PhUSE APAC Connect: Paper - AD06

Harnessing the Power of Safety Database

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- **The views and opinions expressed in this presentation are those of the speakers and do not reflect opinions of any person or organization**

Outline

- Background
  - Challenges reviewing safety of a product profile
- Safety Database and it's purpose
  - Framework and Objective
- Design workflow
- Development and Implementation
- Process map and Case study
- Outcome and Optimization
- Conclusion and Outlook

Background

In the realm of Data Analytics and Statistical Programming, a significant challenge for analytics team involves establishing a real-time, project level safety database. It is critical to review safety of the drug and there is not established process to do it across project(s).

This critical resource would serve to bolster safety signal management and facilitate the ongoing evaluation of a product's benefit-risk profile. Imagine a meticulously structured database designed to house analysis datasets, incorporating intricate derivations, advanced methodologies, sophisticated data handling techniques, and robust imputation algorithms, all alongside the precise analysis-level definitions inherent in a Statistical Analysis Plan (SAP).

Furthermore, this envisioned database would seamlessly integrate pooled design requirements, encompassing various study indications, dosing regimens, developmental phases, platform studies across subjects.

Background

- Critical to review the safety of the drug
- No mechanism or established process across the product program
- What if the critical resource is designed to house analytical requirements
- Seamlessly integrate pooled design and are made centralized
- Realtime access and visibility of entire product program, making smarter decisions fast !

Challenges reviewing safety of a product profile

- Systems though in place but are mostly limited for individual safety case reporting, not for aggregated analysis that includes multiple studies across the product

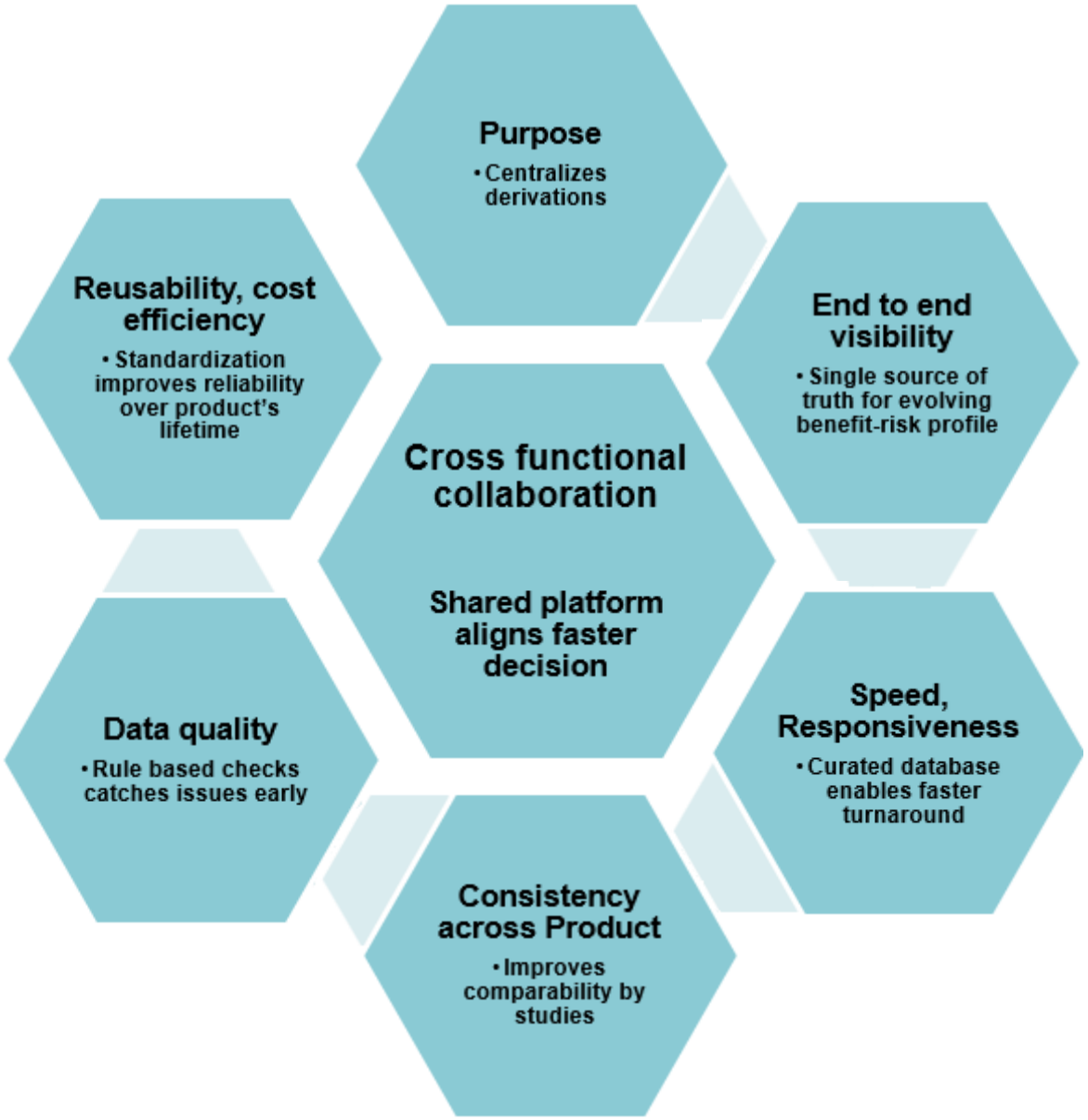
- Tools readily available are ideal for study level safety data visualizations, lack of project level information that provides holistic insight into the product

- Clinical Database can only boast study level data, with limited access. Any additional scope or adhoc requests relevant to FDA/HAQs can demand increased time

- Scope variability driven by evolving outcomes and safety data

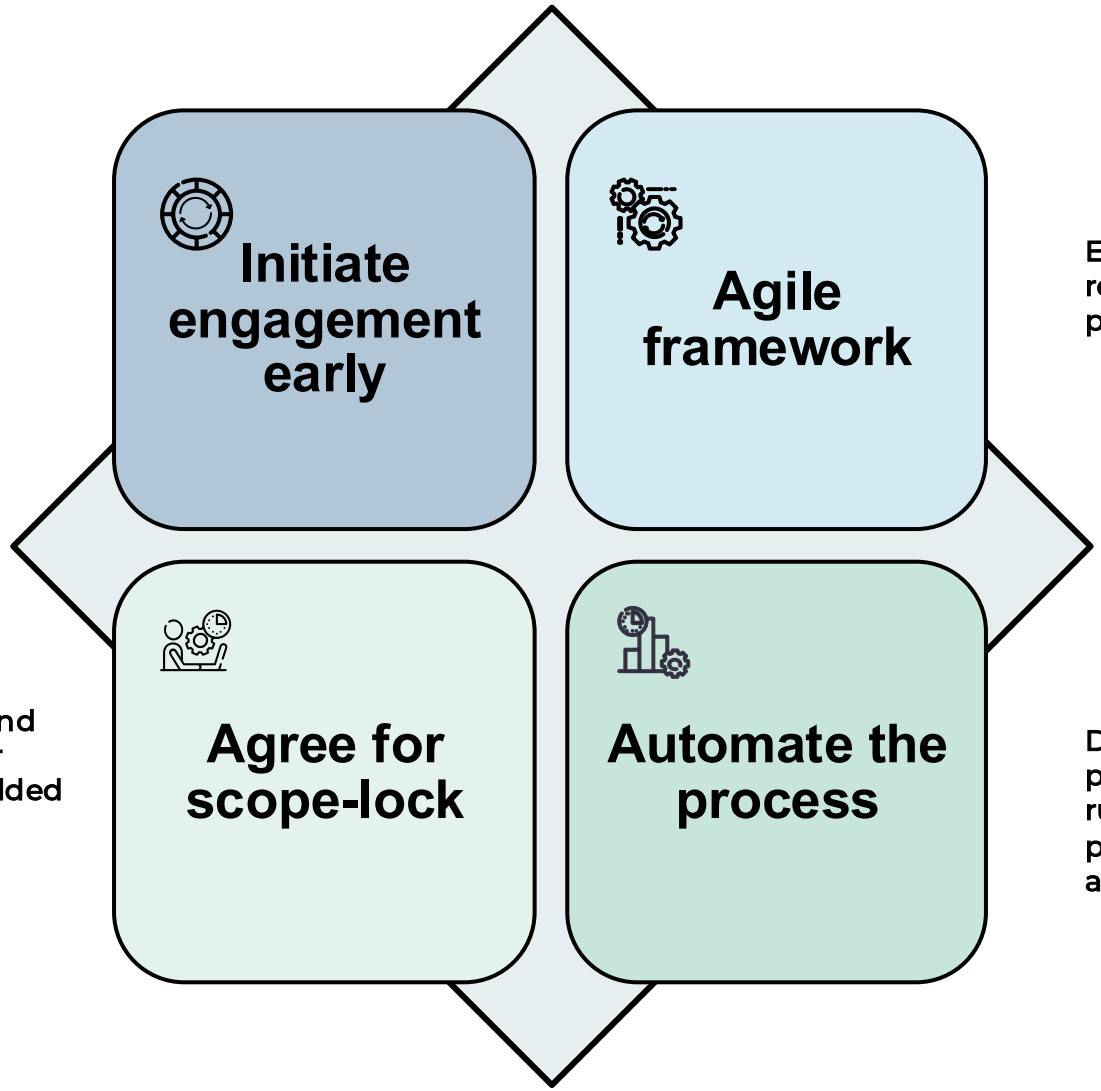
Above challenges could delay in assessment of safety of drug profile, eventually leading to risk.
Safety of any product is paramount and we can't risk !!

Safety Database and it's purpose



Framework for Safety Database & reporting

Iteratively refine requirements throughout scope definition



Engage stakeholders regularly to validate priorities and outcomes

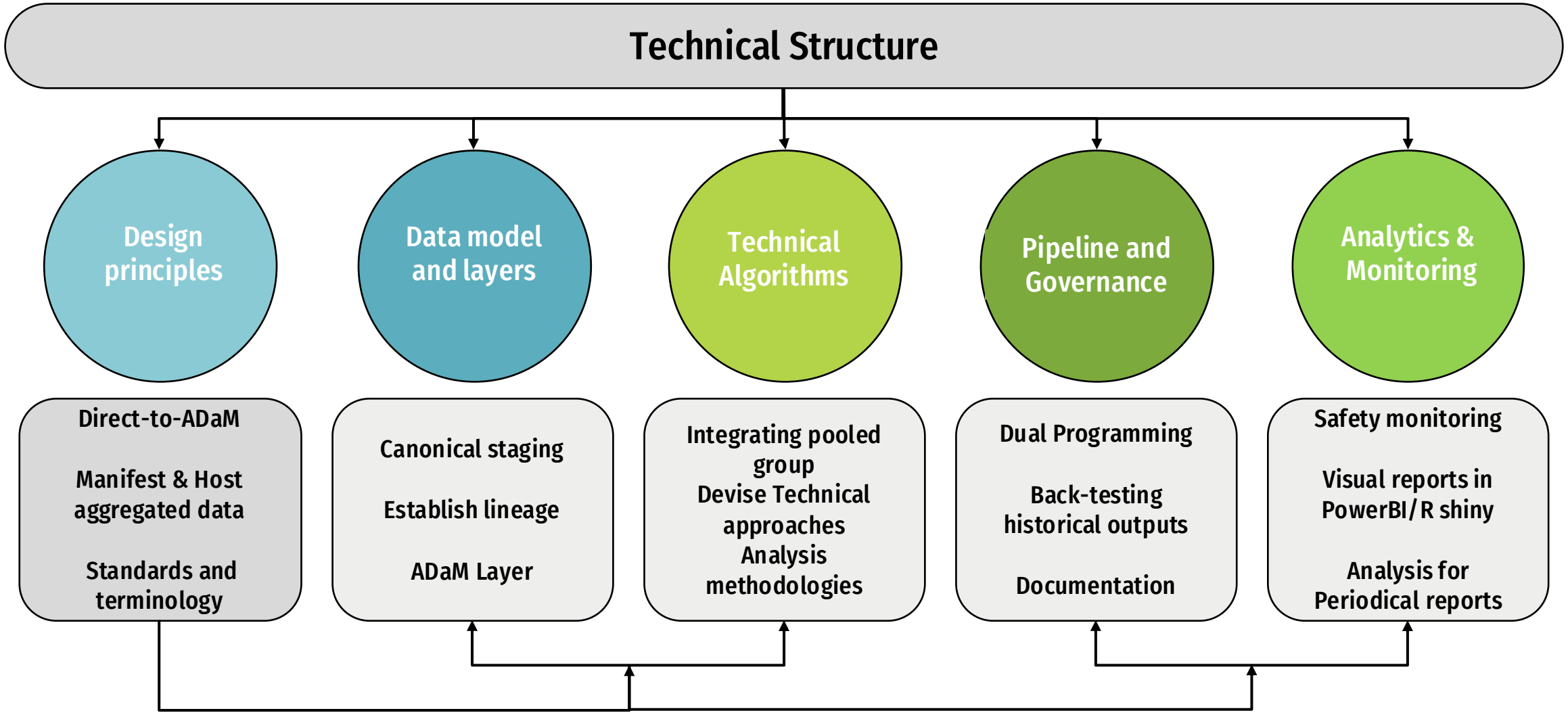
Define the timeline and so no new features or major changes are added without a controlled change process

Data transfer based on periodical needs, batch run, stabilize the programming workflow and deliver efficiently

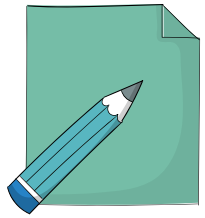
Objective of Safety Database

- Build a real time project level safety database that can support safety monitoring
- Develop a program for delivery of regular standard safety data reports at defined intervals (weekly, monthly etc.) to support routine safety surveillance
- Enhance patient safety: Provide timely, reliable safety insights to investigators to support informed clinical decision-making and risk mitigation at sites
- Single source of truth: Centralize study safety data (Demog, AEs, Exposure, Labs, ConMeds, MH) into a governed repository with consistent definitions and traceability
- Cater the data analysis requirements of periodical annual safety reports
- Regulatory readiness: Ensure inspection-ready evidence (lineage, audit trails, version pinning) and support aggregate reporting obligations

Design workflow



Development and Implementation



CRF to Specs

- SDL to review design and map CRF variables
- Ensure consistency, lineage, traceablility across product
- Master specs to host all n study specs

Devise Algorithm

- SDL consult Stats, PSS to define the scope
- Carefully align study/product level algorithms
- Pooled analysis derivation and blinding rules

Real time refresh - Periodical

- SDL/SP: Refine & Streamline database by establishing regular/frequent refresh
- Impact analysis of data
- Maintain historical data

Database maintenance

- Real time deliver in a week
- Automate the batch scheduling
- Minimize the involvement

1 → 2 → 3 → 4 → 5 → 6 → 7 → 8 → **Launch across new portfolio/ product**

Setup library & Automate snapshot

- Reach out to product POC's or DM team
- Enable data transfer from study to centralized area
- Frequency: Schedule

Canonical Staging

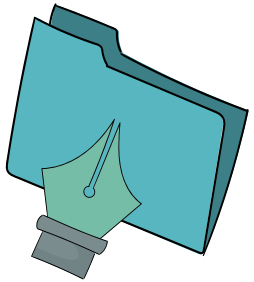
- SP: Harmonize source data as per mapping
- Build template codes to enhance reuse, reliability
- Wrapper macro to invoke codes for each studies

Add New studies

- SP: Incorporate algorithms by study
- Integrate studies to pooled database
- Appropriate blinding for sponsor blinded studies

Scope change New analysis

- Revise the scope based on USM, Clinical outcomes, Safety monitoring
- Clear any backlogs
- Define the timeline and refresh the database



SDL: Safety Database Lead **SP:** Statistical Programmer

Data Integrity

Protecting the integrity of product outcomes are important. Blinding is very essential which strengthens the credibility of the evidence and confidentiality of safety and RECIST/efficacy data

Blinding Challenges: When integrating multiple studies for a drug, obtaining source data can be challenging, following factors include:
➢ For platform studies with similar combination therapies across different indications, access should be endorsed by the relevant product leads before proceeding.
➢ If the study is sponsor-blinded, ensure global safety team does not receive unblinded data. the dataset should be appropriately blinded before sharing with the Safety team.
➢ Late phase study data used for analysis and visualization are appropriately blinded and aligned with the Statistical Integration Plan (SIP).

The Safety Database team should continue to oversee data within the product safety database and evaluate whether additional blinding is needed for any new studies

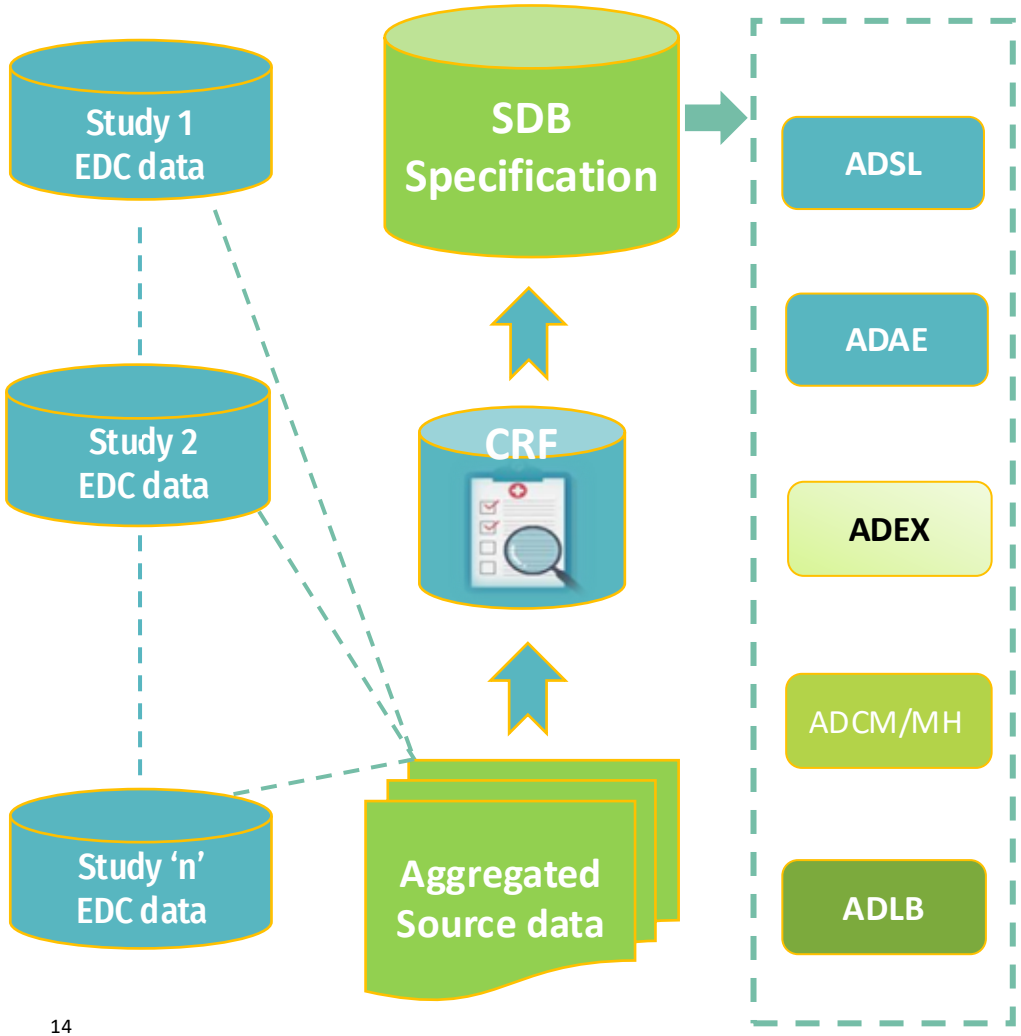
Data Integrity – continued..

Blinding Rules: Devise the rules by identifying the studies to be blinded and list down the variables

Blinding scope:	➢ Prepare the blinding rule for key studies by identifying which variables reveal treatment (e.g., treatment arm, dose level, randomization group, visit/epoch labels). ➢ Mask direct treatment variables or exclude variables that can unblind. ➢ Replace arm-specific names with neutral labels (e.g., "Visit 1/2/3," "Period 1/2")
Exposure and Adverse Events are the Key:	➢ While Adverse event terms and MedDRA coding terms are retained but masking variable that reveal event information like Action taken/relationship to active study drug or combination therapies like AE leading dose reduction/increase/modification/interruption) is utmost important. ➢ AE Severity, seriousness, outcomes, and timing could be included, but ensure no fields reference arm names or investigational product identifiers that differ by arm. ➢ Exclude exposure records with active drug, similarly exposure summary parameters like Intended, total exposure cumulative are to be dropped or masked appropriately etc and drop Lab records.
Governance and access control:	➢ Ensure that a centralized area where blinded datasets are placed and are restricted so that safety team access only to blinded data. ➢ Unblinded data should be fully restricted with the exception of study team members.

SafetyDB Process map

Data Setup Process: Raw to Canonical staging



Implementation Methodology

Pooling of treatment by phase Indication, dose level, mono/comb

Aggregate AEs – TEAEs, Relationship, Outcomes, Action taken

Exposure – Cumulative actual/planned dose, RDI

ConMeds, Medical/Surgical History, WHODD, Immune meditated.

Labs – Std units, visit mapping, ctcae grading, criterion flags

Integrated Safety Database

Periodical Safety reports

Visualization

HAQ/FDA questions

Investigation Brochure

Case study Implementing a Safety Database for an Oncology Asset: Direct-to-ADaM Approach

Problem statement

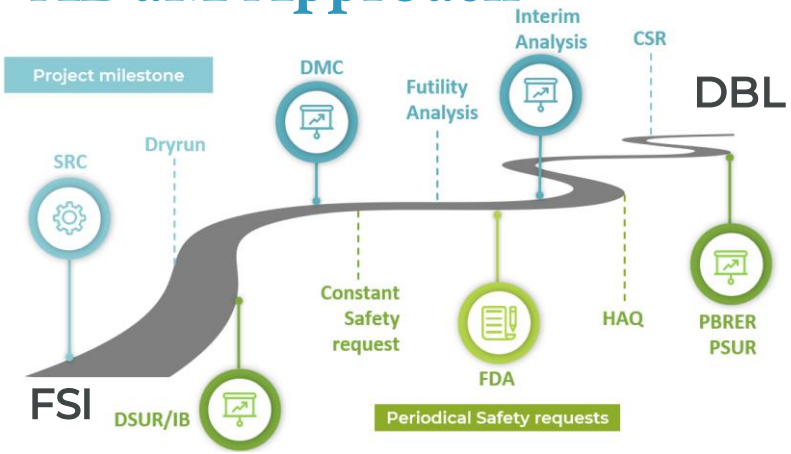
No mechanism to evaluate product studies/indications/phases /dose levels
Can't evaluate benefit risk across asset

Objectives

Deliver real-time safety database
Support aggregate safety reports & annual reports

Baseline constraints

Risked disruption to regular study milestones due to competing priorities
Budget & resource scarcity, limited support for extended scope



Approach and methodology

Agile delivery
Raw to ADaM layer
Standard derivations and governance

Implementation

Strategize
Mapping rules
Establish lineage

Results

Enable faster & high-quality response to FDA/HAQ
Efficiency gains – 2.5 FTE per study
Periodical/Annual reports
Real time Safety monitoring using BI/Shiny

Challenges

Data heterogeneity & Standardization
Blinding
Resource mitigation

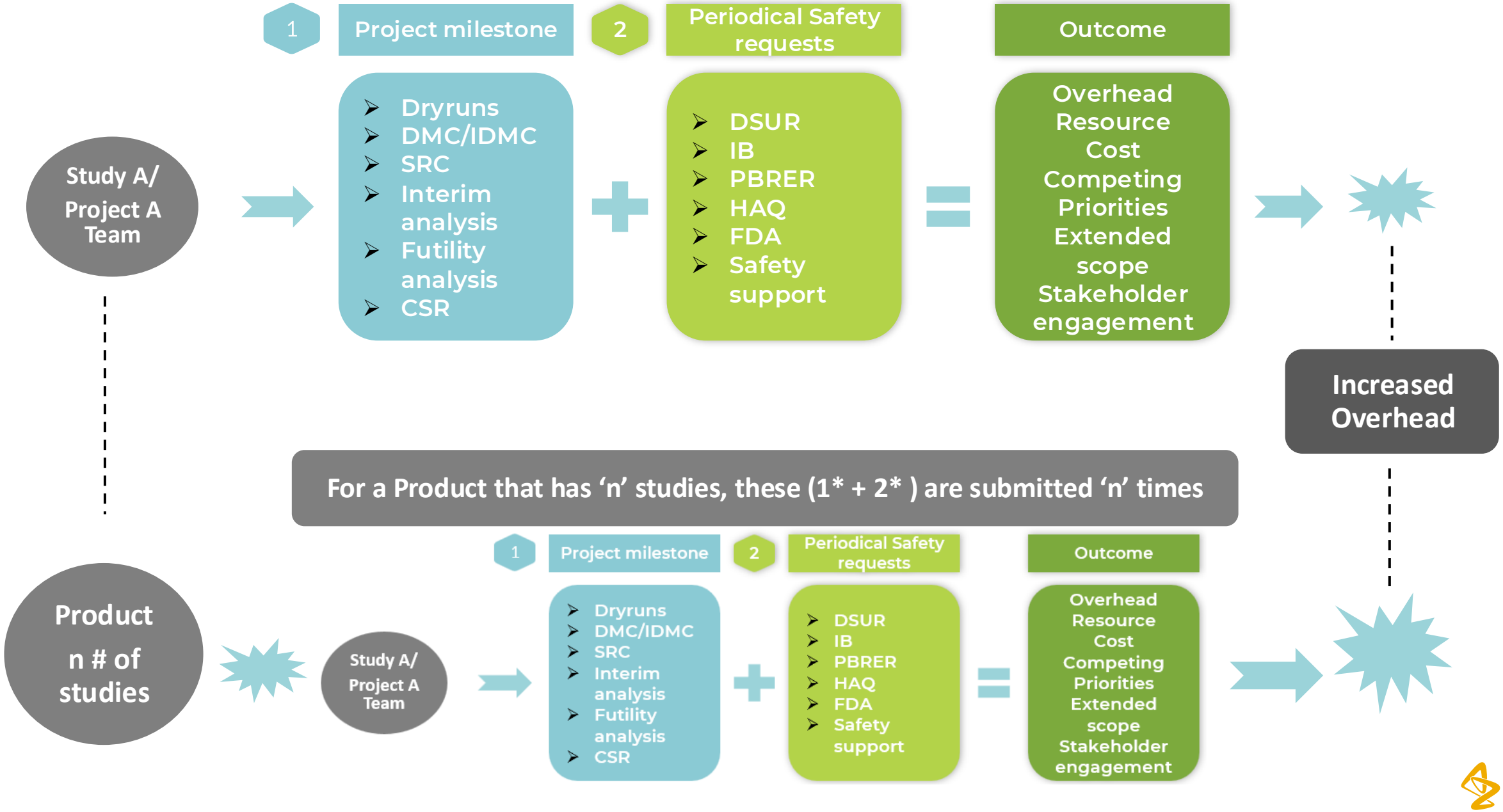
Lessons learned

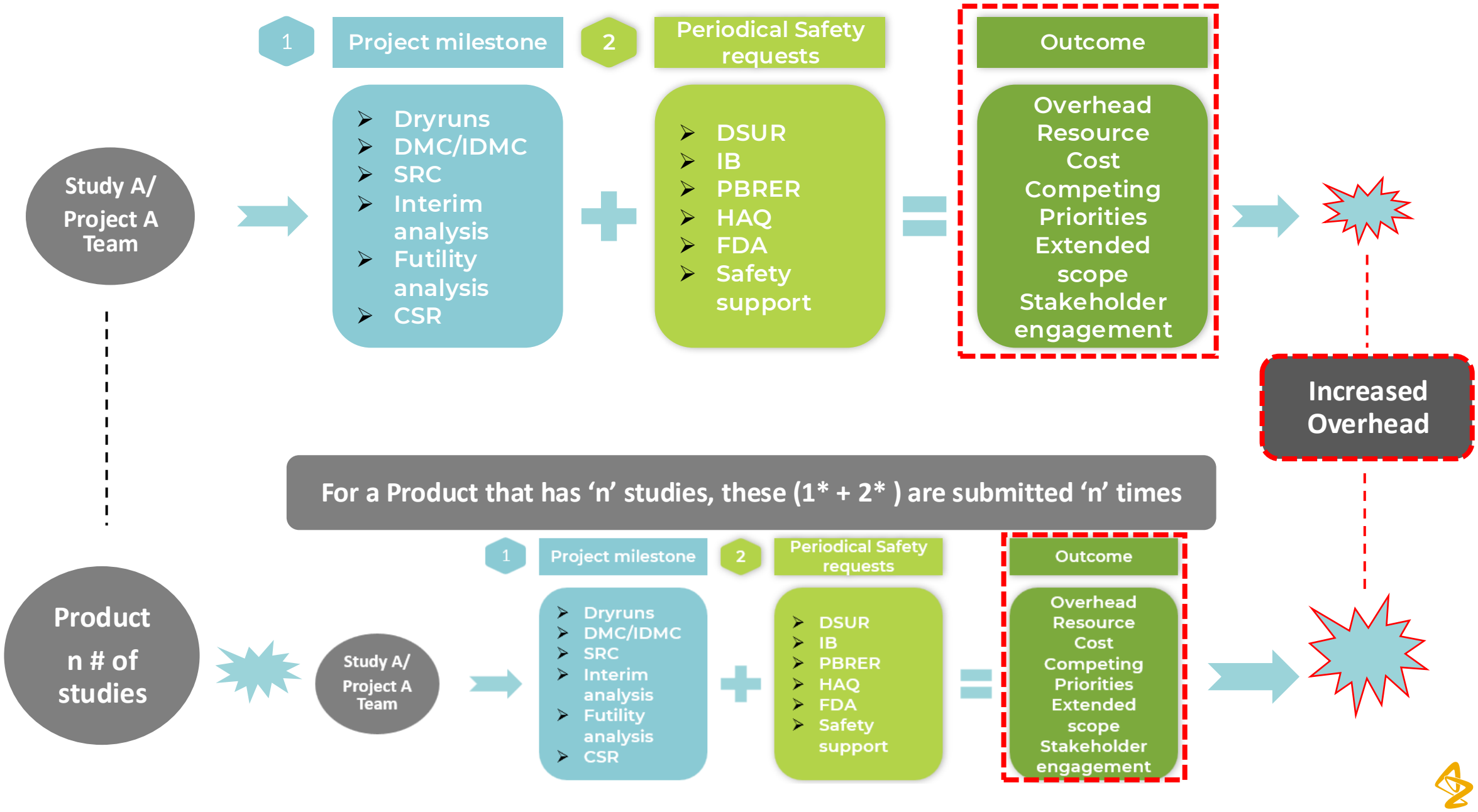
Start small and iterate
Document rigorously

Next steps/ Roadmap

Scale to new/existing potential product
Formalize SLA
Expand to CSR/TLF summaries
Integration

Project Milestones overhead




1
Project milestone
2
Periodical Safety requests
Outcome
Study A/ Project A Team
Dryruns
DMC/IDMC
SRC
Interim analysis
Futility analysis
CSR
DSUR
IB
PBRER
HAQ
FDA
Safety support
Overhead
Resource
Cost
Competing Priorities
Extended scope
Stakeholder engagement
Increased Overhead
For a Product that has 'n' studies, these (1* + 2*) are submitted 'n' times
Product
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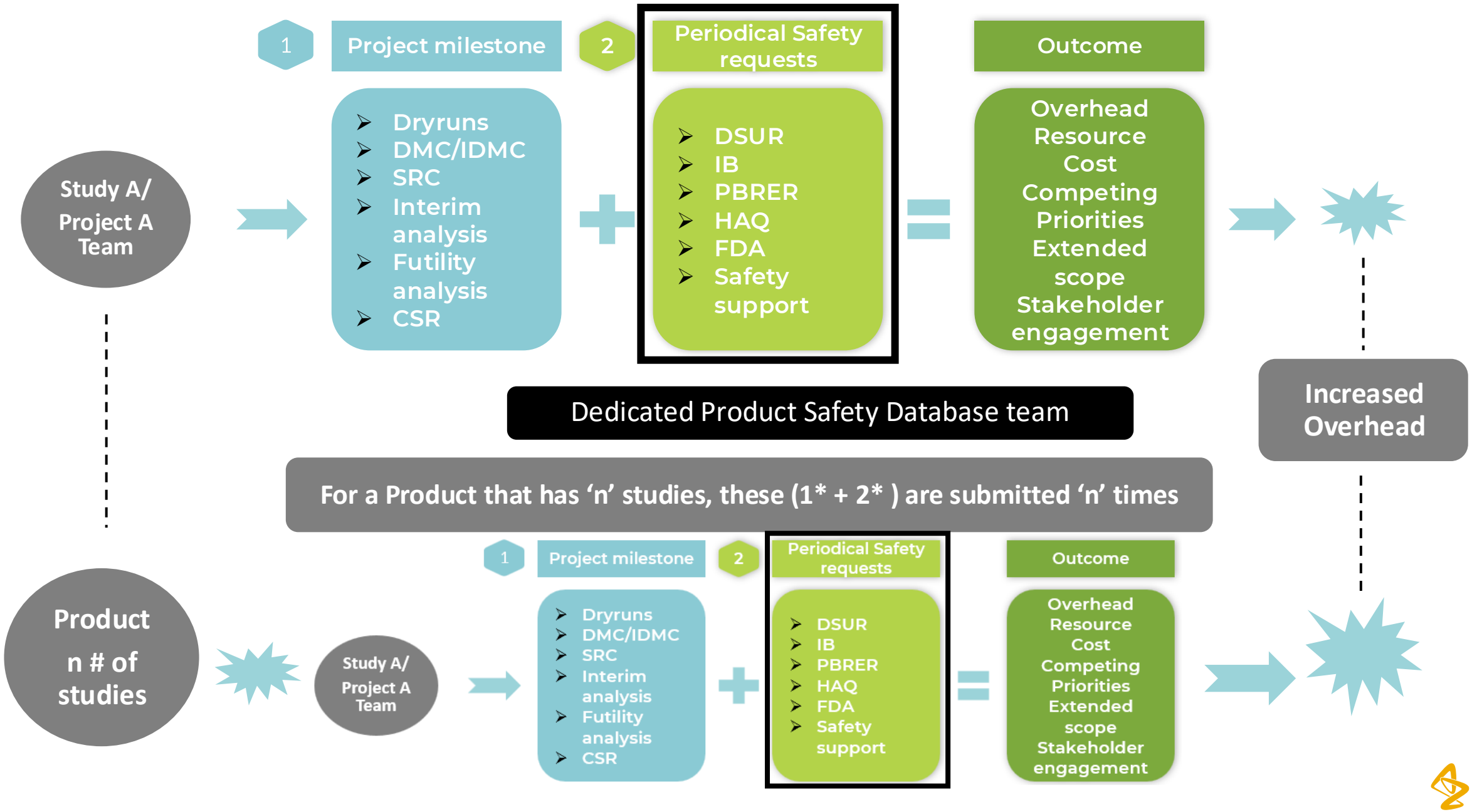
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Dedicated Product Safety Database team
For a Product that has 'n' studies, these (1* + 2*) are submitted 'n' times
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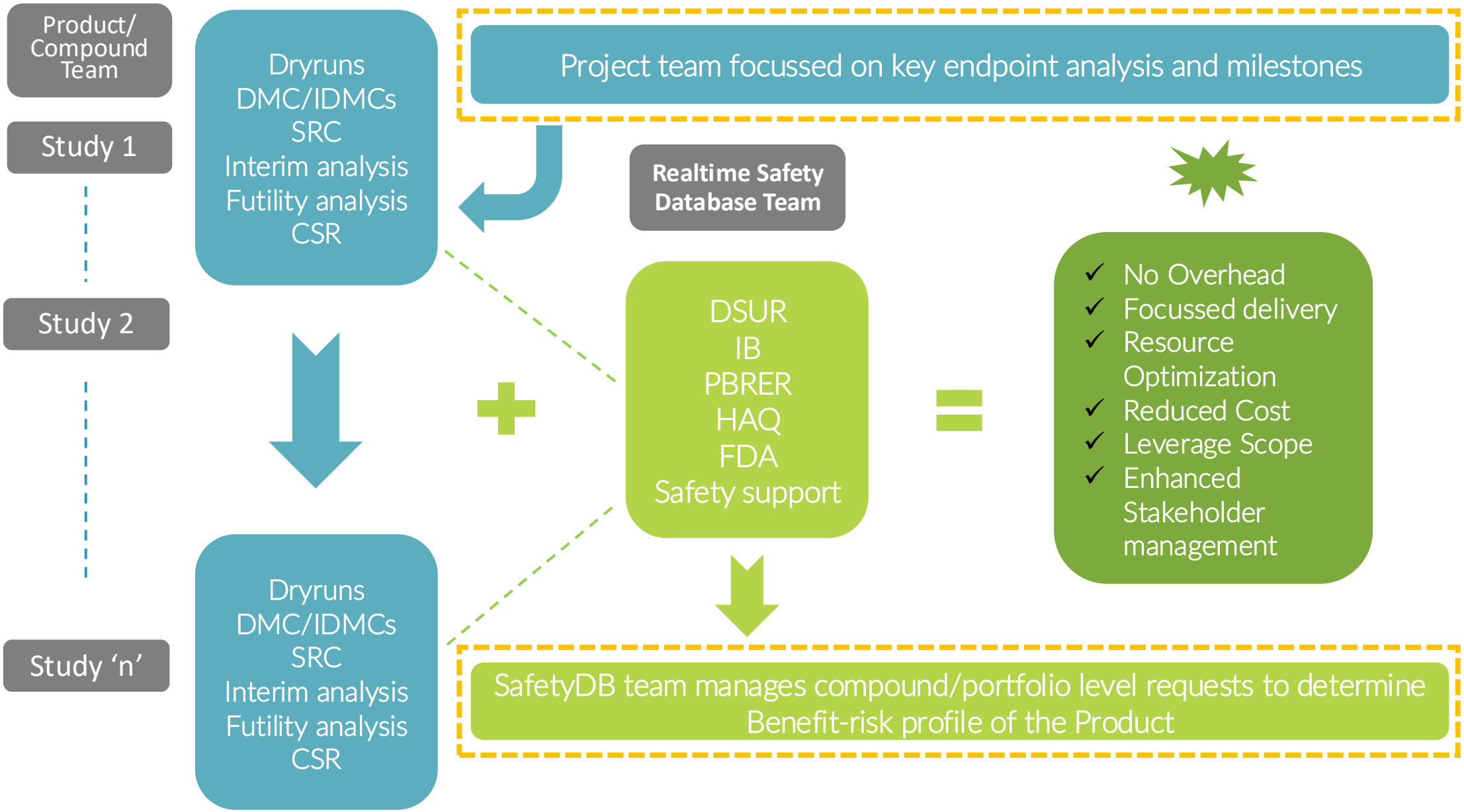
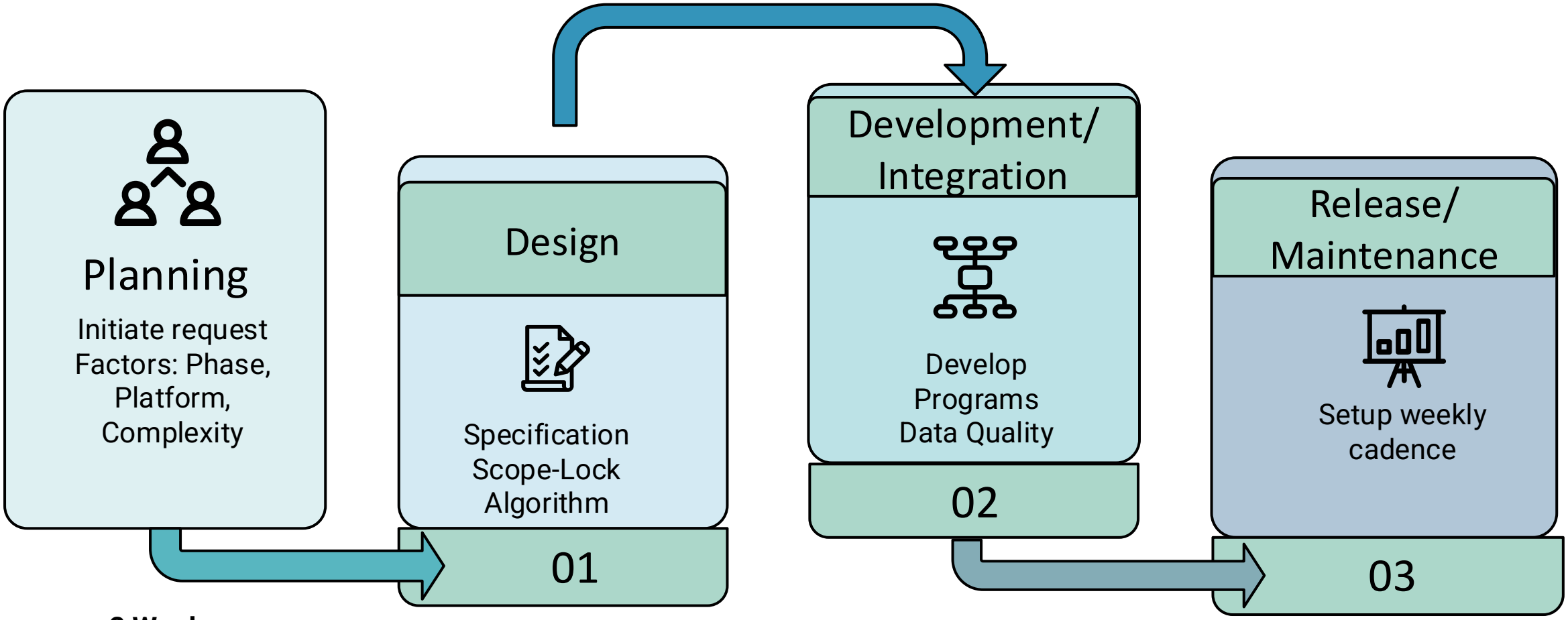
Collaborating Project & Safety Database

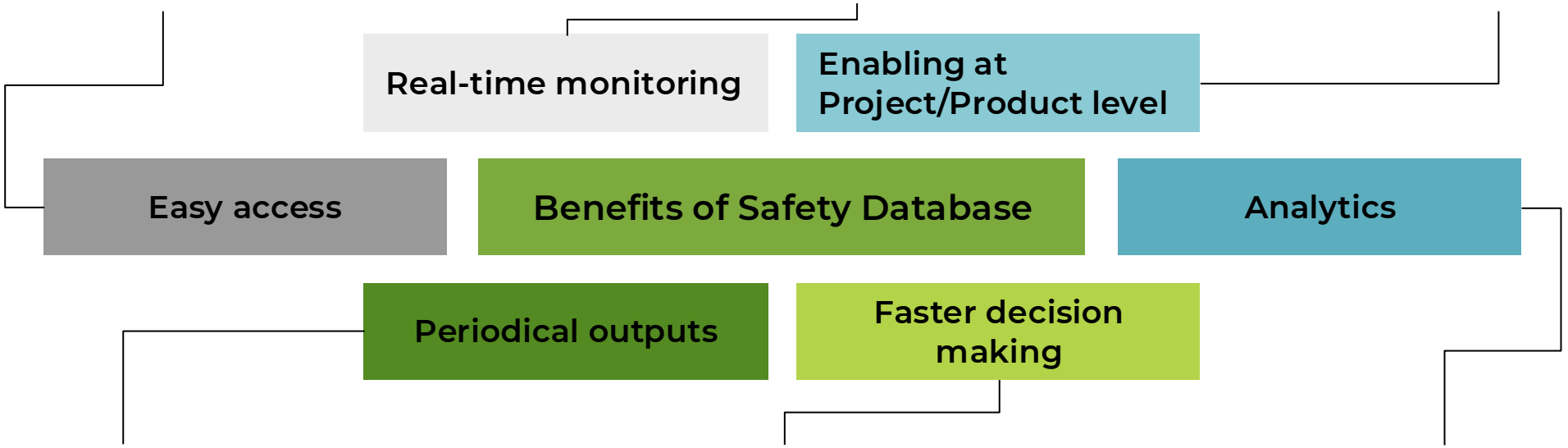


Safety Database Timeline



Outcomes and Optimization

- Monitor progress– Identify trends and potential problems
- Review of emerging safety data and effectiveness of TMGs (toxicity Management Guidelines)
- Insights by Indication, dose-level, regimen, phases



- Cater the analysis requirements of periodical reports like IB, DSUR, PBRER, PSUR's
- Equipped with high-quality and timely responses to FDA/HAQs
- Efficient Visualization in Power BI/Rshiny

Conclusion

- Selecting a safety database is a lengthy process that requires considering multiple perspectives.

- It’s important to involve a diverse, cross-functional team so that expertise and insights from various disciplines can be leveraged to take informed decisions. The Safety Database establishes a single, governed source of truth for product safety, delivering standardized, near real-time insights across studies.

- By curating direct-to-ADaM datasets with robust traceability, terminology governance, and validation, it accelerates regulatory reporting, strengthens signal detection, and improves cross-functional decision-making.

- Early outcomes include faster turnaround and actionable dashboards that enhance patient-centric risk assessment.

Future Scope and Outlook

- Enhancement to efficacy profile of the drug
- Standardize the periodical reports and deliver as part of the database
- Advancement of dynamic macros to reduce turnaround time across products

Q & A

Thank you !!

Contact

If there are any questions about this presentation, please do contact the undersigned.

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