



M*SSING APPLICATION DATA

IMPACT ON NDA AND BLA REVIEWS



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ABSTRACT:

Missing information in an NDA or BLA submission can either have negligible or tremendous impact on the review process. The Computational Science Center (CSC) provides the JumpStart service for NDA and BLA submissions. JumpStart identifies missing information and describes its potential impact for the clinical reviewer’s filing decision. We describe the array of missing information issues uncovered through a systematic analysis of clinical trial data for format, content, and coding quality. Awareness and conformance to our technical requirements can minimize these data quality issues for submissions with standardized data.

BACKGROUND:

At the onset of an application review, the review team must conduct an initial review of the data to understand the content and identify any major gaps prior to filing the application. Missing data is a common occurrence in clinical trials. Reviewers must make a determination on the impact of any missing data on their ability to conduct the analyses needed to evaluate the safety and efficacy of a product for a given indication.

Missing information can be inconsequential. For example:

- Null values for a domain not collected as part of protocol
- Data not in the core set of required SDTM variables (i.e., variables can be required, expected, or permissible).

On the other hand, missing data may lead to:

- Refuse-to-File actions (e.g., missing domains required for safety analysis)
- Imputation of outcomes for missing data

Ideally, if an applicant knows about missing or unpopulated data based on the protocol design or internal policy, it should describe this type of information in the Study Data Reviewers Guide (SDRG). JumpStart uses programming scripts to automate the task of identifying empty variables in an SDTM or ADaM dataset. We describe our experience with the range of missing data in applications that received the JumpStart service and the impact on drug review.

Finding Type	Domains	Finding	Impact
Missing Datasets	ADAE ADSL	A mismatch of the USUBJIDs between the SDTM and ADaM revealed that the ADaM datasets submitted were from a different study.	The sponsor must reconcile the NDA datasets and resubmit, possibly under a new timeline.
	Multiple	Missing domains from the NDA data, likely due to a data transmission error.	The missing datasets house necessary information for review and immediate resolution is necessary.
	TS	Trial Summary domain is missing from the submission.	This dataset is needed to ensure successful loading into JANUS Clinical Trial Repository tool.
Missing Records	DS	Subjects with Fatal Adverse Events have no “DEATH” records in the Disposition domain.	Reviewer may miss these death outcomes if they look only in the DS domain.
	IE	A significant portion of Screen Failures do not have records in IE domain.	Selection of analysis population could not be checked against the inclusion and exclusion criteria.
	DM	Subjects present in study (i.e., data present in other domains), but not in DM domain	Required for tool use, unable to view subject characteristics
	LB	Missing baseline results in LB and EG domains	Unable to execute any analyses that compare to a subject’s baseline readings.
		Missing lab records for adverse events in Investigations SOC	Unable to verify lab related adverse events
Missing Variables	DS	Disposition Category "study completion" missing for certain patients in certain studies	Unexplained disposition – would need informational request and if necessary validation from source .
	DM	Missing date variables from DM	Unable to build study timelines for subjects
	AE	Adverse Event Seriousness Criteria were not collected for all pivotal studies in an application	Difficult to independently verify whether an adverse event was serious or not.
		Missing EPOCH	Occurrence of an event in a particular trial phase not easily verified
Null Values	AE	Null values in AE Toxicity Grade (AETOXGR)	Unable to analyze adverse events by specific toxicity grades
		Null values in dictionary-derived term (e.g., AEDECOD)	These adverse events would be left out of most standard analyses. Important adverse events could be overlooked.

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METHODS:

We performed an inventory of the missing data identified in 35 applications evaluated by the CSC since 2014. A total of up to four studies per application are assessed for data quality in JumpStart; results of the assessment are shared with reviewers in a formal consult to the Review division. We describe the nature of some of the missing data issues and how the potential impact of the missing data was described to reviewers in the JumpStart Data Fitness session.

RESULTS AND DISCUSSION:

- The JumpStart service provides an opportunity to assess the study domains, content, and coding quality prior to the filing meeting.
- Among 10 applications reviewed in 2015, all had some type of missing data. The missing data ranged from entire datasets missing, missing variables, missing records, and null values.
- We notify the reviewer of any vital missing data as soon as it is identified. Missing data is also described at the JumpStart sessions.

CONCLUSION:

Missing data in an NDA or BLA may not be readily identified unless the review is well underway. Jumpstart systematically investigates the data through its tools and identifies missing NDA/BLA content. Due to the inherent nature of standardized data (i.e., SDTM), CSC can quickly assess the impact of missing data on the NDA review and the ability to effectively and efficiently run the analysis tools (e.g., MAED). CSC communicates these issues to reviewers to enable a determination as to whether the issues may result in refuse-to-file actions, information requests with a quick-turnaround time, or no action due to the negligible impact on the review. Applicants should be encouraged to provide information about missing data in the SDRG to help review staff understand the rationale for exclusion. The JumpStart service provides reviewers with a quick assessment of the submitted data so that filing and review decisions can be made early within the review cycle.