

DH06: The Challenges of Using Parent Study Data in a Long-Term Extension Study

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11 November 2024

Agenda

1. Introduction
2. Challenges
3. Case Studies
4. Blinding Considerations
5. Conclusion

Introduction

- Long-Term Extension (LTE) Studies evaluate safety/efficacy/tolerability of long-term exposure to a new drug
- LTEs recruit subjects from parent/feeder studies
- Some or all of the parent study data will be required in the LTE reporting
- LTEs require their own separate protocol, CSR, Study Data Package (SDP), datasets & displays
- Unique challenges!



Challenges

❑ Data Integration

- ❑ Multiple data sources. Try to ensure data collection tools and methodologies are aligned

❑ Subject Identification and Traceability

- ❑ Use a Unique Subject Identifier (USUBJID) that remains consistent across all studies
- ❑ Ensure that the USUBJID is correctly used to match subjects across datasets. Verify that there are no duplicate or missing identifiers

❑ Programming Challenges

- ❑ Define standard procedures for data collection and maintain consistency in how data is collected to avoid discrepancies that could complicate merging

❑ Blinding Issues

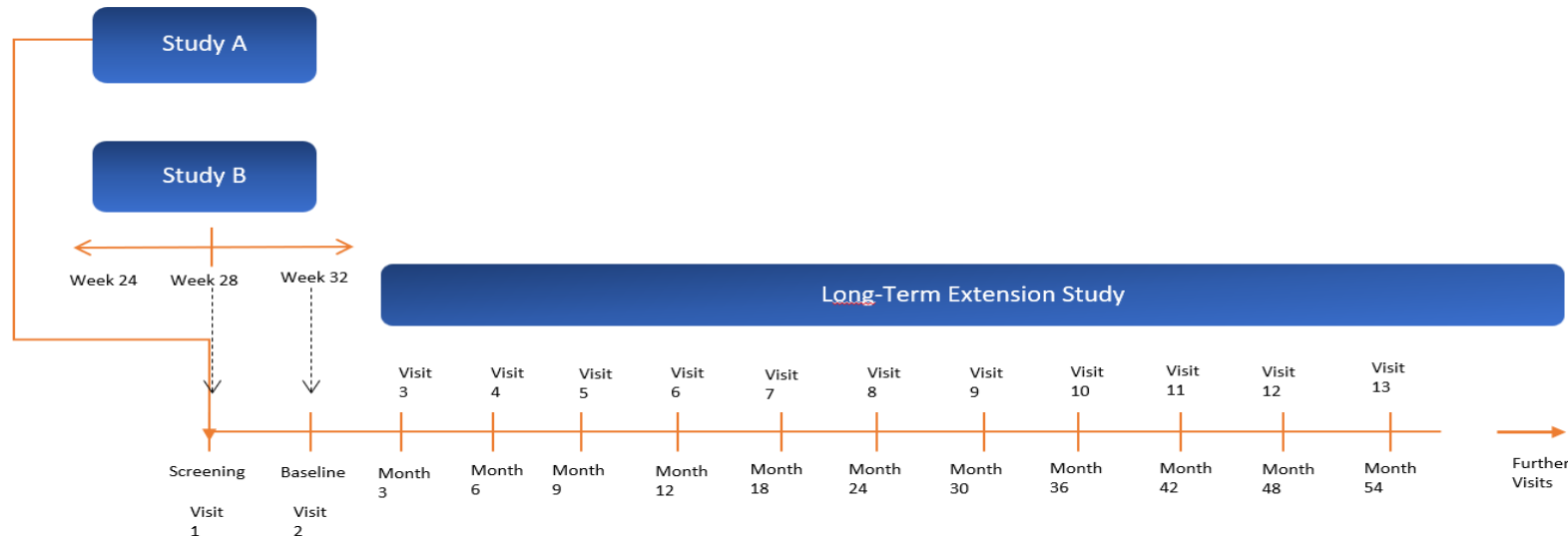
- ❑ Maintaining the blind is crucial to avoid bias. If investigators are aware of which treatment subjects are receiving, they might inadvertently influence the assessment or reporting of outcomes



Example 1

Long-Term Extension Study

- Two parent studies with different dose levels
- Subjects entered LTE at End Of Study from Study A and Week 28 from Study B
- Three clinical databases used for data collection
- SDTM.DM contained one row per subject as per CDISC guidelines
- USUBJID from parent study was maintained to facilitate traceability and data integration



Example 1 (continued)

Long-Term Extension Study

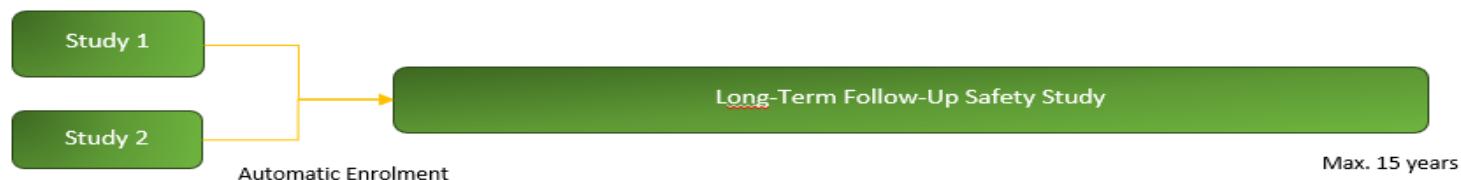
- AE and CM domains based only on LTE data
- If a subject's AE started in the parent study & continued into the LTE, the AE could potentially be entered into both study databases
- Integration at ADaM level, merging parent study ADaMs to create LTE study ADaMs
- Study B Week 28 and Week 32 visits were re-mapped to screening and baseline visits in LTE

STUDYID	PSTUDYID	USUBJID	PSUBJID	SUBJID	PARCAT1	PARAMCD	AVISIT	AVAL
Study A (111111)		111111.789789		789789	HEMATOLOGY	LB0088	Screening	0.05
Study A (111111)		111111.789789		789789	HEMATOLOGY	LB0088	Baseline	0.06
Study A (111111)		111111.789789		789789	HEMATOLOGY	LB0088	Week 28	0.19
Study A (111111)		111111.789789		789789	HEMATOLOGY	LB0088	Week 32	1.41
Study B (222222)		222222.345345		345345	HEMATOLOGY	LB0088	Screening	0.01
Study B (222222)		222222.345345		345345	HEMATOLOGY	LB0088	Baseline	0.6
Study B (222222)		222222.345345		345345	HEMATOLOGY	LB0088	Week 28	0.87
Study B (222222)		222222.345345		345345	HEMATOLOGY	LB0088	Week 32	1.45
LTE (333333)	Study A (111111)	111111.789789	111111.789789	678678	HEMATOLOGY	LB0088	Screening	1.13
LTE (333333)	Study A (111111)	111111.789789	111111.789789	678678	HEMATOLOGY	LB0088	Baseline	1.27
LTE (333333)	Study A (111111)	111111.789789	111111.789789	678678	HEMATOLOGY	LB0088	Month 3	1.32
LTE (333333)	Study A (111111)	111111.789789	111111.789789	678678	HEMATOLOGY	LB0088	Month 6	2.54
LTE (333333)	Study B (222222)	222222.345345	222222.345345	456456	HEMATOLOGY	LB0088	Screening	0.87
LTE (333333)	Study B (222222)	222222.345345	222222.345345	456456	HEMATOLOGY	LB0088	Baseline	1.45
LTE (333333)	Study B (222222)	222222.345345	222222.345345	456456	HEMATOLOGY	LB0088	Month 3	1.98
LTE (333333)	Study B (222222)	222222.345345	222222.345345	456456	HEMATOLOGY	LB0088	Month 6	3.02

Example 2

Long-Term Follow-Up Study

- Auto-enrolment into LTFU study due to an FDA safety mandate



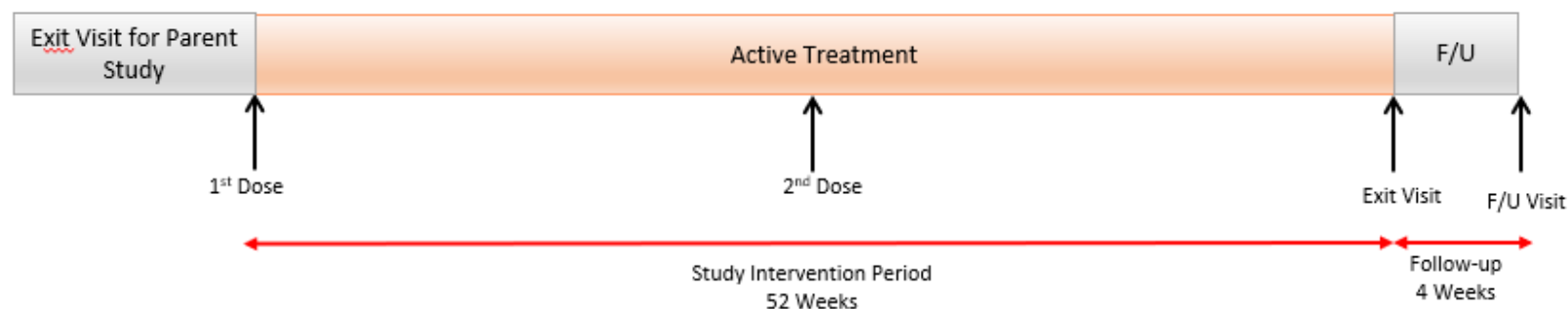
- Subjects kept the same USUBJID in both parent and LTFU study
- All subject data from the completed parent studies and LTFU study integrated at the SDTM level
- Integrated SDTM datasets were used as source data for the integrated ADaM datasets
- Occurrence domains were replicated not recollected
- Only new AEs were reported in LTFU
- Consistency checks performed on merged SDTMs to ensure no discrepancies

STUDYID	USUBJID	AESEQ	AESTDTC	AEENDTC	AETERM	AEBODSYS	AESEV	AEACN	AEREL	AEOUT	TRTEMFL	PERIOD
123456	123456.000001	1	15/02/2023	17/02/2023	Headache	Nervous System	Mild	None	Not related	Recovered	Y	Parent
123456	123456.000001	2	26/04/2023	28/04/2023	Nausea	Gastrointestinal	Moderate	Drug withdrawn	Not related	Recovered	Y	Parent
456789	123456.000001	3	18/06/2023	25/06/2023	Rash	Skin and Subcutaneous	Severe	Dose reduced	Related	Recovered	Y	LTE
456789	123456.000001	4	19/09/2023	Ongoing	Diarrhea	Gastrointestinal	Mild	None	Related	Ongoing	Y	LTE
456789	123456.000001	5	23/06/2023	Ongoing	Headache	Nervous System	Mild	None	Not related	Recovered	Y	LTE

Example 3

Safety and Efficacy Long-Term Extension Study

- Subjects completing one of two parent studies could enrol into an open-label study
- Subjects received two doses of add-on study intervention
- Baseline data for subjects on **Active Treatment** in the parent study was their **Baseline** data in the parent study
- For subjects on **Placebo** in the parent study, their baseline data was their parent study **Exit Visit**
- Baseline derivations were over-written in the LTE ADaMs but other parent study data not retained
- Blinding challenges occurred due to the open-label design & an additional team was required for unblinded data review
- USUBJID carried over from parent study & data was integrated at the ADaM level
- Only new AEs were reported



Example 4

Long-Term Access Programme (LTAP)

- Multiple extension studies, subjects participated in up to 5 studies
- LTAP: collect safety data & allow subjects with severe disease continued trt access
- Subjects entered via 9 routes, permitted gap of up to 6 mths, 6 feeder studies
- Open-label treatment, 2 dose levels (adults/paediatrics) & 3rd added
- Minimal re-collection of baseline characteristics, copied from most recent previous study

Route	Study 1	Study 2	Study 3	Study 4	Study 5	Most Recent Previous Study
1	100001	200010				100001
2	100002	200010				100002
3	100003	200011	200010			200011
4	100004	200012	300013	200010		300013
5	100005	200012	300013	200010		300013
6	100006	200011	300014	200010		300014
7	100007	200012	300013	300014	200010	300014
8	100008	200012	300013	300014	200010	300014
9	100009	200010				100009

Example 4 (continued)

Long-Term Access Programme (LTAP)

- Source Data: LTAP SDTMs, Previous Study ADaMs and GSK Legacy d'sets pre-CDISC
- Total Extent of Exposure on active treatment reported across all previous studies
- USUBJID = Study & Subject IDs from first enrolled trial
- No CRF page to collect previous subject & study info
- Programmers created PRVTRIAL dataset to feed into SDTM Subject Characteristics (SC)
- This approach records the subject's path & allows merging with any previous study
- Manual creation of PRVTRIAL ➡ RISK of Data Errors!
- All studies should have included a Previous Trial CRF Page



Example 4 (continued)

Long-Term Access Programme

SDTM.SC Domain

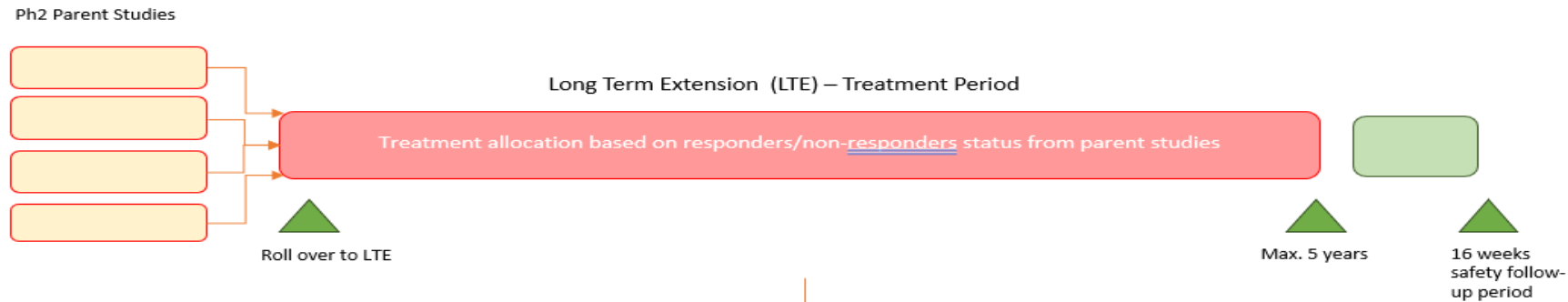
Route	Study 1	Study 2	Study 3	Study 4	Study 5	Most Recent Previous Study
1	100001	200010				100001
2	100002	200010				100002
3	100003	200011	200010			200011
4	100004	200012	300013	200010		300013
5	100005	200012	300013	200010		300013
6	100006	200011	300014	200010		300014
7	100007	200012	300013	300014	200010	300014
8	100008	200012	300013	300014	200010	300014
9	100009	200010				100009

STUDYID	USUBJID	SCSEQ	SCGRPID	SCTESTCD	SCTEST	SCORRES
200010	100001.000001	1	100001.000001	PTYN	Was Subject in Previous Clinical Trial	Y
200010	100001.000001	2	100001.000001	PTSTUDY	Previous Study ID	100001
200010	100001.000001	3	100001.000001	PTSUBJID	Previous Subject ID	000001
200010	100002.000001	1		PTYN	Was Subject in Previous Clinical Trial	Y
200010	100002.000001	2	100002.000001	PTSTUDY	Previous Study ID	100002
200010	100002.000001	3	100002.000001	PTSUBJID	Previous Subject ID	000001
200010	100003.000001	1		PTYN	Was Subject in Previous Clinical Trial	Y
200010	100003.000001	2	100003.000001	PTSTUDY	Previous Study ID	100003
200010	100003.000001	3	100003.000001	PTSUBJID	Previous Subject ID	000001
200010	100003.000001	4	200011.000011	PTSTUDY	Previous Study ID	200011
200010	100003.000001	5	200011.000011	PTSUBJID	Previous Subject ID	000011
200010	100004.000001	1		PTYN	Was Subject in Previous Clinical Trial	Y
200010	100004.000001	2	100004.000001	PTSTUDY	Previous Study ID	100004
200010	100004.000001	3	100004.000001	PTSUBJID	Previous Subject ID	000001
200010	100004.000001	4	200012.000007	PTSTUDY	Previous Study ID	200012
200010	100004.000001	5	200012.000007	PTSUBJID	Previous Subject ID	000007
200010	100004.000001	6	300013.000033	PTSTUDY	Previous Study ID	300013
200010	100004.000001	7	300013.000033	PTSUBJID	Previous Subject ID	000033

Example 5

Long-Term Extension Study with Four Parent Studies

- Treatment allocation in the LTE was based on subject's responder/non-responder status from the parent studies



- Responders stayed on same treatment (1 of 4 active doses or placebo)
- Non-responders moved to highest active dose
- Blinding to dose & frequency maintained until respective parent study was reported

Example 5 (continued)

Long-Term Extension Study with Four Parent Studies

- Previous Trial Participation was incorporated into the eCRF of the LTE study & populated in the SDTM.SC domain

SC (Subject Characteristics)

Previous Trial Involvement (PRVTRIAL)

Previous Trial Involvement Status		SCCAT=PREVIOUS TRIAL INVOLVEMENT
Participated in a Previous Clinical Trial/Study for the Same Study Intervention Given in this Trial/Study	Yes	SCORRES when SCTESTCD=PTYN
	No	

Previous Trial Involvement Details - 1	
Previous Study Identifier/Protocol Number/Identifier	SCORRES when SCTESTCD=PTSTUDY
Previous Center Number	SCORRES when SCTESTCD=PTCENTER
Previous Participant Identifier	SCORRES when SCTESTCD=PTSUBJID

Example 5 (continued)

Long-Term Extension Study with Four Parent Studies

- SDTM.SC had 4 records per subject (PTYN, PTSTUDY, PTSUBJID, PTCENTER) & was used to assign the same USUBJID across all datasets
- SDTM.DQ (Demographic Qualifiers) domain in the LTE study contained all subjects from parent and LTE studies, 2 records per subject with SUBJID from parent and LTE
- ADaM dataset ADDQ facilitated merging from any study
- Integration was performed at the ADaM level

LTE STUDYID	USUBJID	SUBJID
123456	111222.000001	000001
123456	111222.000001	000002
123456	333444.000001	000001
123456	333444.000001	000003
123456	555666.000001	000001
123456	555666.000001	000004
123456	777888.000001	000001
123456	777888.000001	000005

Example 5 (continued)

Long-Term Extension Study with Four Parent Studies

- Variables in ADSL in the LTE study contained parent study information & maintained the required one record per subject

LTE STUDYID	LTE USUBJID	LTE SUBJID	PARENT STUDYID	PARENT SUBJID
123456	111222.000001	000002	111222	000001
123456	333444.000001	000003	333444	000001
123456	555666.000001	000004	555666	000001
123456	777888.000001	000005	777888	000001

- LTE ADaMs included both parent and LTE study data in one dataset by merging source datasets by USUBJID
- All derivations were traceable back to the parent study SDTMs

Blinding Considerations

➤ Ethical Considerations

- If a subject was randomised to *control/placebo arm of parent study* and had a positive outcome it may pose a risk to re-randomise to treatment arm. Similarly, if a subject was randomised to *treatment arm of parent study* with poor results it could be considered unethical to enrol in LTE study.

➤ Long-Term Challenges

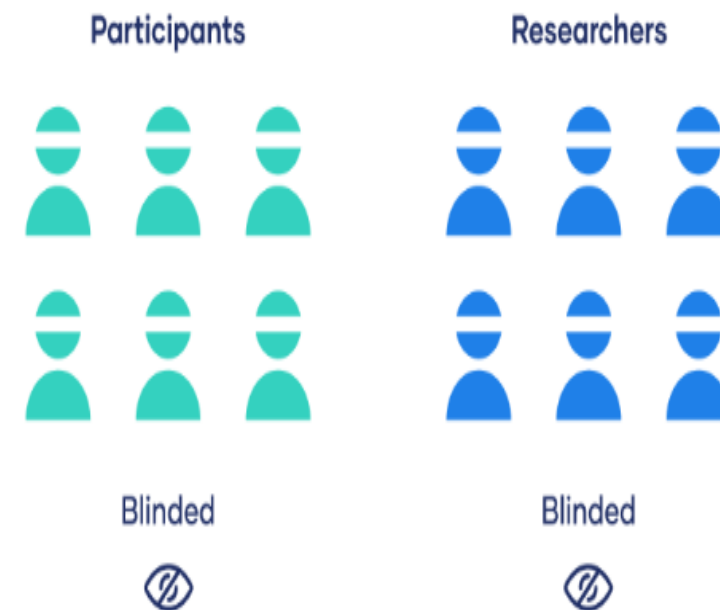
- LTEs often continue for many years with changes likely as new data available. Changes in study design should be carefully monitored to avoid compromising the blind.

➤ Data Interpretation

- Unblinding can lead to biased interpretation. One solution could be to have a separate review team.

➤ Maintenance of the Blind

- Once the parent study results are known this can compromise the blind of the subjects in the LTE study. Test results can also compromise the blind which could inadvertently influence the reporting of outcomes.



Conclusion

- Consistent Data Collection
 - Data structure should be the same where feasible, take time at study set-up
 - Standardising data formats & definitions leads to easier merging & improved dataset quality
 - Include 'Previous Trial Involvement' CRF Page to capture prior Study IDs & Subject IDs
- Transparency and Traceability are KEY
 - Define how USUBJID will be used
 - Plan early & address challenges quickly and efficiently
 - Document data merge process including deviations from the planned merging process
 - Conduct data validation checks
 - LTE datasets exist as a standalone package
- Multiple options to handle data integration BUT our preferred option is Example 5
 - No over-writing of data
 - Traceability
 - Easier programming
 - The path each subject took prior to the LTE is clear



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