

Clinical Protocol Optimization Audit

Administrative Metadata

Sponsor Name: Washington University in St. Louis

Protocol Number: DIAN-TU-001

Study Number / ID:

Protocol Drug Category: CNS / Neurology

Official Title: A Phase II/III Multicenter Randomized, Double-Blind, Placebo-Controlled Platform Trial of Potential Disease Modifying Therapies Utilizing Biomarker, Cognitive, and Clinical Endpoints in Dominantly Inherited Alzheimer’s Disease

Section 1: Executive Risk Scorecard & Corrective Action Plan

The draft protocol was cross-referenced against historical Phase 3 closures for CNS / Neurology over the past 5 years.

Rank	Category Failure Mode	Matched?	Severity	Corrective Action Plan (Steps to Avoid Failure)
#1	Caregiver/Proxy Burnout (CAR_01)	NO	—	N/A - Protocol design does not exhibit this risk factor.
#2	Screen Failure Volatility (INC_04)	YES	High	['Review and potentially revise eligibility criteria to ensure they are not overly rigid.', 'Implement a flexible screening process that allows for adjustments based on participant feedback.', 'Consider a pre-screening phase to identify potential participants before the formal screening process.']
#3	Sponsor Strategic/Financial Pivot (BUS_01)	NO	—	N/A - Protocol design does not exhibit this risk factor.
#4	Slow Accrual Cost Abandonment (BUS_03)	YES	Medium	['Establish a robust recruitment strategy to ensure timely participant enrollment.', 'Monitor recruitment metrics closely and adjust strategies as needed to avoid delays.', 'Consider incentives for sites to enhance recruitment efforts.']
#5	Loss of Commercial Viability (BUS_02)	NO	—	N/A - Protocol design does not exhibit this risk factor.

DIAGNOSTIC CONCLUSION:

Your protocol actively matches 2 of the top 5 category failure modes for CNS / Neurology. Design Risk Profile: **MEDIUM RISK.**

Section 2: Targeted Operational Assessments

2.1 Site Execution & Enrollment Friction (Coordinator Assessment)

Based on the provided protocol for the DIAN-TU-001 study, several potential areas of friction and complexity can be identified that may impact site execution, visit windows, and staff workload:

- ### 1. ****Complex Visit Windows****
- ****Cognitive Run-In (CRI) Period****: The CRI period allows for continuous enrollment but requires a minimum of 8 weeks between the last cognitive battery administration and the baseline cognitive battery for a drug arm. This could lead to scheduling challenges and delays in participant transition to treatment arms.
 - ****Multiple Visit Types****: The protocol includes various visit types (screening, entry, annual visits, and follow-ups) with different procedures and timelines. This complexity may lead to confusion among staff and participants regarding what is required at each visit.

- **Variable Timing**: The timing of visits is flexible ($\pm$ days), which can complicate scheduling and tracking for both participants and site staff, especially when coordinating multiple assessments (e.g., MRI, PET scans, cognitive tests).

2. **Staff Workload Bottlenecks**

- **High Volume of Assessments**: Each visit involves numerous assessments (clinical, cognitive, imaging, and laboratory tests). The requirement for trained personnel to conduct these assessments, especially cognitive testing, may strain staff resources, particularly at sites with limited personnel.
- **Home Health Nurse Involvement**: For participants living far from the DIAN-TU site, home health nurses are utilized for certain assessments. This adds logistical complexity and may require additional training and coordination to ensure consistency in data collection.
- **Frequent Monitoring for ARIA**: The need for regular MRI scans to monitor for ARIA (Amyloid-Related Imaging Abnormalities) adds to the workload. The protocol specifies that safety MRIs should be performed at various points, which may require additional staff time for scheduling, conducting, and interpreting these scans.

3. **Site Execution Friction**

- **Participant Recruitment Challenges**: The study targets a rare population (mutation carriers for dominantly inherited Alzheimer's disease), which may lead to difficulties in recruitment and retention, especially given the geographical dispersion of potential participants.
- **Complex Consent Process**: The informed consent process is multi-step and may require participants to review multiple consent forms (main and drug-specific). This complexity can lead to delays in enrollment and may require additional staff time to ensure participants fully understand the study.
- **Genetic Testing and Blinding**: The protocol includes genetic testing that must be conducted without disclosing results to maintain blinding. This adds an additional layer of complexity in managing participant expectations and ensuring compliance with the study design.

4. **Interim Analyses and Adaptability**

- **Adaptive Design**: The protocol allows for interim analyses and potential changes to drug arms based on findings. While this flexibility is beneficial, it may create uncertainty and require ongoing adjustments in site operations and participant management.

Recommendations for Mitigating Friction:

- **Streamlined Communication**: Establish clear communication channels among site staff, participants, and home health nurses to ensure everyone is aware of visit requirements and timelines.
- **Training and Resources**: Provide comprehensive training for staff on the protocol and procedures, particularly for cognitive assessments and ARIA monitoring.
- **Participant Engagement**: Develop strategies to keep participants engaged and informed throughout the study, especially during the CRI period, to enhance retention and compliance.
- **Efficient Scheduling**: Utilize scheduling software to manage visit timelines and ensure that all necessary assessments are completed within the required windows.

By addressing these areas, the site can improve execution efficiency and participant experience, ultimately enhancing the study's success.

2.2 Patient Burden & Attrition Vulnerabilities (Advocate Assessment)

The clinical study protocol for DIAN-TU-001 outlines a comprehensive approach to investigating potential disease-modifying therapies for Dominantly Inherited Alzheimer's Disease (DIAD). However, several aspects of the protocol raise concerns regarding patient burden, caregiver burnout, invasive testing, and travel logistics.

Patient Burden

1. **Frequent Assessments**: Participants are required to undergo a variety of assessments, including cognitive testing, MRI scans, lumbar punctures, and PET imaging. The frequency of these assessments can be overwhelming, especially for individuals who may already be experiencing cognitive decline or other health issues.
2. **Cognitive Run-In Period**: The cognitive run-in (CRI) period is designed to establish a trial-ready cohort, but it involves multiple

visits and assessments over an extended period (up to 3 years). This can lead to fatigue and stress for participants, particularly those who are asymptomatic but at risk.

3. **Complexity of Procedures**: The protocol includes a wide range of procedures that may be difficult for participants to understand and comply with, potentially leading to anxiety and confusion.

Caregiver Burnout

1. **Involvement of Study Partners**: The requirement for a study partner to accompany participants during visits can place additional emotional and physical demands on caregivers. This can lead to caregiver burnout, especially if the caregiver is also managing their own health or stressors.
2. **Time Commitment**: The extensive time commitment required for both participants and their caregivers can strain relationships and lead to feelings of frustration or helplessness, particularly if the caregiver is also balancing other responsibilities.

Invasive Testing

1. **Lumbar Punctures**: The requirement for lumbar punctures to collect cerebrospinal fluid (CSF) for biomarker analysis is invasive and may cause discomfort or anxiety for participants. This procedure is necessary for some drug arms, but it adds to the overall burden of participation.
2. **PET Imaging**: The use of PET imaging, particularly with tracers like [18F]MK-6240, involves exposure to radiation and may raise concerns about safety and long-term effects, especially for participants who may already be vulnerable due to their condition.

Travel Logistics

1. **Geographic Dispersal of Participants**: Many participants may live far from the DIAN-TU sites, necessitating travel for assessments. This can be a significant burden, particularly for those with mobility issues or those who require assistance.
2. **Home Health Nurse Visits**: While the protocol allows for some procedures to be conducted at home by trained nurses, the logistics of coordinating these visits can be complex and may not be feasible for all participants, particularly those in rural areas.
3. **Travel for Specialized Assessments**: Participants may need to travel to specialized sites for certain assessments (e.g., PET scans), which can be time-consuming and costly, further complicating their participation in the study.

Conclusion

While the DIAN-TU-001 protocol aims to advance understanding and treatment of DIAD, it is essential to consider the potential burdens placed on participants and their caregivers. Strategies to mitigate these burdens, such as reducing the frequency of invasive procedures, providing more support for caregivers, and improving travel logistics, could enhance participant retention and overall study success.

2.3 Regulatory Deviation & Compliance Liabilities (FDA Auditor Assessment)

Fuzzy Inclusion/Exclusion Rules

1. **Genetic Status**: Participants who are mutation non-carriers are excluded from the study. However, those who do not know their genetic status but are at 50% risk (e.g., children or siblings of known mutation carriers) can be included. This creates a fuzzy boundary regarding genetic knowledge and eligibility.
2. **Cognitive Status**: The inclusion criteria allow for participants who are cognitively normal (CDR 0) or have mild cognitive impairment (CDR 0.5 or 1). The distinction between these categories can be subjective, leading to variability in participant selection.
3. **Age Range**: The study includes participants within a specific age range relative to their expected age of symptom onset (EYO). The flexibility in defining this range (e.g., -10 to +10 years for secondary prevention) may lead to inconsistencies in participant eligibility.

Adaptive Unblinding Risks

1. **Genetic Disclosure**: Participants may choose to remain blinded to their genetic status, which poses a risk of unblinding if they later learn their status through other means. This could affect their participation and the integrity of the study.
2. **Interim Analyses**: The protocol allows for interim analyses that could lead to early termination of drug arms based on biomarker results. If participants are aware of their treatment assignment during these analyses, it could bias their responses and affect the study's outcomes.
3. **Placebo Group Dynamics**: The inclusion of mutation-negative participants in the placebo group to maintain blinding regarding genetic status could lead to complications if their status is revealed, impacting the study's blinding integrity.

Potential GCP Compliance Flags

1. ****Informed Consent Process****: The complexity of the informed consent process, especially with multiple drug arms and the potential for two-step consent, may lead to confusion among participants. Ensuring that all participants fully understand the consent forms is crucial for GCP compliance.
2. ****Adverse Event Reporting****: The protocol outlines specific criteria for reporting adverse events (AEs) and serious adverse events (SAEs). Any failure to adhere to these reporting requirements could raise compliance issues.
3. ****Monitoring and Auditing****: The protocol emphasizes the need for regular monitoring and auditing of participant data. Any lapses in this process could lead to compliance issues, especially if adverse events or protocol deviations are not documented appropriately.
4. ****Data Handling and Record Keeping****: The requirement for accurate and timely data entry into the electronic case report forms (eCRFs) is critical. Delays or inaccuracies in data handling could lead to compliance flags during audits.

Summary

The DIAN-TU-001 protocol presents several complexities that could impact compliance with GCP guidelines. The fuzzy inclusion/exclusion criteria, risks associated with adaptive unblinding, and potential compliance flags related to informed consent and adverse event reporting must be carefully managed to ensure the integrity of the study and the safety of participants. Regular training and monitoring of site staff, along with clear communication with participants, will be essential in mitigating these risks.