Guidance for Investigators
Subject Recruitment & Retention

Meeting of Investigators supported by the NHLBI Clinical Trials Planning Studies for Rare Thrombotic and Hemostatic Disorders (U34) program

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1. Getting Started
   - Guidelines and Regulations – International Conference on Harmonisation (ICH), FDA, NHLBI, AccrualNet™

2. The Recruitment Plan
   - Benchmarks
   - Strategies
   - Barriers to participation & subject withdrawal

3. Recommendations

4. References
The Investigator should be familiar with both International Conference on Harmonisation\(^1\) and FDA guidelines for Good Clinical Practice and human subject protection.

The Investigator should understand and apply the NIH/NHLBI guidelines and procedures for recruitment and retention.
International Conference on Harmonisation

Good Clinical Practices

**Purpose of ICH:**

Unify standards to facilitate mutual acceptance of clinical data by regulatory authorities ...

Establish ethical and scientific quality standards for protection of human subjects

Sections Covered by GCP:

- Institutional Review Board (IRB)
- Sponsor
- Protocol
- Regulatory Documents
- **Investigator**
Investigator Responsibilities Under GCP

- **Education and Experience**
  Commensurate with disease process studied

- **Comply with GCP**
  Human subject protection

- **Complete FDA 1572** (if applicable)
  Investigator Agreement (Form 1572\(^2\) and 1572 Guidance\(^3\))

- **Adequate Resources**
  Institutional support, appropriate personnel, etc.

- **Medical Care**
  Appropriate care available

- **Communicate with IRB**
  Submission and approvals, reporting obligations, etc.

- **Comply with Protocol**

- **Other**
The Code of Federal Regulations (CFR) is an annual collation of guidelines and rules that are published in the Federal Register. Title 21 (food and drug) and Title 45 (human subject protection) contain information that is essential for conducting clinical trials.

**Title 21 Part 50 - Human Subject Protection**
- FDA regulated trials, requirements of informed consent, vulnerable populations (employees, prisoners, pregnancy, fetuses & neonates, children, etc.)

**Title 21 Part 56 – Regulations & Guidelines for IRB**
- IRB organization, membership, and function

**Title 45 Part 46 – DHHS Protection of Human Subjects**
- IRB functions, operations, and records, etc.
NHLBI Guidelines

- All studies for which the success of the overall grant or contract depends on the timely recruitment of human subjects should have accrual monitoring plans.

- Principal Investigator (PI) and Institution Business Official (BO) will receive a letter reminding them of NHLBI’s milestone accrual policy.

- Thirty days to provide policy.
Investigator develops recruitment plan with benchmarks (may collaborate with NHLBI)

NHLBI review of benchmarks and compatibility with the budget

Not uncommon for request for revisions

Investigator attaches recruitment plan to the proposal submission

Failure to submit the plan will likely delay the approval of NHLBI funding
NHLBI GUIDELINES

NHLBI will review recruitment & retention 25%, 50%, and 75% of the projected recruitment period

Suboptimal Performance Zones\textsuperscript{7}:

\textbf{Yellow Zone: accrual > 75% but less than 100%}

NHLBI may increase monitoring frequency and may request a corrective action plan realistic enough to meet enrollment criteria by end of enrollment period.
**Amber Zone** - accrual is <75% but still at or above the minimally acceptable levels.

The investigator may be required to submit an analysis of recruitment, identified barriers, and an associated corrective action plan. The NHLBI may also request a budget review.

**Red Zone** - accrual is below minimally acceptable levels:

- <25% of the benchmark at the 25% time point OR
- <25% of the benchmark at the 50% time point OR
- <50% of the benchmark at the 75% time point

NHLBI will consider restricting, withholding or discontinuing funds.
Investigators applying for or having been approved for NHLBI funding are required to establish and monitor adherence to recruitment benchmarks.

**Failure to meet recruitment benchmarks may lead to withholding or permanent discontinuation of funding.**
Previous presentation demonstrates the value of alternatives to the standard two arm RCT
Recruitment

- Review Preparatory to Research (RPR)
- Networking
- Advertisements
- Informed Consent
- Understanding Barriers
RECRUITMENT PLAN

Review Preparatory to Research (RPR)

Method to identify prospective study subjects prior to commencement of study enrollment. This may help Investigators to get a “head start.”

With IRB approval, the Investigator may use the RPR to review patient information to evaluate inclusion/exclusion criteria, disease history, etc.

Patient information obtained during this review must be destroyed once eligibility is determined. This information may not be used for any data to be collected for purposes of the research study.
RECRUITMENT PLAN

Networking
- Others interested in the disease to be studied
- Find resources to conduct the clinical research
- Professional associations
- Attend conferences and conventions

Advertisements
Investigators may or may not find advertisements to be helpful for the study of rare hematological diseases. If used, it is important for the Investigator to understand the regulations regarding advertisement for research, such as:
- Information that may be included
- Where and how the advertisements displayed
- IRB approvals
RECRUITMENT PLAN

Highlights of Recruitment Plan:

1. Determine Investigators role in recruitment
2. Evaluate feasibility of sample size and Availability of eligible participants
3. Establish referral sources and networking
4. Establish Benchmarks
5. Determine Strategies
6. Begin Enrollment
7. Evaluate effectiveness of recruitment and retention metrics
8. Adjust and implement recruitment & retention efforts accordingly
Understanding Barriers to Research
Important in order to proactively reduce or eliminate impact from some of the following:

- Belief that standard therapy is best
- Lack of awareness of clinical trials
- Fear, distrust, suspicions, apprehensions, and skepticism
- Individual values and beliefs
- Logistical barriers
- Socioeconomic barriers
RECRUITMENT STRATEGIES: NETWORKING

- Accessing, Assessing and Utilizing Patient Databases
- Keeping Patients Informed and Engaged
- Partnering with Patient Support Groups
Staff in specialty clinics crucial resource
Their relationship with patients can help
Buy in from them on the benefits of the proposed trial important
Their access to patient data bases is invaluable
Clinic patient database can be used
  to flag patients who may be recruit-able based on age, disease stage and / or stated interest in participating in trials
  Identify patients who have expressed interest in trials that address a specific research question
  Identify referring physicians and informing them about a prospective trial
“Top recruitment strategy for trials with rare disease” (DeWard et al. 2012)

- Make discussion of clinical studies routine part of clinic visit
- Using IRB/REB approved materials (flyers, letters, emails, web postings) or add a “Research Corner” to newsletter to keep patients aware of current trials
- Live events to bring patients, especially those who have not been seen for a while, into clinics to talk about current thought and research directions
NETWORKING: PATIENT SUPPORT GROUPS

- Regular engagement with national and local support groups
- Developing educational materials about the trials and distributing to support group
- Social Media – Advocacy groups using social networking more and more. Some success stories of the use of social networking to recruit patients
- For profit organization [http://www.patientslikeme.com/](http://www.patientslikeme.com/) maybe a useful resource to identify patients
PLEASE NOTE..

Regardless of the recruitment strategy ...

The Investigator (or any research study staff) **may not** approach a prospective subject until the research study is “introduced” to that patient by a member of his or her health care team.
STRATEGIES FOR RETENTION

- Assess Patients ability to participate
- Logistics & Support
CRUCIAL FIRST STEP: ASSESSING PATIENT’S ABILITY TO PARTICIPATE

- Consent Process - An opportune time to begin relationship building between the study staff and the study subject. May result in better study compliance and higher retention rates.
- Review the requirements of the trial and ensure feasibility
  - Number of assessments
  - Duration
  - Timing of Clinic Visits (frequency & length)
- Identify potential obstacles
  - Transportation – sponsors sometimes provide funds or there maybe help from support groups
  - Child Care – Try to arrange based on convenience of childcare or identify resources such as support groups to pay for
  - Travel / Vacation logistics – plan ahead for sample collection / mailing etc.
Letters to employers or schools to explain the importance of the patient’s participation in the study

Determine whether family dynamics are a barrier to participation and attempt to help resolve them

Assess compliance regularly

Send reminder text message or email on day before visit

Ensure timely reimbursement to subjects
AccrualNet™8

The National Cancer Institute’s resource for the process of recruiting and retaining participants to clinical trials

- Integrating recruitment & retention during protocol design
- Guidance for selecting investigative site
- How to maximize enrollment and retention

Subject accrual, recruitment & retention are an integral parts of the protocol lifecycle

(https://accrualnet.cancer.gov/)
RECOMENDATIONS

1. Review and apply regulatory guidelines and regulations (e.g., ICH GCP, FDA, IRB)
2. Understand and follow the NHLBI requirements
3. Submit a recruitment plan with the proposal
4. Use AccrualNet™ as a source for information
5. Be creative with recruitment techniques or strategies.
REFERENCES


