The good, the bad and the NTFs – the role of Notes to File and Protocol Deviations in audit readiness

UNC Research

Clinical Research Compliance Office
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Presenters

Objectives

By the end of the presentation, attendees should be able to identify:

- The Purpose and Intended Use of Notes To File (NTFs) & Deviation reporting
- Effective Use of NTFs
- Alternatives to NTFs
- Best Practices for NTF Content
- Best Practices for Protocol Deviations

Notes to File

Purpose and Intended Use Notes to File

Role of NTFs

NTFs document decisions, deviations, or changes not recorded elsewhere in the clinical trial.

Integration in Trial Files

NTFs become part of essential files like Trial Master File or Investigator Site File for transparency.

Usage Guidelines

NTFs should be used sparingly and are not replacements for formal regulatory documentation.

Guidance

Absence of Regulatory Guidance

No formal regulatory rules exist for Notes to File, causing inconsistent usage across and within organizations.

Risks of Misuse

Lack of standards leads to increased risk of misuse and overuse of NTFs in organizations.

Need for Internal Policies

Best practice to create internal policies and training to ensure proper NTF management and compliance.

Alignment with Quality Systems

Effective NTF frameworks should align with broader quality management and compliance systems.

Frequent Challenges

Breadcrumb Effect Risks

NTFs can reveal underlying issues during inspections, triggering deeper regulatory investigations.

Audit Findings in NTFs

Audits often find unreported deviations and may highlight a needed CAPA that was not completed hidden within excessive NTF documentation.

Regulatory Scrutiny from Overuse

Excessive NTF use attracts regulatory attention and signals process and documentation weaknesses. High NTF volumes in any studies can indicate regulatory and protocol compliance concerns.

Criteria for Appropriate Use

Characteristics of Effective NTFs

Effective NTFs are clear, concise, and properly linked to related documents in the TMF for transparency.

ALCOA-C Principles

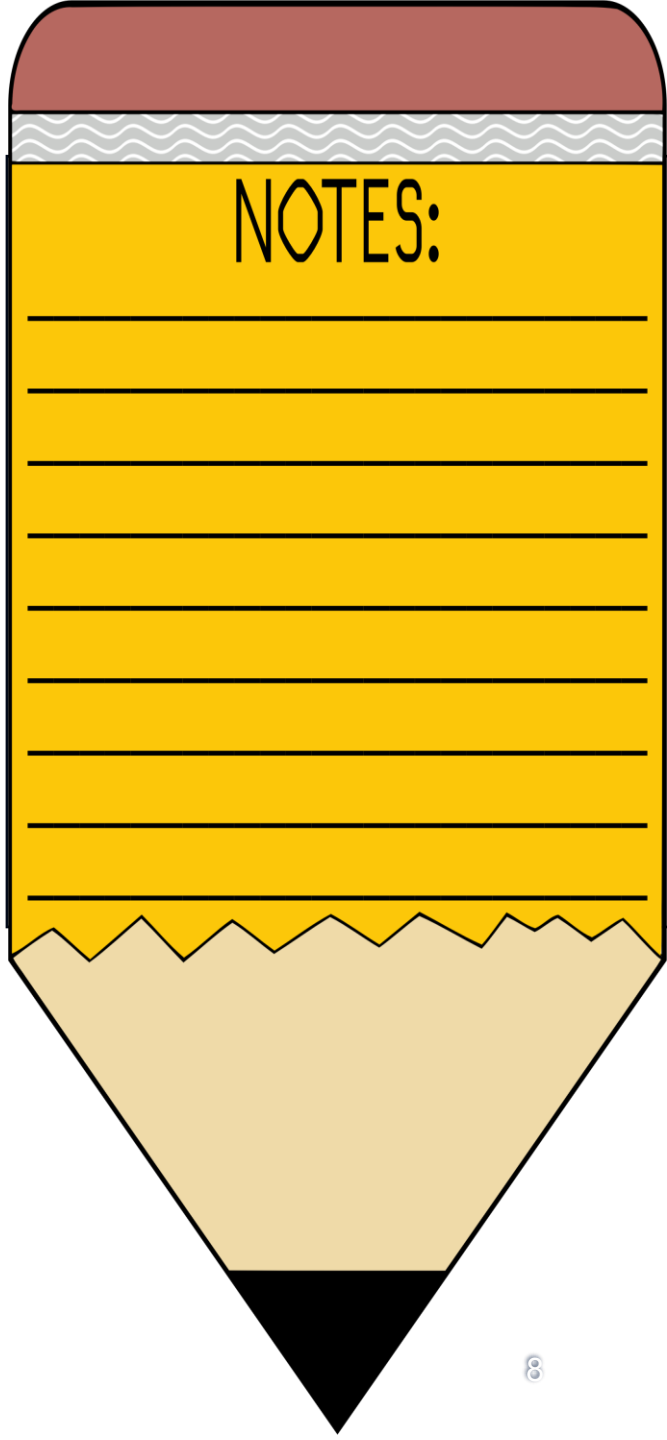
NTFs must follow ALCOA-C principles ensuring data is attributable, legible, contemporaneous, original, accurate & complete

Appropriate Use vs. Misuse

NTFs should not document protocol deviations or routine tasks.

Limited and Critical Use

NTFs are reserved for essential information where no other documentation method exists for trial understanding.



Documentation Options

Quality Event Documentation

Quality Event Documentation supports compliance and tracks process issues clearly and reliably that result from team meeting discussions.

Issue/Action/Decision Logs

Logs centralize problem tracking, actions, resolutions, and accountability for meetings and issues.

Consider Making Notes Directly on Document in Question

For example, correction and/or late entry on source documentation

Operational Manuals, SOPs & WIs

Manuals, SOPs & Work Instructions document standard operating procedures ensuring consistency and regulatory compliance.

Preventing Notes to File

Oversight and Reviews

Regular audits and reviews help identify trends and potential gaps in documentation quality.

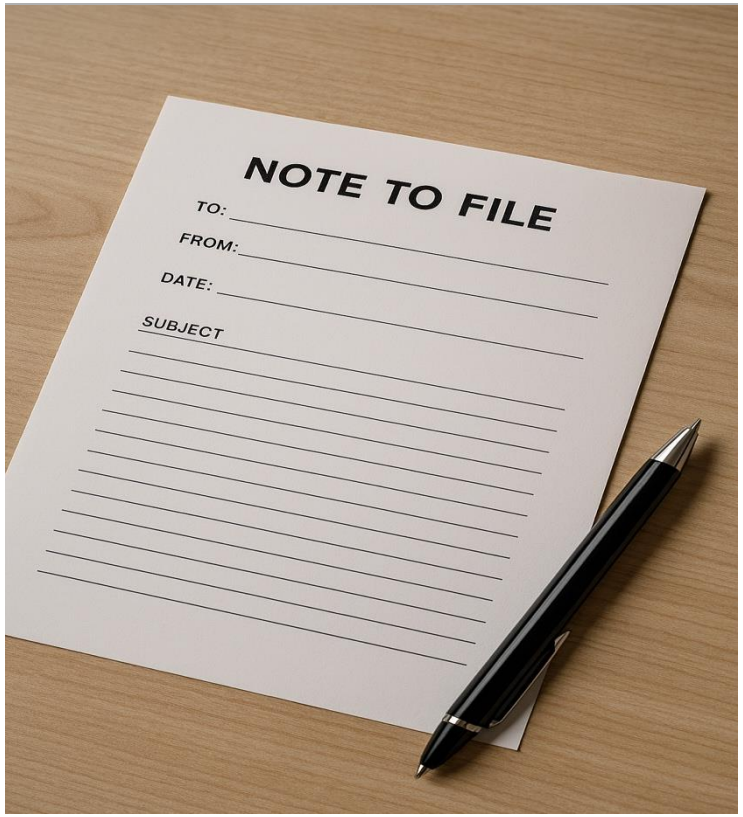
TMF Quality Checks

A TMF with oversight and Quality Control checks ensures documentation accuracy and completeness.

Training

Training site staff with clear rules and instructions prevents unnecessary NTFs and promotes better documentation.

Content of Notes To File



NTF Components

An NTF should include date, to/from fields, a short title, and a detailed body for clarity and compliance.

Detailed Documentation

The NTF body should address who, what, where, when, and why to fully document the issue and context.

Action and Resolution

Document actions taken and resolution clearly; unresolved open actions should never be left pending.

Good Note to File

Scenario & subject

- Delay in implementation of IRB approved protocol

Details:

- Outline of key dates and direction from Sponsor, including Site's actions
- Pulls information from IRB, emails

Action Taken:

- NTF filed in Regulatory binder

Linked Documents:

- IRB and Sponsor Correspondence

Bad Note to File

Scenario:

- Multiple missed visits documented only in NTFs without corrective actions.

Subject:

- Missed Visits.

Details:

- Vague statement – 'Several visits were missed due to scheduling issues.' Which visits? What issues? How many is several? Single participant or multiple?

Issues:

- No specifics, no root cause analysis, no corrective action.

Impact:

- Used as substitute for proper deviation reporting and CAPA.

Guidance for Implementation

Early Team Engagement

Engage clinical and quality teams early to ensure proper use of NTFs from study initiation.

Avoid Overuse of NTFs

Prevent NTFs from becoming a catch-all by limiting their use to necessary documentation only.

Structured Documentation Systems

Address process gaps with systems like routine reviews, logs, and manuals to ensure transparency and clarity.

Enforce Compliance and Training

Study teams must enforce standards and provide retraining to staff when misuse patterns appear.

Protocol Deviations

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The investigators should not implement any deviation from, or changes of, the protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects…
ICH GCP 4.5.2 (R2)

ICH (R3)…these are categorized into "Important Protocol Deviations" (significantly impacting subject safety/data integrity) or minor deviations.

Reporting deviations is not about assigning blame

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Protocol Deviations

Protocol Deviations

Protocol deviations involve any departures from the approved clinical trial plan regardless of cause.

Trial Integrity

Deviations can affect data reliability, participant safety, and the overall validity of clinical trial results.

“Important protocol deviations” vs “protocol deviations”

From DRAFT FDA guidance document (Dec 2024): “important protocol deviation is a subset of protocol deviations that **might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject’s rights, safety, or well-being**”

Regulatory Compliance

Timely recognition and management of deviations ensures adherence to Good Clinical Practice and regulatory standards in addition to protecting participants.

Consequences

Impact on Data Integrity

Protocol deviations can compromise data accuracy, leading to exclusion of data and reduced statistical validity.

Participant Safety Concerns

Deviations may increase safety risks and reduce intervention effectiveness for trial participants, especially for missed safety assessments.

Regulatory and Financial Consequences

Frequent deviations can trigger audits, trial suspensions, increased costs and increased workload for site staff.

Real-World Scenarios

Eligibility Deviations

Enrolling participants who do not meet eligibility criteria can compromise trial results and must be avoided.

Dosage and Testing Errors

Incorrect dosing and missed laboratory tests are common deviations potentially impacting participant safety and data quality.

Documentation and Protocol Breaches

Incomplete adverse event records and protocol non-adherence highlight need for thorough documentation and monitoring as well as oversight.

Preventive Measures

Robust training, clear communication, and proactive monitoring are essential to minimize protocol deviations.

Compliance and Oversight

Regulatory Guidelines

Authorities like FDA, EMA, and ICH set guidelines for managing protocol deviations in clinical trials.

Documentation and Reporting

Sponsors and investigators must document deviations, report promptly, and take corrective actions to ensure compliance.

Transparency and Trust

Maintaining regulatory compliance ensures transparency and trust in the clinical research process.

DOCUMENTING AND COMMUNICATING DEVIATIONS

Deviation Documentation
Accurately document the nature, cause, and corrective actions of protocol deviations for clarity and traceability.

Reporting Requirements
”important” deviations must be reported to sponsors, ethics committees, and regulatory agencies to ensure compliance and oversight per their guidelines

SOPs and Consistency
Standard operating procedures define timelines and responsibilities to maintain consistent reporting across trial sites.

Benefits of Reporting
Timely reporting ensures accountability, supports risk assessment, and promotes continuous improvement in trials while also protecting participant safety.

Deviations Done Well

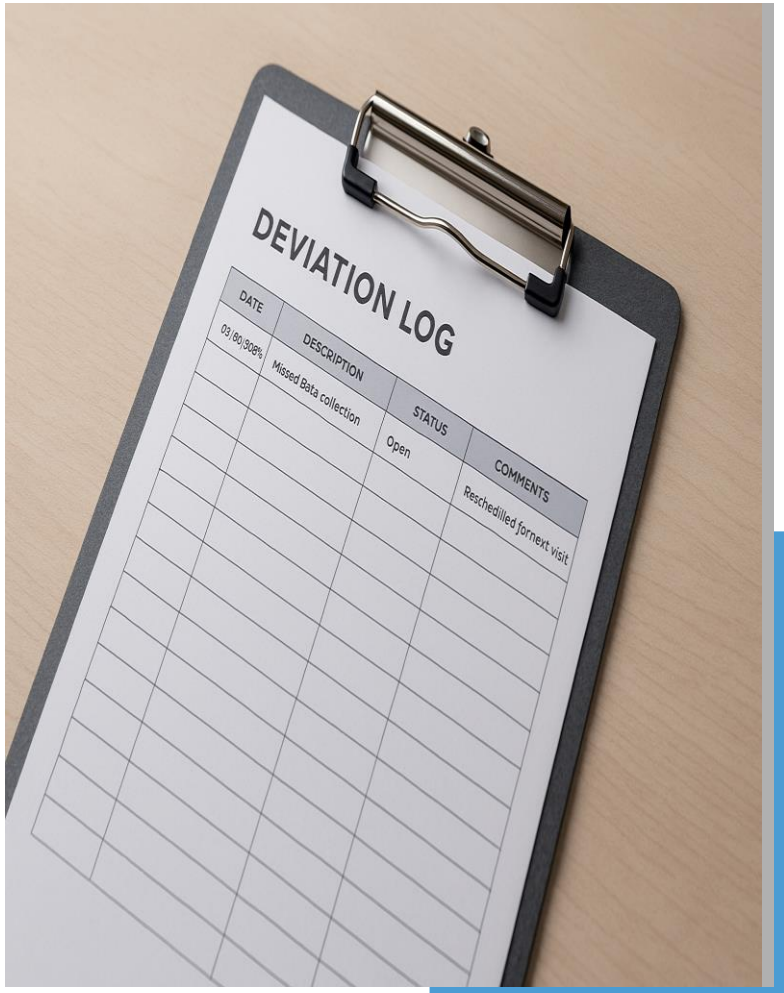
Deviation: participant visit out of protocol window

Cause: snow day

Impact to participant safety and/or data integrity: Per PI, no effect to safety or data integrity

Corrective and/or preventative action:

- **corrective action: report as deviation, reschedule visit as able, discuss with sponsor**
- **preventative action: consider scheduling visits early in protocol window to allow for rescheduling if possible, consider seeking approval for remote or video visits to decrease deviations**



DEVIATIONS DONE POORLY

Deviation: participant visit out of protocol window
Cause: snow day

Impact to participant safety and/or data integrity: not assessed by PI

Corrective and/or preventative action: none, who can control the weather?

Guidance for Protocol Deviations

Managing Protocol Deviations

Minimize impact of protocol deviations through proactive management and regulatory adherence.

Best Practices

Design practical protocols, provide training, implement monitoring, and maintain transparent reporting.

Collaboration Importance

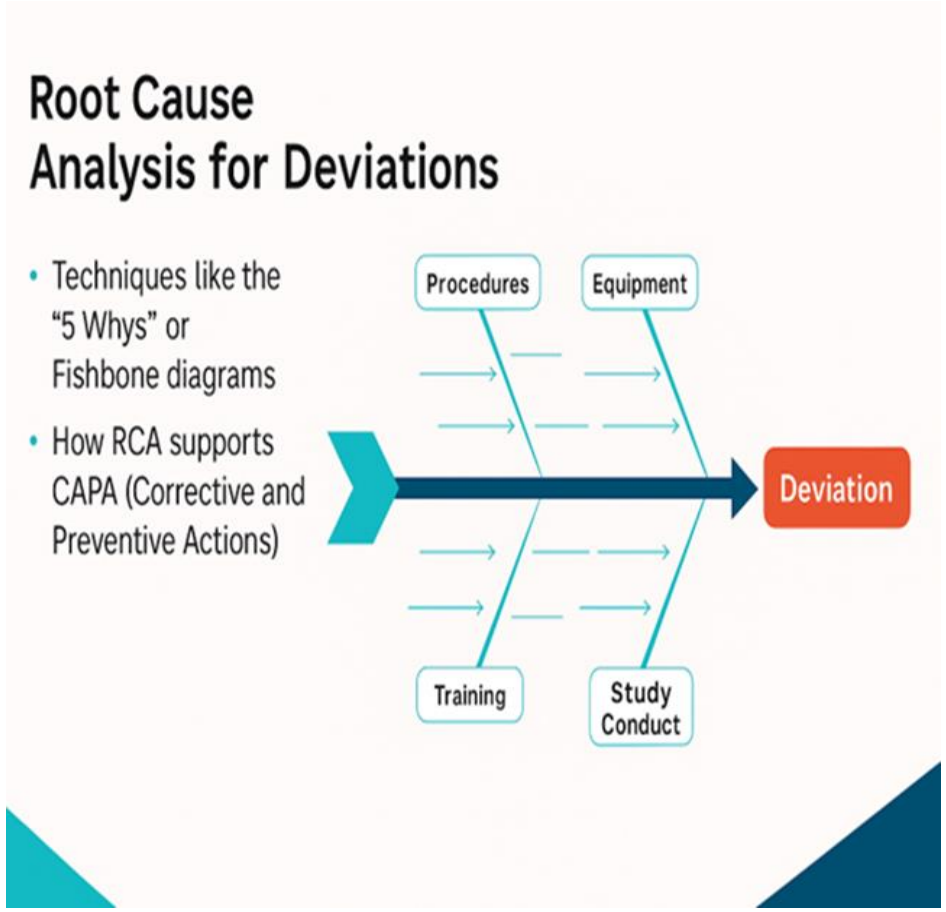
Collaboration among sponsors, investigators, and regulators ensures safety and data integrity.

Quality and Reliability

Prioritize compliance and continuous improvement to uphold high standards in clinical trials.

What do you do when things don’t go quite right

Root Cause Analysis & Corrective Action/Preventative Action



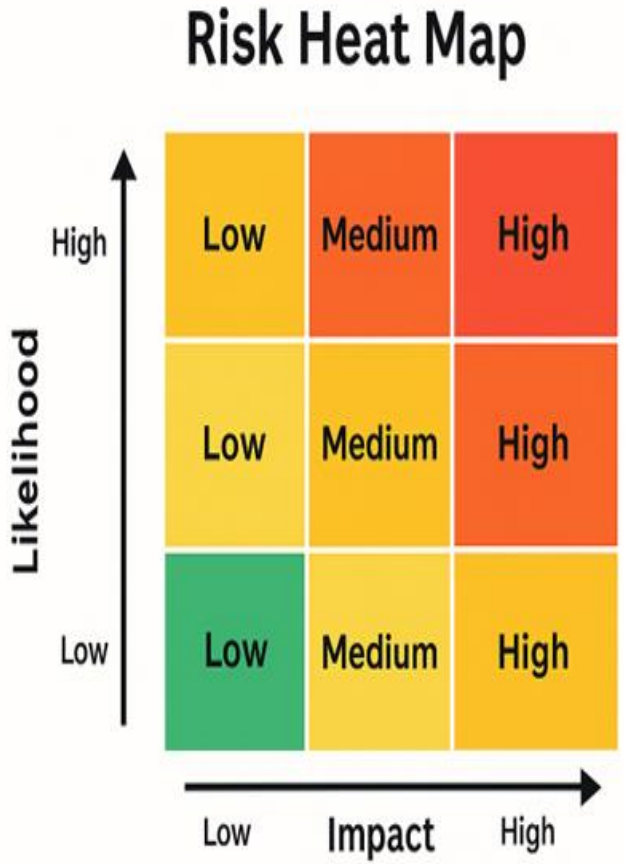
- RCAs & CAPAs work best when focusing on system problem
- CAPAs must include a timeframe for re-evaluation

Risk of Deviations

Risk Heat Map

Explanation:
The heat map evaluates risk based on Likelihood vs Impact.
Green = Low risk
Yellow = Medium risk
Red = High risk

Example:
- **High Impact & High Likelihood**: Incorrect dosing across multiple patients → Immediate CAPA required
- **Low Impact & Low Likelihood**: Minor documentation



We’re here to help!

- CTQA@unc.edu
- We can help with RCAs, CAPAs and any compliance questions you have
- We also do “friendly” audits as requested

References

- SQA Connect Lounge: Note to File for Clinical Studies: Friend or Foe

- Management of Protocol Deviation and Effective CAPA – presentation by Deepali Khandagale

- https://www.fda.gov/regulatory-information/search-fda-guidance-documents/protocol-deviations-clinical-investigations-drugs-biological-products-and-devices

QUESTIONS

Evaluation

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