Excellence In Peripheral Artery Disease Thrombin Receptor Antagonist Intervention In Claudication Evaluation *(XLPAD-TRACE Trial)*

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Protocol training v3.0 1-30-17

Outline

- Study protocol training
- Good clinical practice requirements for the study

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Rationale

- Antiplatelet agents have demonstrated a modest improvement in claudication free walking distance, however these effects have not been replicated in rigorously conducted RCTs[1]
- Clopidogrel has not been shown to be superior to aspirin alone in improving walking distance in patients presenting with intermittent claudication (IC)[2]
- However, blocking protease- activated receptor-1 (PAR1) with vorapaxar has recently been shown to reduce the need for revascularization in patients with PAD on background antiplatelet therapy, albeit with increased rates of moderate and severe bleeding[3]

[1]Banerjee et al. Curr Opin Cardiol 2015; [2]Singer et al. J Am Heart Assoc 2012
[3]Bonaca et al Circulation 2013

Rationale & Hypothesis

- These findings confirm for the first time that limb events are likely thrombotic in nature and are potentially modifiable by anti-platelet and/or anti-thrombotic agents
- However, the effect of vorapaxar on walking distance in patients with IC remains unexplored
- **Hypothesis:** We hypothesize that addition of vorapaxar to daily background antiplatelet therapy (APT), in patients with established PAD and IC would lead to an improvement in patient IC symptom status

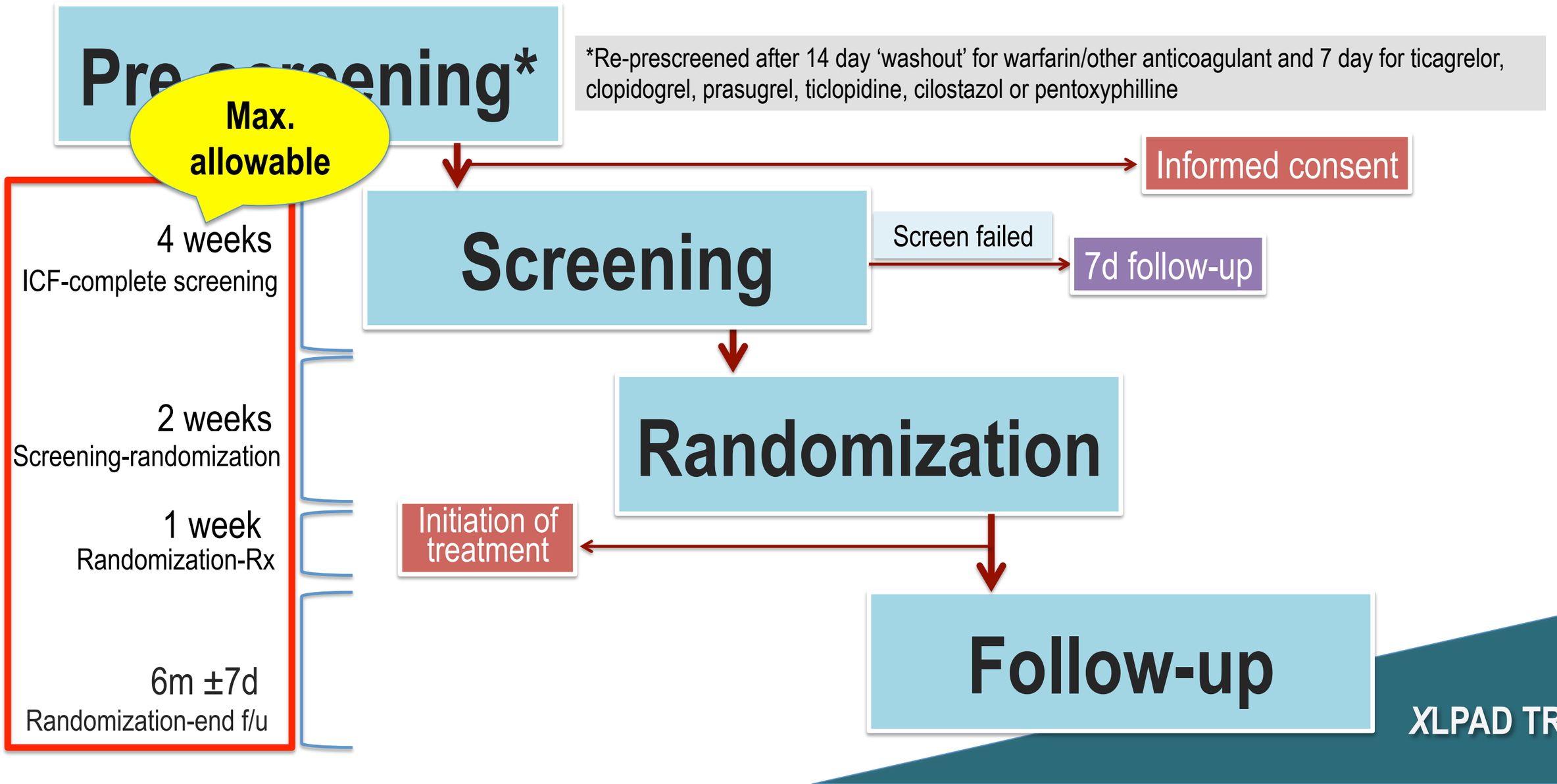
Study Objectives & Endpoints

- **Primary trial objective:** To evaluate whether addition of daily vorapaxar 2.08 mg vs. placebo on background APT for 6 months to patients with PAD & IC treated with standard medical therapy (SMT) would lead to an improvement in the peak walking time (PWT)
  - **Primary endpoint:** Change from baseline to 6 months in the PWT on a graded treadmill test (GTT per Gardner protocol) between participants enrolled in the test and control arms
  - **Secondary endpoints:** Change from baseline to 6 months in the claudication onset time (COT) on GTT; walking impairment questionnaire distance scores (WIQ) and self-reported quality of life score using the Medical Outcomes Study 12-Item Short form survey (SF-12)
  - **Tertiary endpoints:** The first occurrence of (a) clinically indicated lower extremity endovascular or surgical revascularization procedure; (b) all-cause death, MI, ischemic stroke; (c) severe bleeding defined according to the GUSTO classification during the entire study duration post- randomization

Study Design & Methods

- **Study design:** Multicenter, double blind, phase 4, placebo controlled RCT
- **Study participants:** Participants can be identified through referrals from primary care, ambulatory care, cardiovascular and vascular surgery clinics, referral from general internal medicine, hospitalists, cardiology and vascular surgery services or by patient self-referral to the research team or to providers participating in this clinical research study
- **Background APT:** At least one aspirin dose within 5 days prior to randomization at 325 mg dose in aspirin naïve patients or at 81 mg dose in patients on chronic (within 5 days) aspirin
- **Standard medical therapy (SMT):** Presence of any two of the listed classes of agents (ACEI, ARB, statin and beta-blocker drugs + ability to perform at least 15 min of home walking a day, at least 3 times/ week, at ≥20 steps/min)
- **Test arm:** Vorapaxar 2.08 mg/d + background APT + SMT
- **Control arm:** Placebo + background APT + SMT

Study Design & Methods: 4 Steps



XLPAD TRACE

Study Design & Methods: 4 Steps

Pre-screening*

*Re-prescreened after 14 day 'washout' for warfarin/other anticoagulant and 7 day for ticagrelor, clopidogrel, prasugrel, ticlopidine, cilostazol or pentoxyphilline

ICF-complete screening

Record activity of 2 preceding weeks

Single step screening-randomization

Screening

Informed consent

Screen failed

7d follow-up

Randomization

Initiation of treatment

Follow-up

6m ±7d
Randomization-end f/u

XLPAD TRACE

Pre-screening Criteria*

1. Laboratory values available ≤1 year of the date of screening: hemoglobin ≥9 g, platelet count ≥50,000 mm^3 or ≤600,000 mm^3
2. No h/o stroke or TIA
3. No allergy to aspirin
4. ≥40 years of age
5. Presence of documented PAD by ABI <0.80 at rest or ≥20% drop in claudication limited exercise ABI in any limb and one of the following criteria in the corresponding limb: (a) Prior surgical and/or endovascular lower extremity (infra-renal aorta to pedal arteries) (b) Known flow-limiting stenosis (≥70%) by clinically indicated angiography, computed tomographic (CT) or magnetic resonance imaging (MRI) tests or by Duplex ultrasonography (DUS) defined standard clinical criteria
6. Documented IC Rutherford/Becker (RC) category ≥2
7. Presence of any two of the listed classes of agents: ACEI, ARB, statin and beta-blocker drugs
8. No MI or percutaneous coronary intervention (PCI) with DES within the past 11 months
9. No planned surgical or endovascular procedures for the treatment of IC for the expected duration of the study
10. No warfarin or other chronic oral anticoagulant use within the last 14d
11. No use of ticagrelor, clopidogrel, prasugrel or ticlopidine within last 7d
12. No contraindication(s) to the use of antithrombin or APT (history of intra- cerebral hemorrhage or ICH, presence of intracerebral mass, recent or <12 weeks gastrointestinal bleed requiring blood transfusion, any blood transfusion within the last 6 weeks, any trauma requiring surgery within the last 4 weeks or any surgical or endovascular procedure ≤4 weeks
13. No use of cilostazol and/or pentoxyphilline within last 7 days
14. Severe psychiatric or behavioral illness that in the judgement of the investigator precludes study participation
15. No h/o major or minor lower extremity amputation
16. Severe heart, vascular and lung disease in the discretion of the investigator that precludes study participation
17. Ability to walk for at least 15 min/day, at least 3 days/week, at ≥20 steps/min

*Re-prescreen after 14 day ‘washout’ for warfarin and 7 day for ticagrelor, clopidogrel, prasugrel, ticlopidine, cilostazol or pentoxyphilline

Screening: ICF-Completion (4 weeks)

Completion of all of the following screening procedures in any order:

1. A 2-week monitored home walking (MHW) regimen (at least 15 min/day, at least 3 days/week, at ≥20 steps/min, documented using a patient diary
2. History & physical (H&P)
3. GTT: Patients will undergo two treadmill tests within at least 1 hour or a maximum of 2 week from the first, and the longer of the 2 PWTs will be selected as baseline if the PWTs recorded at baseline are within 30% of each other. A third GTT could be performed if the prior GTT derived PWTs vary by >30% of each other. The highest of all performed GTT will serve as the baseline value. Patients on background pentoxyphyline or cilastazol should discontinue the drugs prior to baseline GTT testing. These drugs will remain discontinued up until completion of the 6- month follow-up GTT.
4. Laboratory values available ≤1 year of the date of screening: hemoglobin ≥9 g, platelet count ≥50,000 mm^3 or ≤600,000 mm^3
5. Ankle brachial index (ABI) assessment
6. WIQ
7. SF-12

Randomization: ≤2 weeks of Screening (1:1)*

Meet all inclusion and none of the exclusion criteria:

Inclusion criteria	Exclusion criteria
Treadmill PWT= 2-10 min on Gardner protocol	MI or percutaneous coronary intervention (PCI) with DES within the past 11 months
Estimated survival ≥1 year in the judgment of the site investigator	Positive pregnancy test
At least one aspirin dose within 5 days prior to randomization at 325 mg dose in aspirin naïve patients or at 81 mg dose in patients on chronic (within 5 days) aspirin	Planned surgical or endovascular procedures for the treatment of IC
Presence of any two of the listed classes of agents: ACEI, ARB, statin and beta-blocker drugs	Warfarin or other chronic oral anticoagulant use within 14 days
	Contraindication to the use of antithrombin or APT (history of ICH, presence of intracerebral mass, recent or <12 weeks gastrointestinal bleed requiring blood transfusion, any blood transfusion within the last 6 weeks, any trauma requiring surgery within the last 4 weeks or any surgical or endovascular procedure ≤4 weeks
	Use of cilostazol and/or pentoxyphilline within 7 days

*Randomization to initiation of study treatment ≤7 days

Study follow-up: 6 months±7 days from Randomization

1. The trial will be considered complete with regard to the primary endpoint after all enrolled subjects have completed a 6-month follow-up evaluation, have died, have a documented premature withdrawal, or whose follow-up window at 6 month has closed with documented 3 unsuccessful attempts to contact the patient
2. Patients who discontinue study medication should be followed till the end of the study
3. Adherence to MHW for 1 week will be assessed in all patients in each study arm at 3-month ±7 days from randomization by phone follow-up
4. Follow-up phone call by a study coordinator at 90±7 days to reinforce MHW (±by reviewing of MHW diary entries), compliance with study and clinically indicated medications and determine study related adverse or severe adverse events (AE/SAE) or other pertinent medical history
5. End of study testing at 6 months from randomization should also be performed ±7 days of the scheduled date, and should include GTT, H&P, WIQ, SF-12 and study drug pill-count. Patients will be required to return all study drug bottles and remaining study drug pills at the end of study
6. End of study GTT will also include the baseline GTT regimen
7. Patients who are pre-screened will be recorded; those who are then eligible for screening and undergo successful screening procedures, however not randomized will be termed as screen failures. Participants who discontinue study participation by withdrawing consent following randomization will be termed dropouts
8. If P2Y12 agents are required during the study period from randomization to final 6 month GTT, clopidogrel is the preferred agent in this class for study participants

Study follow-up Scheme: 6 months±7 days from Randomization

Test	Pre-screening	Screening		Randomization	90±7 day call	180±7 day visit
		Enrollment	Baseline tests			
Pre-screening criteria	X					
Screening criteria		X				
Inclusion/exclusion				X		
Informed consent		X				
H&P			X			X
Rutherford category			X			X
GTT			X			X
ABI			X			X
WIQ			X			X
SF-12			X			X
MHW assessment			X			X
Dispense study drug				X		
Medication compliance					X	X
AE/SAE assessments			X		X	X

Recruitment

- Study sample size=200
- Sites: Up to 20 U.S. sites
- Expected randomized patients: 1.7 patients per site per month
- EDC: IMEDNet (online data entry and study management portal, except for study drug management; separate training)
- Rigorous f/u to avoid drop-out & perform only clinically necessary revascularization
- HIPPA authorization in addition to ICF, where necessary
- Monthly study site teleconferences (till completion of requirement); q2 monthly thereafter
- Coordinating site business/emergency contact phone numbers

AE/SAE

- Adverse event (AE) and serious adverse events (SAE) will be collected and reported to the local IRB and study coordinating center IRB from enrollment to completion
- Causal relationship to the observed AE or SAE to the study drug will also be collected and reported
- Data safety monitoring board (DSMB) will review all AEs and SAEs
- Risk-based monitoring (at least 1 site visit to 75% of enrolling sites)
- Independent DSMB & CEC

Study Drug Handling

- All study drugs (active drug/matched placebo) must be accounted for and tracked on a paper log provided for the study: from time of initial receipt through dispensation and final disposal/return of leftover study drug
- Accountability log should indicate the date received and dispensed, kit number(s), and amounts dispensed to the participant, amounts, and condition of materials returned/ destroyed/disposed by the participant
- Prior to dispensing, the PI, study site pharmacist or study coordinator trained on the study protocol will be responsible for ensuring that the participant has been properly consented, enrolled, instructed and a written prescription order for the drug is signed by the PI
- **Unblinding:** Unblinding of participant treatment assignment can be made by calling the coordinating center business/emergency phone number

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PI Commitments: Investigator Qualifications and Agreements

- Properly qualified to assume responsibility for conduct of the study
- Thoroughly familiar with the investigational product (IP), and its appropriate use
- Willing to comply with GCP and applicable regulations and be prepared for audits and monitoring
- Maintain a Delegation of Responsibilities log

PI Commitments: Medical Care of Trial Participants

- Ensure that all trial-related medical decisions are made by an investigator who is a qualified physician
- Provide adequate medical care for participants who experience adverse events
- Notify the participant's primary physician of his/her participation (as appropriate)
- Make an effort to learn why participants withdraw

PI Commitments: Communication with the IRB/IEC

- Obtain written approval before the study begins
- Provide the IRB with the current package insert
- Provide the IRB/IEC with all documents subject to its review throughout the trial

PI Commitments: Compliance with the Protocol

- Conduct the trial in compliance with the protocol
- Deviate only with agreement from the sponsor and prior review/ approval from the IRB/IEC or unless medically necessary to provide clinically indicated patient care
- Document and explain all deviations

PI Commitments: Investigational Product (IP)

- Responsible for the product, its usage, and its storage
- May delegate to a Pharmacist under the PI's supervision
- Maintain IP records
- Store as specified by the sponsor and in accordance with applicable regulatory requirement(s)
- Use IP in accordance with the protocol

PI Commitments: Randomization & Unblinding

- Follow the study randomization procedures
- Ensure that the randomization code is only broken in accordance with the protocol
- Promptly document and notify the sponsor of any unblinding (for blinded trials)

PI Commitments: Informed Consent

- Adhere to GCP and the ethical principles that have their origin in the Declaration of Helsinki
- Update consent document when new information becomes available
- Avoid:
  - Coercion or undue influence
  - Language that causes the participant to waive any legal rights
- Fully inform participant of all pertinent aspects of the trial
- Use understandable language (8th grade reading level)
- Provide enough time for participants to review consent & ask questions

PI Commitments: Informed Consent

- Essential elements of an informed consent include:
  - Number of subjects involved in the study
  - Description of risks, benefits, and alternatives
  - Information about compensation/care for injury
  - Statement regarding confidentiality of records
  - Description of possible unforeseen risks
  - Circumstances for termination without subject consent
  - Consequences of withdrawing from the study
  - Statement that new research findings will be shared
  - Contact information for questions/concerns

PI Commitments: Records and Reports

- All changes to a CRF/source doucments must be dated and signed such that the original data is not obscured
- Retain essential documents for at least 2 years after the last approval of a marketing application
- Provide monitors, auditors, IRB/IEC, or regulatory authorities with direct access to trial records
- Record and report AE/SAE(s) thoroughly
- Make records available to monitors, auditors and inspectors
- Longest requirement should be followed for record retention if study or institutional requirements vary

PI Commitments: Essential Documents

- Investigator of Record (IoR)
- CVs for PI and Sub-Investigators
- Licenses, as appropriate
- Training records for all study personnel
- Protocol/amendment signature page and Financial Disclosures
- IRB membership list or roster
- IRB approvals – of protocol, consents, ads, handouts
- Communication – with IRB, sponsor, if applicable

PI Commitments: Progress Reports to Sponsor/ IRB/IEC

- Submit a written report at least annually and in accordance with the IRB's request
- Submit a written report if there are changes that might significantly change the conduct of the trial and/or increase risk to subjects

PI Commitments: Safety Reporting

- Immediately report all SAEs to the sponsor*; follow-up with a written report

  EXCEPTION: SAEs identified in protocol as not requiring immediate reporting

- Identify study participants using codes rather than personal identifiers
- Comply with applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority(ies) and the IRB/study coordinating center*

*Sponsor/coordinating center: Dallas VA Research Corporation

PI Commitments: Safety Reporting

- Report AE/SAEs and/or lab abnormalities critical to safety evaluations to the coordinating center per protocol
- Provide the sponsor and IRB with additional requested information
  - Autopsy report in the event of a death
  - EKG or other supporting documentation

PI Commitments: Premature Termination or Suspension of a Study

Condition	Notify
Study terminated/suspended	All participants
PI terminates study	Institution, sponsor, IRB*
Sponsor terminates study	Institution, IRB*
IRB terminates study	Institution, sponsor*

* *Notify in writing*

PI Commitments: Final Report(s)

- At study completion, the investigator should provide:

Documentation	Provided to
Notification of study completion	Institution*
Summary of the trial's outcome	IRB/IEC
Any required report(s)	Regulatory Authority(ies)

**Where applicable*

Examples of Common Non-Compliance

- Insufficient evidence of Investigator involvement/oversight
- No documented delegation of responsibility/scope of work
- Failure to adhere to protocol requirements
- Inadequate source documents
- Changes made to original records without audit trail of when, why, by whom
- Failure to report AEs/SAEs appropriately
- Participants not signing most current version of consent form
- Inadequate product accountability records

Resources

- Electronic Code of Federal Regulations
  - http://www.ecfr.gov/cgi-bin/text-idx?c=ecfr&tpl=%2Findex.tpl
- Office for Human Research Protections (OHRP)
  - http://www.hhs.gov/ohrp/
- ICH E6 Guideline
  - http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline.pdf