignment on identified risks (which should be supported by human data from the product itself), potential risks (for which events typically would have been observed in clinical trials), noting as well as other safety topics of interest (e.g. based on epidemiology of the patient population or customary regulatory concerns). Risks classified as important risks should be noted. Other safety topics of interest may be elevated to important identified or potential risks based on the emerging safety data.
2. Basis for inclusion as a safety topic of interest such as findings from preclinical studies or early human clinical trials or reported for products with a similar mechanism of action.
3. How safety events of interest will be identified for review, e.g. MedDRA Preferred Term (PT), Standardized MedDRA Query (SMQ), Higher Level Term (HLT) grouping, novel PT grouping (e.g. company MedDRA query), or designated outlier values for laboratory, vital sign or ECG measurements.
4. Requirement for rigorous event classification via expert adjudication using pre-specified medical concept definitions (e.g. MACE in clinical trials with non-cardiologist investigators).
5. For safety topics of interest, additional non-routine safety data collection, which is needed for future analyses, should be specified, such as collection of:
   - Baseline medical history that informs patient risk of having an event
   - Supplemental case report forms (CRFs) to obtain details, such as: presenting symptoms, severity assessments specific to the event, diagnostic criteria (e.g. clinical signs, laboratory or imaging results), information about resolution with or without continued administration of drug and treatments administered, family history, and relevant social history
   - Specialized safety assessments (e.g. ophthalmologic or neurological examinations)
   - Risk minimization measures introduced during the course of development that may have influenced the subsequent rate of adverse event occurrences
6. Protocol exclusion criteria or risk minimization actions which may limit generalizability of the clinical trial safety data; an example is abacavir (indicated for the treatment of HIV-1 infection) for which patients who carry the HLA-B*5701 allele are at high risk for experiencing a hypersensitivity reaction and screening for the HLA-B*5701 allele has been found to decrease this risk [11].

When planning collection of the data needed to characterize the safety topics of interest, the following dimensions should be considered: nature of the event, frequency, severity, duration, and reversibility. This information ideally should be captured in a table which is periodically updated, taking into account the evolving safety knowledge of the product (See Table 2 for a hypothetical product example). As noted in ICH E19, Optimisation of Safety Data Collection [12], in later stages of development, more selective data collection may be adequate for safety topics of interest which have been sufficiently characterized.

Proactive assembly of information about the epidemiology of the study population is an important component to safety planning. Background reference rates for adverse events anticipated to occur in the study population, particularly ones which have the potential to be fatal or serious, should be assessed. Such reference rates may be applied to all studies for the same target population. Data previously reported from clinical trials or registries or generated from healthcare claims databases can be informative. These reference rates are critical in the quantitative assessment of frequency of anticipated events from ongoing clinical trials, though admittedly challenging to identify for some events or study populations (see ASAP Section 5).

Pooling Strategies

Aggregation of safety data across studies, often referred to as pooling of data, should be considered to attain a larger sample size for estimating the incidence rates of uncommon events and, if applicable, relative rates between the experimental drug and control group. Safety data aggregation may be facilitated by programmatic integration of the respective clinical study data. Pooling of safety data should be aligned with an appropriate approach for the analysis of the aggregated data. A discussion of the challenges and advantages of programmatic integration of data is beyond the scope of this paper. However, as a general rule, safety data can be pooled from studies with similar populations and/or populations with similar safety profiles.

Table 2 Sample table for the safety topics of interest

Safety topic of interest	Basis for inclusion	Identification of events for review	Use of event adjudication	Special collection forms or safety studies	Relevant restrictions#
Identified risks					
Risk #1 Thrombocytopenia*	Platelet count decreases with product dosing in Phase 1 studies	Haematopoietic thrombocytopenia SMQ (Narrow) AEs Measured Platelet counts $<50\times10^3$/L	No	Thrombocytopenia supplemental CRF completed for: AEs identified by SMQ Events of Platelet count $<50\times10^3$/L	Study exclusion criteria: Platelet count $<100\times10^3$/L
Potential risks					
Risk #1 Serum sickness*	Reported in products of same class and in the Phase 2 study	Hypersensitivity SMQ (Narrow)	Blinded internal adjudication (per pre-specified procedures and case definition)	Serum sickness supplemental CRF	Study exclusion: Prior h/o serum sickness
Other safety topics of interest					
Safety topic #1 MACE (defined as non-fatal myocardial infarction [MI], non-fatal stroke and CV death)	Increased risk in the study population	Adjudicated - CV death - Nonfatal MI - Nonfatal stroke	Blinded external CV Endpoints Committee (see Charter for details)	CV event supplemental event CRFs	Study exclusion: No h/o MI or stroke in previous 3 months

*Considered important risks

#e.g. protocol exclusion criteria or risk minimization actions limiting data on certain patient populations

Studies also may be pooled according to dosing regimen or special populations of interest (e.g. renal or hepatic impairment or according to disease severity). If the populations or safety profiles are different, but relative risk or risk difference relative to a control can be assumed to be the same across populations, then the measures of association can be combined across studies. Other important considerations when pooling safety data across studies are the study design features, including control groups, study drug doses, and length of follow-up time. If drug exposure varies among the studies to be pooled, exposure adjusted incidence rates or event proportions for a time common to all studies should be considered before pooling. An alternative approach would be to use a survival analysis method to account for varying follow-up durations across different studies. Methodologies used to pool data, from simple unstratified analysis to patient level data meta-analysis, have been discussed in other publications [3, 13].

For each identified pool of data, the following should be specified (ideally in a table):

Target Patient Population

Disease indication (or indications) and any important subpopulations (such as pediatric or elderly populations or patients with organ impairment).

Controlled or Uncontrolled

Placebo or active comparator controlled or no comparator.

Projected Number of Subjects Included (Per Treatment Group)

May also include projected patient years of exposure and intended numbers of patients exposed for > 1 year at initial submission for chronically administered drugs or projected exposure in key patient subpopulations (e.g. elderly patients).

Rationale

Purpose for evaluating the safety data with this pooled dataset.

To enable effective pooling and efficient reporting, it is important to have well-defined data architecture that aligns with regulatory data standards and standardizes coding dictionaries (e.g., MedDRA, WHO-Drug) across studies. Specification of an organization's data architecture strategy is beyond the scope of the ASAP, although the ASAP could specify program-specific topics such as integration of legacy studies.

ASAP Section 3: Data Analysis Approaches

The purpose of this section is to lay out foundational analysis rules for the safety data in general and specific analysis approaches for known safety topics of interest (such as the ones in Table 2). Alignment and central documentation of the basic calculation conventions and analysis rules drive harmonization in the safety-related outputs [14, 15].

Foundational Analysis Rules

The following is a list of key topics:

Evaluable patients: Which patients will be included in the safety analyses? In particular, will patients be excluded who never had any study drug exposure?

Exposure: How will study drug exposure be calculated? What exposure categories will be used?

Treatment emergent events: Define the first day included in the analyses (usually the first day drug is given). Cite the last day when an event would still be considered as "treatment-emergent" (for example, 30 days after last dose of study drug or after 5 product half-lives).

Exposure-adjusted analyses: How will exposure adjusted rates be calculated (e.g. exposure adjusted event rates vs exposure adjusted incidence rates)? [16].

Safety metrics: How will "at risk" time be defined? For example, will treatment breaks count? Also, for drug-device combinations, different start dates for possible device related vs. drug related events may be needed unless the question of interest is for the product-device combination as a whole.

Other clinical safety data (such as laboratory data, vital signs and ECGs): Specify definition of the baseline measurement (e.g. last day before treatment, average of multiple measurements), post-baseline periods and visit windows, as well as definitions of markedly abnormal values.

Event severity grading: Toxicity grading criteria employed should be specified here (e.g. Common Terminology Criteria for Adverse Events, CTCAE), with version numbers and references. Definitions of clinically relevant outliers should also be specified.

Safety-modifying factors: For example, baseline medical history or concomitant medications of interest. How will they be incorporated in the key analyses? How will the impact of individualized risk management measures such as established safety biomarkers be addressed? Alternatively exploratory evaluation of genomic or other biomarkers may be noted.

Analyses across studies: Outline methods that address Simpson's paradox (i.e. when groups of data show a particular trend, but this trend disappears or is reversed when the groups are combined together) [17].

The coding dictionary versions (e.g., MedDRA version) and any upgrade cadences should be mentioned in this section.

Analysis of Key Safety Topics of Interest

For important program safety questions that drive the benefit-risk evaluation, certain safety topics need to be more methodically quantified and characterized. For such key safety topics of interest, some effort should be spent in getting the question right, by thoroughly evaluating the quantity to be estimated—i.e. the so-called estimand. For efficacy parameters, sponsors are now expected to apply the estimand approach [18, 19] to foster this type of thinking. This approach also can be applied to the key safety topics of interest [20], starting with the question: what really is the risk parameter desired to be estimated? For some adverse events, the estimand may simply be the probability that an exposed patient experiences the event, which is estimated by the *crude incidence rate*, defined as number affected / number exposed. However, depending on the trial duration and the safety topic, other estimands may be more appropriate.

In situations with varying durations for different patients, the crude incidence rate is no longer informative. Especially for the common events in longer observation, risk per time unit, or "hazard" is of interest. In cases where the hazard is not constant over time, the time course of the risk could be elucidated by calculating risk separately for, say, monthly time windows, using the life-table method [21]. In general the safety profile can be characterized over time either by time period or in accumulation. For benefit-risk evaluation, those estimands should be on par with those for efficacy. There are events where each occurrence carries risk for severe sequelae, e.g. serious infections. In those cases, estimands like the ones above that only consider first occurrences are not appropriate.

For longer term trials with varying durations for different patients, "time to first event of occurrence" may be important to know, particularly for events that tend to happen sooner or later with high likelihood (e.g. bone marrow depression for a cytotoxic cancer drug, or MACE). Events which manifest with multiple occurrences per patient should not be ignored if each occurrence carries risk for the patient (e.g. serious infections). Here, the most meaningful estimand might be the hazard to experience the event at any given time, for the first or a repeated time. A final example is for acute injection site reactions. Here, the exposure of interest consists of disjointed time windows after each injection. A decision is needed about whether probability per patient, per patient year, or per injection would be the most meaningful estimand. Regarding the last two examples, it may not be possible to extract distinct episodes of repeat occurrences from a standard adverse event CRF. Rather, a special CRF may need to be designed. This point underlines the importance of the ASAP process in planning ahead for what analyses will be needed while the CRF design of the pivotal trials still can be influenced.

One topic covered by the estimand approach that has received considerable regulatory scrutiny lately is the specification of how to handle intercurrent events, such as drug interruptions, drug discontinuations, or use of rescue medications—all of which could create bias in estimating the risk parameter. Summarily analyzing all safety data—whether or not patients received rescue medication or had treatment disrupted—would be the right estimand to describe the risk of a treatment policy (i.e. a prescribed regimen) as it is likely to play out in real-world medical practice. If that is the goal, then in the case of infusion reactions, for example, all infusions, including those for which prophylactic steroids were given, should be included. However, this approach may not be the proper estimand to describe the safety risk that the new treatment carries per se. If that is the goal, only infusion reactions without premedication should be included in the assessment. This example highlights how the handling of intercurrent events should be considered in "getting the question right". In summary, clarity around the estimand should drive the definition of the analysis population, the handling of intercurrent events, and the statistical model and estimate to be used.

ASAP Section 4: Analysis of Key Gaps and Future Data Collection

ASAP Sections 2 and 3 define the safety topics of interest and current approaches for data collection and analyses in the ongoing clinical trials. ASAP Section 4 describes any remaining "known unknowns", which are anticipated to persist after initial submission of the product for marketing authorization. These "known unknowns" may be based on standard health authority expectations for longer term treatment safety data or benefit-risk considerations for particular patient subpopulations, which may be under-represented in the clinical trial program. The implications of these knowledge gaps for the development program, including after transitioning to the post-marketing setting, should be carefully considered.

One type of gap relates to unaddressed questions regarding the safety profile of the product, for example, gaps in knowledge regarding the duration or reversibility of events. A new study, substudy or extension of a current study may need to be conducted to address these questions. Another type of gap relates to the ability to generalize the results from clinical development to the broader patient population

intended for treatment post-approval. Consideration of protocol inclusion and exclusion criteria may identify important excluded subpopulations. Alternatively, clinical trials may have enrolled limited numbers of subgroups of patients (e.g. patients with renal impairment). For global regulatory submissions, the impact of regional safety concerns (e.g., related to differences in standard of care, AE diagnostic criteria, or epidemiology of the population in a region) may need to be assessed. Lastly, procedural gaps or methodological/technical gaps which could have impacted the clinical trial data collection should be considered (e.g. missing data due to inability of patients to complete protocol study activities due to a pandemic). For each gap, the following points should be documented:

- Description of the gap
- Reason for concern (source of the gap)
- Projected impact at filing
- Key information needed to address the gap
- Proposed action(s) to close the gap

Plans to address key gaps which will not be closed during clinical development typically would be reflected in the risk management plan. Furthermore, these gaps should be considered if new clinical trials for expanded indications are designed. Remaining gaps may relate to better characterization of the risk for uncommon or longer latency events. Alternatively, critical gaps may remain in understanding the safety profile for important, potentially higher risk patient populations, such as pediatric or elderly patients or patients with hepatic impairment.

ASAP Section 5: Ongoing Aggregate Safety Evaluation (OASE)

This section describes the process for program-level, strategic OASE of the accumulating safety data by the SMT [1, 3] over time and across trials [22–25] in the development program. As the clinical trial database expands, aggregate analysis becomes essential for adequate detection and evaluation of signals. Evaluation of blinded and/or unblinded data pooled across studies provides greater discernment of emerging safety concerns and greater precision for assessment of specific event rates, especially for uncommon events and in patient subgroups.

The SMT will determine the periodicity (for example on a quarterly basis) and parameters required for review of the aggregate clinical trial safety data, which may vary across programs, depending upon the product, stage of development, number of studies underway, and other factors. A thorough review, with potentially more extensive data outputs, should be done in conjunction with the annual investigator brochure update. In addition, while not addressed here, a number of clinical trial programs also will have an independent DMC which conducts regular unblinded reviews of data from an ongoing study or group of studies as specified in the DMC charter.

OASE focuses on assessing the safety topics of interest (Section 2), as well as assessing the totality of the safety data, which may reveal new safety concerns. The ASAP process seeks to ensure alignment between product-level aggregate safety assessments and study-level evaluation of the safety data. Technical details regarding statistical methodology, data analyses and summaries, as well as desired graphical displays, could be specified in an appendix or a separate OASE plan. The OASE plan is a living document and can be updated periodically, as appropriate.

Objectives of unblinded OASE for completed and open label studies (i.e. studies where review of the unblinded data would not jeopardize the integrity of the trial) are to:

- Support continual characterization of the product safety profile
- Leverage the results for planning and preparation of safety-related documents and regulatory filings
- Facilitate responses to health authority requests related to specific safety inquiries

In addition, some sponsors have been developing and implementing innovative procedures for review of aggregate blinded clinical trial safety data [26–33]. Quantitative methods are available for assessing evidence for risk elevation in the accumulating blinded data, along with prior information about background event rates. These methods can be used to make inferences regarding observed rates for safety topics of interest (ASAP Section 2) and anticipated serious adverse events that are known to occur in the patient population regardless of study participation.

Objectives of OASE for ongoing blinded studies are to:

- Assess the overall safety data of a development program (without unblinding)
- Detect emerging safety signals
- Evaluate risk elevation for selected events (see Discussion section)

In general, sponsors have well established processes for ongoing review of product data including medical assessment of individual clinical trial serious adverse event reports to meet regulatory reporting requirements [34, 35]. The OASE process described in the ASAP is designed to complement and interface with these existing processes, focusing on quantitative analysis of aggregate safety data across patients and studies.

As discussed below, aggregate safety assessments should involve both a rigorous application of quantitative frameworks [36–39] as well as weighing evidence based on qualitative clinical considerations.

Application of Quantitative Frameworks

Assessing large numbers of diverse safety events requires thinking outside the box of traditional significance testing and multiplicity adjustment. Quantitative frameworks ideally should incorporate prior information, such as reference background event rates; simulations of likely scenarios for calibrating the operating characteristics of proposed procedures; and data pooling across multiple studies to increase precision of event rate estimates. Thresholds may be identified (for example 80% probability of a risk elevation compared to a reference rate), which could trigger a more detailed review of a particular event. Assessment of a single threshold for an event rate of concern typically will not provide an adequate quantitative framework. Rather a collection of thresholds (e.g. 70%, 80%, or 90% probability of a risk elevation) could help SMTs judge the strength of evidence and how, for example, changes in the background reference rate or the addition/subtraction of one event might impact the quantitative data assessment.

OASE should employ a flexible approach designed for learning and decision-making [34] and employ a process that:

- Engages and leverages collaboration between clinicians, statisticians and epidemiologists in the application of medical judgment within a quantitative framework
- Supports the iterative nature of the process and the continuum between clinical trial safety monitoring and post-marketing safety surveillance
- Allows for changing data sources and methodologies while maintaining a consistent process

Statistical summaries should be included in an OASE plan that help the SMT judge whether there is a reasonable possibility of a causal association of certain adverse events with product administration.

Specific details should be provided about which measures will be used to characterize the safety topics of interest and at which timepoints during the program. Decisions about the measure of association (such as, risk difference, risk ratio or odds ratio) to be used for comparing treatment groups (e.g. high and low dose vs control) should be specified. If the length of follow-up varies between studies to be pooled, exposure adjusted incidence rates should be considered. Safety topics of interest could be summarized by simple proportions for risk intervals (for example, every 3 months and overall at 12 months) or alternatively using a survival analysis method.

In a blinded analysis, only the pooled rate can be observed, representing a weighted average of rates from the control and treatment arms. Based on background rates, known treatment effects and other prior knowledge, comparisons can be made between what has been observed and what was expected. Estimates and probabilities of relative risk elevation for ongoing blinded studies may then be calculated for select safety topics of interest and anticipated serious adverse events.

Reference Background Rates

A safety signal often needs to be interpreted on top of a "noise level" of background events for the patient population. Efforts should be directed at determining reference background rates for the safety topics of interest and selected anticipated events for the study population. Clinical trials with standard of care or placebo arms in a similar patient population can be used as a source for background rates. In other cases, where background rates are not available, they could be generated by conducting analyses of relevant observational data sources such as registries, longitudinal healthcare insurance claims databases, electronic medical records (EMRs) or other available real world evidence databases and identifying a cohort of patients that mimics the clinical trial population.

Monitoring Criteria and Tools

Customized reports (data outputs) should be used by the SMT to assist with ongoing monitoring and review of the accumulating clinical trial safety data. Monitoring tools can facilitate exploration, visualization and reporting of the clinical data [40, 41]. Optimally these tools:

- Directly access and monitor data
- Use tabular and graphical features for ease of data review
- Switch between tabular and graphical displays of patient data
- View and compare data across different time periods to identify trends and outliers
- Drill down to monitor data at an individual patient level (if needed)

Application of Medical Judgment

Quantitative frameworks need to be combined with a dynamic collaborative process for engaging with medical professionals from pharmacovigilance, clinical, epidemiology, and other disciplines [42]. With this approach, the

emphasis is shifted from analyses with statistical testing and confirming (strict or implicit) to assessments with learning and decision-making—in other words, medical judgment within a quantitative framework. Quantitative frameworks can help the SMT to judge the strength of evidence contained in the data, to streamline evaluations of the accumulating data, and to improve assessments about the benefit risk profile of a product. However, cross-disciplinary scientific engagement is needed to integrate medical judgment and quantitative expertise [1].

A systematic approach is needed to develop clinical as well as statistical understanding of the safety profile [43]. Medical experts identify the most important clinical questions while statisticians frame the context of the analyses. Complex challenges exist in evaluating the relationship of study drug with adverse events (and other safety information), accounting for duration of exposure time, subgroup differences and other clinical considerations. Statistical methods impart objectivity, but ascertainment of a causal association requires evaluation of factors beyond quantitative analysis to which medical experts can best contribute. For example, biological plausibility considerations, relevant preclinical data, product class safety knowledge, and laboratory or vital sign trends may inform interpretation of the statistical conclusions and provide needed context.

The SMT should choose reports specific to the program which evaluate the overall safety profile of the product as well as potential risk elevation for the safety topics of interest or anticipated events. As data are reviewed, the need for additional reports may be identified. In the event that the current set of reports specified in the ASAP (or OASE plan) are insufficient, the safety physician and statistician should collaborate with other SMT members to develop alternative project-specific reports. An iterative process for planning aggregate reviews of safety data can help to streamline the sets of analyses resulting in a lower volume but more informative flow of output to review.

Expedited Safety Reports Based on Aggregate Data Review

In addition, sponsors need to consider how decisions will be made about the submission of expedited safety reports to health authorities (e.g. when a sponsor determines there is a reasonable possibility of a causal association of product with the occurrence of a serious medical event) based on aggregate data reviews [6]. Each development program should evaluate the need for a Safety Surveillance Plan (SSP) to describe the process of aggregate review which will inform the decision to submit an IND Safety Report [6]. Typically this process will involve unblinded review of the safety data by a DMC or SAC. The decision regarding the need for a SSP may be influenced by the number of serious adverse events predicted for the clinical program. The SSP or equivalent document may be included as an appendix to the ASAP. The SSP would describe the process of aggregate review for the important identified and potential risks as well as other anticipated events which have the potential to be reported as serious adverse events [6]. Anticipated adverse events may be identified due to being common in a general population with similar demographics, prevalent in the disease under study or known adverse reaction of concomitant medications being administered per protocol. Of note, anticipated adverse events may overlap with safety topics of interest for the product. For previously recognized identified risks, the objective of continued monitoring is to confirm the nature, severity and rates of the relevant adverse reactions are consistent with that previously communicated. An example SSP is provided in an appendix of the ASAP Template (Supplemental Materials).

As noted above, some sponsors are using quantitative methods for assessing evidence for risk elevation in the accumulating blinded clinical trial safety data. With this approach, potential safety concerns identified by the SMT during blinded review could be referred as needed to a SAC/DMC for unblinded assessment. Directions from the SAC/DMC about safety events recommended for IND safety reporting based on aggregate review would be communicated to the SMT (using established lines of communication) while maintaining the blind for individual safety reports.

ASAP Section 6: Communication of Safety Information

Communications Throughout the Drug Development Life-Cycle

This section describes communication activities of safety information throughout the drug development life-cycle. Consistent, accurate and transparent safety messaging for a product is critical. Aggregate safety assessment planning should include how information will be communicated on a compound level to stakeholders inside and outside of the sponsor organization. The content, format and timing for the information is typically governed by global, regional, or national guidance and regulations and sponsor standard operating procedures. Early in product development, external target audiences for safety communications consist of regulators, investigators, institutional review boards, and clinical trial participants. The audience expands over time to include researchers, healthcare providers, patients, payors and other interested persons.

Typical elements of safety communications include summary information on study populations and disease

Table 3 Types of safety communications

Internal	External
Development	
Target Product Profile	Clinical Study Protocol—Risk Section of Study Protocols
Data read-outs to support go/ no-go decision-making	Clinical Study Report—safety sections
Clinical Development Plan	Public disclosures of trial results (e.g. press releases, scientific journals, Clinical Trial.gov)
Development Risk Management Plan (dRMP)/Core Safety Profile	Investigator's Brochure (IB)—safety sections
"Safety Storyboard"	Reference Safety Information (RSI)/
	Development Core Safety Information (DCSI)
	Risk Language/Core Informed Consent Form (safety data layperson summary)
	Development Safety Update Report (DSUR)
	Briefing documents for regulatory discussions
	IND Aggregate -Reports
	Dear Investigator Letters
Regulatory Submission and Post-marketing	
Core RMP/Core Risk Profile	Briefing documents and presentations for Advisory Committees
Company Core Safety Information (CCSI)	Common Technical Document—Integrated Summary of Safety (ISS) and Summary of Clinical Safety (CSS)
Company Core Data Sheet (CCDS)	Health authority query responses
"Safety Storyboard (including post marketing data)"	Post-marketing studies (protocols, reports)
	Periodic Safety Update Report—PBRER
	EU Risk Management Plan, Risk Evaluation and Mitigation Strategies
	Local labeling (e.g., US Prescribing Information, Summary of Product Characteristics, Canadian Product Monograph)
	Dear Healthcare Care Provider Letters
	Health Technology Assessment documents

characteristics, study drug exposure, serious and non-serious adverse events, dose modifications/reductions, treatment discontinuations, and adverse drug reactions. Of particular relevance are the important identified and potential risks, other safety topics of interest and missing information. Information on important risks may include source and strength of evidence, potential mechanism as well as characteristics, such as frequency, severity, time-to-onset, reversibility, long term outcomes and associated risk mitigation activities. ASAP Sects. 2 to 5 drive preparations for generating the content for the safety communications.

During the life-cycle of a drug, there are a multitude of safety communications that are encapsulated in various internal and external documents. Internal strategic documents (e.g. target product profile, clinical development plan) may describe future plans and aspirational messaging. However, the majority of safety communications targeting internal and external audiences contain information reflecting current knowledge of the product safety profile. The following table lists different types of safety communications during clinical development, for regulatory submissions, and continuing into post-marketing safety management (Table 3).

Safety Storyboard

Given the multitude of documents summarizing safety information (see Table 3), we propose the development of a safety storyboard to help ensure consistency of safety messaging across documents. The safety storyboard links with the aggregate safety assessment planning process and summarizes, in a structured way, the available safety information. As an internal document, the safety storyboard can be adapted to the specific needs of an SMT or sponsor. It provides a format for cross-functional discussions of available evidence that will inform potential future claims with the idea of keeping the end goal in mind. The safety storyboard could take the form of a written document or slide deck.

The safety storyboard evolves and expands over time. Early in development, the focus is on preclinical safety findings and any dose limiting toxicities observed in early dose-ranging studies. Later in development, high level conclusions regarding the overall safety of the product, as well as for the safety topics of interest, should be included. At submission for regulatory approval and moving into post-marketing, the key messages should become increasingly well defined (enhanced by pooled clinical safety data). The safety storyboard should cite the important identified risks (if any) and potential risks as well as associated risk management. Risk minimization actions, if applicable, and how

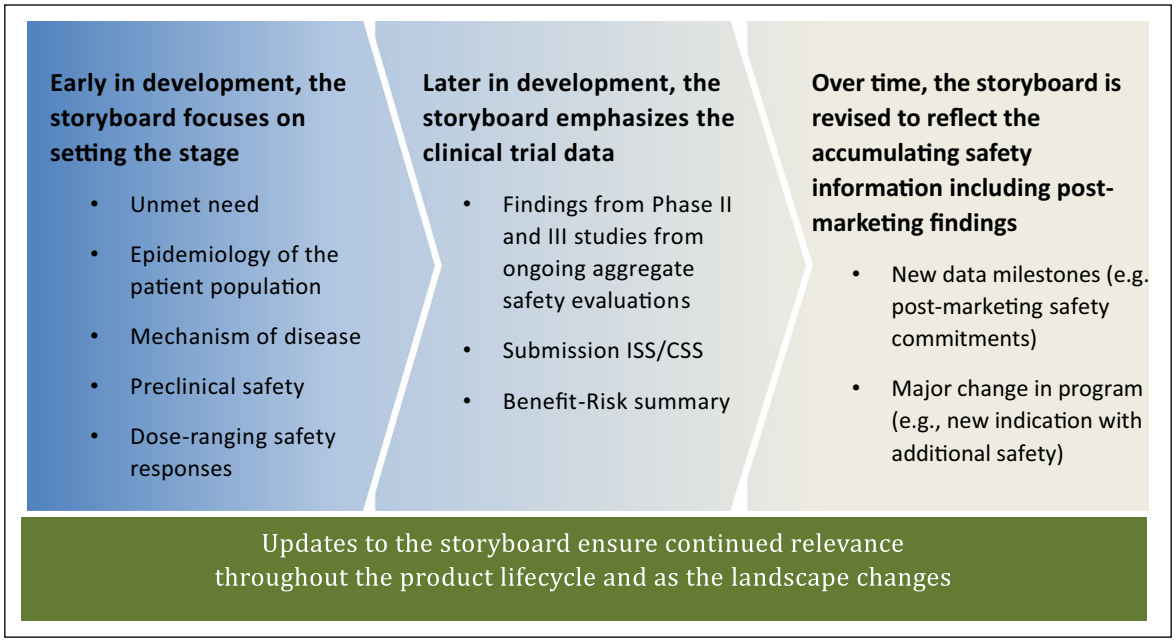

Fig. 1 Evolution of content of safety storyboard over the product life cycle

they affect the interpretation of the observed safety profile should be discussed. If important new risks emerge from post marketing reports or safety studies, this information should be added. Figure 1 illustrates the evolution of the safety storyboard.

Discussion

In this paper, we have identified and described components of product-level safety assessment that should be considered for all development programs. The ASAP process builds upon the innovation of the PSAP [3] and re-imagines safety evaluation as a continuum of safety monitoring during clinical development, safety specification at submission, and post-marketing safety surveillance. The proposed process leverages the scientific expertise and medical judgment of multidisciplinary SMTs to prepare for the evaluations of safety data that are needed for learning and decision-making process throughout the product life-cycle.

The ASAP provides a guide for systematic product-level safety planning, standardized data collection and analyses, knowledge gap assessment and safety related communications. Aggregate safety assessment facilitates the understanding of the drug's emerging safety profile, enables timely safety signal detection, answers key clinical questions, and lays the foundation for future regulatory submissions and post-marketing activities. The ASAP's modular and flexible structure allows easy integration into existing processes and adaptability to different program types and phases without redundancy in documentation. Importantly, implementation of the ASAP process promotes multidisciplinary safety planning, which is critical to fully characterize product risks and potential risk minimization measures for achieving and maintaining a robust benefit-risk assessment of the product.

The ASAP puts more emphasis on interdisciplinary safety planning and collaboration than a traditional statistical analysis plan. A previous survey of pharmaceutical companies highlights the benefits of a multidisciplinary approach to aggregated safety assessment [44]. The ASAP is intended to prompt thoughtful consideration about what data are needed to answer key questions related to the product's safety that are important to regulators, prescribers and patients. The ASAP process drives alignment on the safety topics of interest for the product and how the safety data will be analyzed in a standardized manner across the program. Out of these discussions may come the realization that additional "non-routine" actions are needed, such as collection of specific medical history or additional safety assessments, supplemental case report forms for collecting important event details and risk factors, expert event adjudication or development of new search criteria to identify relevant events for more in-depth review. More careful safety planning will help minimize the lack of critical data on safety concerns that could derail an otherwise promising development program. In addition, the ASAP challenges the multidisciplinary team to identify gaps in knowledge that the SMT purposefully acknowledges will remain at the time of the initial regulatory

Table 4 ASAP implementation

Objection	Mitigation recommendations
Perceived effort outweighs potential benefits	Gain endorsement from cross-functional management and confirm support for resources
Not enough resources	Leverage modularity of the ASAP and existing company procedures to minimize additional workload
Another document to manage	Employ a pilot program to assess benefits, costs, and create "ASAP champions"
Redundant with existing processes	Taylor a pragmatic approach based on complexity, size, speed, risk level, and stage of development
Small programs may not warrant the effort	Clearly outline the benefits and long-term efficiencies including:
Uncertainty around fate of early phase programs	Promotes shift from a reactive to proactive mindset
	Helps ensure collection of the right data
	Aligns project-level and study-level efforts for data aggregation
	Optimizes safety labeling and potential differentiation
	Offers a single point of reference for project safety standards
	Leads to a better characterized safety profile, increasing the changes of a more efficient and successful regulatory review
	Harmonizes safety communications

filing. The SMT should then initiate planning as to how those gaps are to be filled during the post-marketing period.

The ASAP also attempts to address the changing global regulatory landscape [4] regarding aggregate safety assessments. Traditionally, aggregate safety data has first been assembled and evaluated at the time of the initial regulatory submission of a product. Regulatory authorities are expecting product-level aggregate assessment to start earlier in clinical development, including for studies that remain blinded to treatment assignment [6]. Consequently, the ASAP speaks to the potential for blinded aggregate safety data reviews, especially for programs with multiple ongoing studies, to facilitate earlier signal detection.

Another important feature of the ASAP is a focus on documentation of the SMT's alignment on current key safety messages and forthcoming data to expand these messages. This alignment may take the form of a "safety storyboard", which is periodically updated to reflect expanding knowledge of the product's safety profile. The safety storyboard facilitates consistency in the safety messaging across internal and external documents.

Despite the many benefits of the ASAP process as described above, challenges to implementation may be raised that must be addressed for the ASAP to be successful. Some possible objections and strategies to mitigate these concerns are outlined in Table 4.

Conclusion

As attention of regulators and industry shifts from separate analyses of efficacy and safety to a joint consideration of benefits and risks, the value of a similar instrument for upfront planning of benefit-risk assessment becomes clearer. Another ASA safety working group, in collaboration with DIA, is focused on the process of benefit-risk assessment planning, which connects with the execution of the ASAP. As O'Neill et al. [45] noted, there is an imbalance in quantitative thoroughness between efficacy and safety, and "*progress in evaluating benefit:risk will be a function of how quickly the culture of quantitative safety assessment changes in the future*". More than 10 years later, it is time to close this gap, and the ASAP is put forth as a tool to achieve this goal.

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Conflict of interest
BAH is an employee of AbbVie outside the submitted work. DB is an employee of Takeda. JK reports personal fees from consultancy for pharmaceutical industry outside the submitted work. RK is an employee of AstraZeneca. CM is an employee of UCB Biosciences outside the submitted work.

Supplementary Information

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