THE UNIVERSITY OF ARIZONA Research & Partnerships

FISHBONE DIAGRAM

Cause-and-Effect Analysis

1. Purpose & Scope

This procedure establishes a standard approach for clinical trial study teams to apply Fishbone (Cause-and-Effect) Diagrams during root cause analysis (RCA). It is applicable to any investigation involving protocol deviations, data quality failures, patient safety events, regulatory findings, or operational inefficiencies within a clinical trial.

When to Use This Tool

- A specific problem, deviation, or quality issue has been identified, and root cause is unknown.
- The team needs to structure a brainstorming session to explore all possible contributing factors.
- Interactions between process factors need to be mapped before corrective actions are defined.
- A CAPA (Corrective and Preventive Action) plan requires documented root cause evidence.
- During a regulatory inspection or audit to demonstrate structured problem-solving.

Key Benefits for Clinical Trial Teams

- Provides a visual, structured framework that prevents important causes from being overlooked.
- Creates a documented, audit-ready record of the team's root cause investigation process.
- Helps distinguish root causes from symptoms, leading to more durable corrective actions.
- Supports compliance with ICH E6(R2) GCP requirements for quality systems and risk management.
- Reduces recurrence of issues by targeting systematic causes rather than individual events.

2. Background — The Fishbone Diagram

Originally developed by Professor Kaoru Ishikawa, the Fishbone Diagram (also called an Ishikawa Diagram or Cause-and-Effect Diagram) is a quality management tool widely adopted across regulated industries. In clinical research, it is used to investigate the multiple interacting factors that can contribute to trial failures, data discrepancies, and compliance gaps.

The diagram takes its name from its appearance: a central arrow pointing to the problem (the "fish head") with branches extending from it (the "bones") representing categories of causes. Sub-causes branch off these main bones, creating a hierarchical map of contributing factors.

TIP *A well-constructed Fishbone Diagram does not assign blame — it identifies system and process factors that can be addressed through sustainable corrective actions.*

The 6 M's Framework

Category (M)	Standard Definition	Clinical Trial Application
Manpower	People and human resources	Investigators, CRAs, study coordinators, data managers, statisticians — training, experience, workload
Methods	Procedures, processes, regulations	Protocol design, SOPs, ICH/GCP guidelines, visit procedures, data collection methods
Materials	Supplies, ingredients, inputs	eCRF, patient diaries, source documents
Machinery	Equipment and technology	EDC systems, imaging systems, clinical databases
Measurement	Data capture and indicators	Efficacy endpoints, safety assessments, data queries, protocol-defined visit windows
Mother Nature	Environment and externalities	Site geography, patient population availability, pandemic effects, regulatory landscape

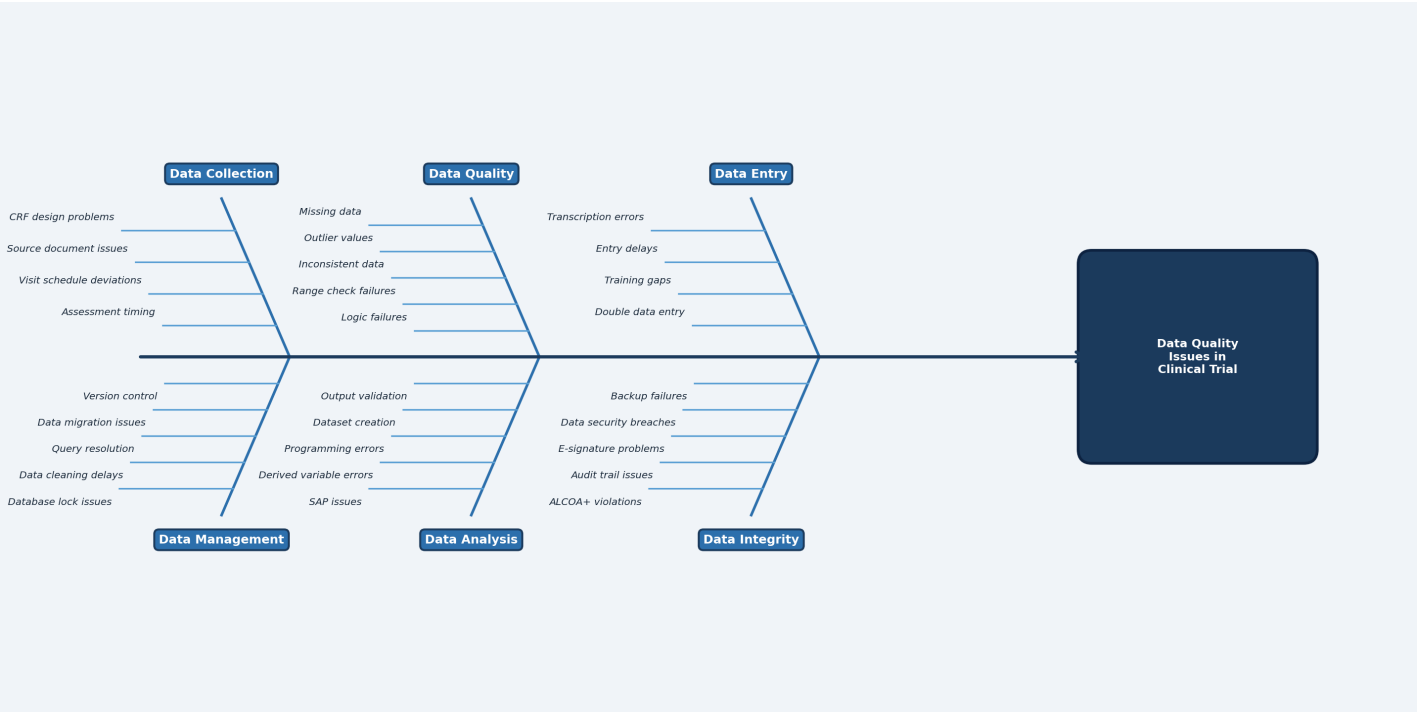
3. Step-by-Step Procedure

The following eight steps should be followed by the study team facilitator when conducting a Fishbone root cause analysis session:

1. Define and agree on the problem statement. Write it clearly in objective, measurable terms — state what is wrong, where, when, and to what extent. Avoid embedding assumptions about causes. Place this in the "fish head" box.
2. Draw the diagram spine. In a meeting or on a shared digital whiteboard, draw a horizontal arrow pointing right. Write the agreed problem statement at the arrowhead inside a box.
3. Identify major cause categories. Draw diagonal branches from the spine — these are the "ribs." Use the 6 M's as a starting point and adapt category names to your trial context (e.g., "Regulatory / Ethics," "Data Management," "Site Operations").
4. Brainstorm causes within each category. For each rib, the team asks: "Why does this happen in this category?" Record each suggested cause as a sub-branch. All ideas are captured without judgment at this stage. Causes may appear under multiple categories.
5. Drill deeper with sub-causes. For each cause identified, ask "Why?" again to uncover the underlying driver. Continue layering sub-causes until the team reaches a root level that can realistically be acted upon.
6. Challenge sparse categories. When the group runs low on ideas, deliberately revisit categories with fewer entries. Ask probing questions: "What else could contribute here?" or "Has this happened before, and why?"
7. Prioritizes root causes for action. Review all identified causes and reach team consensus on which are most likely driving the problem. Circle or highlight these. Focus corrective actions on root causes — not surface-level symptoms.
8. Assign ownership and follow up. Use a CAPA log or responsibility matrix to document each root cause, the corrective action planned, the owner, and the target date. Attach the completed Fishbone Diagram to the CAPA or deviation record.

4. Example: Data Quality Issues

This example illustrates how a study team might investigate systemic data quality failures during a clinical trial. The six cause categories reflect the main functional areas responsible for data integrity.



Problem Statement

Data Quality Issues in Clinical Trial — defined as systematic data discrepancies, missing data points, or ALCOA+ violations identified during data review or regulatory inspection, occurring across multiple sites or data collection cycles.

Cause Category Breakdown

Category	Contributing Causes
Data Collection	• CRF design problems causing ambiguous data fields • Source document inconsistencies (missing or illegible entries) • Visit schedule deviations resulting in missing assessments • Assessment timing issues relative to protocol windows
Data Quality	• Missing data due to incomplete source documentation • Outlier values not flagged or reviewed by site staff • Inconsistent data entry across sites (no standard training) • Range check failures not resolved in query management • Logic check failures in EDC validation rules
Data Entry	• Transcription errors from paper source to eCRF • Entry delays causing data lock timeline pressures • Inadequate training of site staff on EDC system • Double data entry discrepancies not reconciled

Data Management	• Database lock issues due to unresolved queries • Data cleaning delays from late query responses • Query resolution backlogs impacting timelines • Data migration errors during system transfers • Version control failures in database amendments
Data Analysis	• Statistical Analysis Plan (SAP) issues identified post-lock • Derived variable calculation errors in programming • Programming errors in analysis datasets • Dataset creation problems
Data Integrity	• ALCOA+ principle violations (data not attributable, legible, contemporaneous) • Audit trail gaps or system access anomalies • Electronic signature process non-compliance • Data security breaches or unauthorized access • Backup and recovery system failures

6. Blank Template — For Study Team Use

Use the form below to document your team's Fishbone root cause analysis. Complete the problem statement first, then work through each cause category systematically. This completed form should be attached to the relevant CAPA, deviation report, or quality event record. A fishbone template can be found on https://asq.org/-/media/public/sixsigma/tools-exchange/fishbone-cause-and-effect-diagram.xls

Field	Enter Details
Study / Protocol Number	
Date of RCA Session	
Facilitator Name	
Participants / Functions Present	
Related CAPA / Deviation Reference	

Problem Statement	*Describe the problem clearly: What is wrong? Where? When? How often? What is the measurable impact?*

Cause Category	Identified Causes (add as many lines as needed)
Manpower (People / Training)	
Methods (Protocol / SOPs / Process)	
Materials (Supplies / eCRF / IMP)	
Machinery (Systems / Technology)	
Measurement (Data / Endpoints)	
Mother Nature / Environment	

Root Cause Prioritization

After brainstorming, review all identified causes with the team and reach consensus on the most likely root causes. Record them below:

#	Root Cause Identified	Owner	Target CAPA Date
1			
2			
3			
4			
5			

Sign-off	*Facilitator signature & date:* _____ *Reviewed by:* _____

Corrective Action

Once your team identifies a root cause using a Fishbone diagram, the very next step is to **verify the root cause with data** and then brainstorm targeted corrective actions**.**