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From Missing to Meaningful: Tackling Partial Dates in Clinical Trials

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ABSTRACT

Handling partial or missing dates is a recurring challenge in clinical trials, often necessitating imputation for key analyses like identifying treatment-emergent events. While many sponsors default to their Statistical Analysis Plan (SAP) for guidance, a universal approach is still lacking. Leveraging the existing guidance laid out in the PHUSE's 'SDTM ADaM Implementation FAQ,' we fine-tuned a more robust data imputation guideline using de-identified clinical data from approximately 50 clinical trials (eligible for Medidata analysis through Medidata's data collaboration program). Our paper will present these optimized guidelines, discussing specific scenarios, critical variables, and common pitfalls. This enhanced summary of scenarios will provide a customizable foundation for date imputation that can be further enhanced to fit your trial needs, bolstering the integrity of clinical trial data for regulatory submissions.

INTRODUCTION

Incomplete or missing data is a frequent challenge in clinical trials, with dates representing one of the most affected data elements. This is understandable, as individuals often struggle to recall precise dates for events in the distant past. Consequently, the start and stop dates for data related to Concomitant/Prior Medications (CM) and Adverse Events (AE) are frequently recorded with partial or missing information. To extract meaningful insights from this data, it is imperative to address these gaps by substituting the missing values with plausible values, a process called 'imputation.' This approach enables sponsors and researchers to draw reasonable conclusions while maintaining the integrity of the data as much as possible. Imputation is achieved at the Analysis Data Model (ADaM) dataset creation stage, usually relying on the imputation guidelines drafted by statisticians as a part of the study's Statistical Analysis Plan (SAP). Each study is unique, so there might be subtle differences in the imputation approach. In this paper, we have explored anonymized/de-identified clinical data from approximately 50 clinical trials (eligible for Medidata analysis through Medidata's data collaboration program), thus casting a wide net to identify the common variables that drive optimal imputation, as well as drafted some example cases to showcase the imputation strategies. This information can be used to draft sponsor-specific rules and possibly automate the date imputation process.

VARIABLES AND RULES THAT DRIVE THE IMPUTATION OF DATES

- ANCHOR DATE:
A fixed reference point for imputation is often based on significant study dates like the first or last treatment date. It serves as a benchmark for adjusting other dates.
COUNTER DATE:
The complementary date is relative to the one being imputed, such as using the event start date to inform the end date, and vice versa. Its relation to the anchor date is key in determining imputation methods.
CUTOFF DATE:
Sets an upper limit for imputed values to ensure relevance. It's typically the end of participation date or last contact date, chosen to avoid speculative imputation.
TIMEPOINT VARIABLES:
When available, reference time points and their relative variables are crucial in accurately determining imputed dates. These variables can offer insights into the appropriate handling of dates based on the event's status or timing in relation to treatment.
- RULES:
●Absolute vs. Average Approach: Defaulting to the extreme start or end of a period (e.g., month, year) versus an average scenario (mid-month, mid-year) provides a more balanced estimate.
- Drug Half-life Driven Anchor Date: Utilizing the treatment end date or a period extended by the drug's half-life to impute dates for 'treatment-emergent' events, ensuring imputation aligns with pharmacological insights.

Category	Imputation Rule	Example Cases	XXSTDTc	XXENDTc	RFXSTDTc/ RFSTDTc	RFXENDTc/ RFENDTc	IMPUTED STDT	IMPUTED ENDT	XXENRTPT	XXENTPT	RFPENDTc
Day value of the end date is missing	Impute the DAY as the end of the month. If the imputed date > RFPENDTc, the value is updated as RFPENDTc.	ENDTc has MONTH and YEAR, the same as the treatment start date year and month, and the event start date < treatment start date. In this case, the event end date is imputed as the treatment start date, based on XXENTPT and XXENRTPT values.	2016-01-15	2016-08	2016-08-10	2016-08-20		2016-08-10	COINCIDENT	FIRST DOSE DATE	2016-09-12
	Also, XXENRTPT and XXENTPT, along with the event start date, if available, are considered where applicable to pick the appropriate Day value when the MONTH and YEAR are the same as the Treatment start date, treatment end date, and other relevant dates, etc.	Same scenario as above but XXENTPT and XXENRTPT values are missing. In this case, the event end date is imputed as the end of the month. ENDTc is partial and is after Treatment end date but Imputing it to end of the month would make the imputed date greater than RFPENDTc. Thus, RFPENDTc is considered as the Imputed date.	2016-01-15	2016-08	2016-08-10	2016-08-20		2016-08-31			2016-09-12
			2016-01-15	2016-09	2016-08-10	2016-08-20		2016-09-12			2016-09-12
Month value of the end date is missing	Impute the Date as the end of the Year. If the imputed date > RFPENDTc, the value is updated as RFPENDTc.	ENDTc has only a Year value, the same as the treatment start date year, and the event start date < treatment start date. In this case, the event end date is imputed as the treatment end date, based on XXENTPT and XXENRTPT values.	2016-01-15	2016	2016-08-10	2016-08-20		2016-08-20	COINCIDENT	END OF TREATMENT	2016-09-12
	Also, XXENRTPT and XXENTPT, along with the event start date, if available, are considered where applicable to pick the appropriate date.	Same scenario as above but XXENTPT and XXENRTPT values are missing. In this case, the event end date is imputed as a minimum of the following values: End of the year, RFPENDTc.	2016-01-15	2016	2016-08-10	2016-08-20		2016-12-31			2017-09-12
		ENDTc has only a Year value, the same as the treatment start date year and the event start date > treatment end date. In this case, the event end date is imputed as a minimum of the following values: End of the year, RFPENDTc.	2016-08-25	2016	2016-08-10	2016-08-20		2016-09-12			2016-09-12
		If Year and Day are present with month missing disregard the day value populated and apply the same rules as defined for when only year is available.	2016-01-15	2017---25	2016-08-10	2016-08-20		2017-12-31			2018-09-12
End date is completely missing, or Year is missing	XXENRTPT and XXENTPT, along with the event start date, if available, are considered to impute the end date as an appropriate end date, such as the treatment end date, RFPENDTc, etc.	XXENRTPT states as 'ONGOING', and thus, the end date will NOT be IMPUTED.	2016-01-15		2016-08-10	2016-08-20			ONGOING	END OF STUDY	2016-09-12
		The event start date < treatment start date, and the end date is missing. In this case, the event end date is imputed as the treatment end date, based on XXENTPT and XXENRTPT values.	2016-01-15		2016-08-10	2016-08-20		2016-08-20	COINCIDENT	END OF TREATMENT	2016-09-12
	Please note that If ENRTPT relays that the event is still 'ongoing' or the status is 'unknown', the end date is not imputed.	The event start date > treatment end date, then the event end date is imputed as minimum of the following values: End of the year, RFPENDTc.	2016-08-25		2016-08-10	2016-08-20		2016-12-31	COINCIDENT	END OF STUDY	2017-09-12
Day value of the start date is missing	Impute the DAY as the Day value of the treatment start date for the following scenarios: 1. The month and year of the event are the same as the month and year of the treatment start date, and the event end date ≥ treatment start date. 2. The month and year are the same as the month and year of the treatment start date, and the event end date is missing.	The start date's month value < treatment start date, and the end date < treatment starts. Thus, the imputed start date is the 1st of the month.	2016-01	2016-07-31	2016-08-10	2016-08-20	2016-01-01				2016-09-12
		The event start date's month/year is the same as the treatment start date's month/year and the event end date > treatment start date. Thus, the start date will be imputed as the treatment start date	2016-08	2016-08-15	2016-08-10	2016-08-20	2016-08-10				2016-09-12
		The event start date's month/year is the same as the treatment start date's month/year and the event end date is missing thus the start date will be imputed as the treatment start date	2016-08		2016-08-10	2016-08-20	2016-08-10				2016-09-12
	If NOT, impute as the 1st of the Month.										
Month value of the start date is missing	When MONTH and DAY are both missing, then impute the MONTH and DAY as the MONTH and DAY value of the treatment start date for the following scenarios: 1. The year of the event is the same as the year of the treatment start date, and the event end date ≥ treatment start date. 2. The year of the event is the same as the year of the treatment start date, and the event end date is missing.	Event end date < treatment start date and hence, the start date is imputed as 1st January.	2016	2016-07-30	2016-08-10	2016-08-20	2016-01-01				2016-09-12
		Event start date's year value is the same as the treatment start date's year value, and the end date > the treatment start date. Thus, it is imputed as the treatment start date.	2016	2016-08-15	2016-08-10	2016-08-20	2016-08-10				2016-09-12
		If present, we disregard the 'DAY' value and apply the same rules as when 'DAY' and 'MONTH' are missing.	2016---20	2016-09-15	2016-08-10	2016-08-20	2016-08-10				2016-09-12
	If NOT, impute as the 1st of January. *When DAY is available, along with YEAR, then disregard the Day value and use the same logic steps as above.	If the year is the same as the treatment start date and the end date is missing, then impute the start date as the treatment start date.	2016		2016-08-10	2016-08-20	2016-08-10				2016-09-12
Start date is completely missing or, Year is missing	Impute as treatment start date if end date ≥ treatment start date	End date > treatment start date and thus event start date is imputed as the treatment start date.		2016-08-15	2016-08-10	2016-08-20	2016-08-10				2016-09-12
	Impute as 1st January of the same year as end date, if end date < treatment start date	Event end < treatment start thus event start date is imputed as 1st January of the same year as the event end date.		2015-07-15	2016-08-10	2016-08-20	2015-01-01				2016-09-12