

Using Milestones to Drive Progress in Clinical Trials An NHLBI Perspective

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Disclosure

- These views are those of the presenters and do not represent official NHLBI or NIH positions

Milestones: An NHLBI Perspective

- Challenge
 - NHLBI trials not finishing on time or within budget
 - Expectations not clear among stakeholders
- Solution
 - NHLBI is undertaking a comprehensive assessment and overhaul of how we manage clinical trials
 - Using standard performance-based milestones
 - Linking funding to performance

Milestones: An NHLBI Approach

- Define critical clinical trial activities
 - Key elements that will ensure trial functions efficiently and effectively
- Work with investigators to develop standard processes to assess trial progress
- Mutually agree to clear deliverables

Effective Milestones

Linked to Time and Consequences

Milestone	Potential Consequences of Missing Milestone
<ul style="list-style-type: none">• Specific number of sites activated by specific date	<ul style="list-style-type: none">• Linked to future funding
<ul style="list-style-type: none">• Achievement of enrollment targets at specific time-points	<ul style="list-style-type: none">• Triggers NHLBI review, potential corrective action plan, study close-out
<ul style="list-style-type: none">• Third party agreement executed by specific date	<ul style="list-style-type: none">• Linked to future funding
<ul style="list-style-type: none">• Data quality standards met on a regular basis	<ul style="list-style-type: none">• Triggers site visit, linked to future funding

Weak Milestones

Lack Specifics

- Measures too much or too little
 - Number of site audits without a denominator
- Measures useless data
 - Screening numbers vs. screening/enrollment ratio
- Time points not well defined
 - At trial initiation, what defines “start”?
 - Number of sites not enrolling vs. not enrolling within last 30 days

REPRIEVE – Case Study

- Tests efficacy of pitavastatin to reduce major adverse cardiovascular events in HIV-infected subjects with ASCVD Risk Score $< 7.5\%$



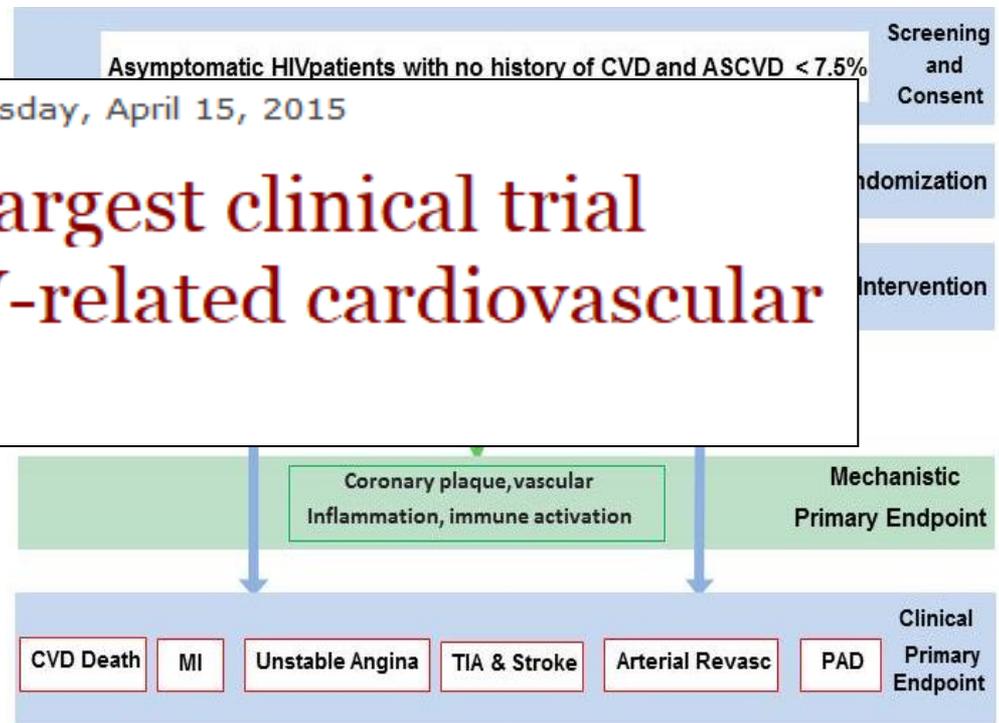
Randomized Trial to Prevent Vascular Events in HIV

- Enrollment 10/1/17
- PI: Grinberg, MGH

For Immediate Release: Wednesday, April 15, 2015

NIH launches largest clinical trial focused on HIV-related cardiovascular disease

- Partnership with NIAID & AIDS Clinical Trials Group (ACTG), Kowa donating study drug & placebo



Trial start up: Using Milestones to Drive Progress



Randomized Trial to Prevent Vascular Events in HIV



- **2015 Award Requires Completion of 2014 Milestones**
 - **In ~8 months most critical start-up activities completed**

Milestones

Key Elements Critical to NHLBI

Study Phase	Milestone
Study Start-Up	IRB approval of DSMP prior to award or enrollment
	IND/IDE approved prior to award
	Third-party agreements signed prior to award
	DSMB protocol approval within specified months of award
Study Conduct	“Ready to recruit” by specific date
	Enrollment completed by specific date
	% retention (based on study power) at time points
	% data completeness at agreed upon time points
	ClinicalTrials.gov registration by required time point
Study Close-Out	Database lock by specific date
	Publication within 12 months of study completion
	Timely close-out within 120 calendar days

Milestones

Key Time Points Critical to NHLBI

Study Phase	Milestone Time Point
Study Start-up	Concept approved to IND/IDE approved
	Concept approved to third party agreements signed
	Grant award to final protocol DSMB approved
	Final protocol to first site open for enrollment
Study Conduct	Site open to first patient first visit
	First patient first visit to last patient last visit
	Last patient last visit to data base lock
Study Close-out	Data base lock to grant closeout
	Study completion date to publication
	Study completion date to ClinicalTrials.gov submission

Milestones

Linking Funding to Performance

- Milestones embedded in funding announcement and award notices
 - Publicly defines performance expectations
 - Communicates consequences of study milestones
 - Ensures mutual agreement to critical elements before start of study
- Phased awards with interim decision points
 - Allows for early termination of studies that are not feasible

REPRIEVE: It Takes a Village!

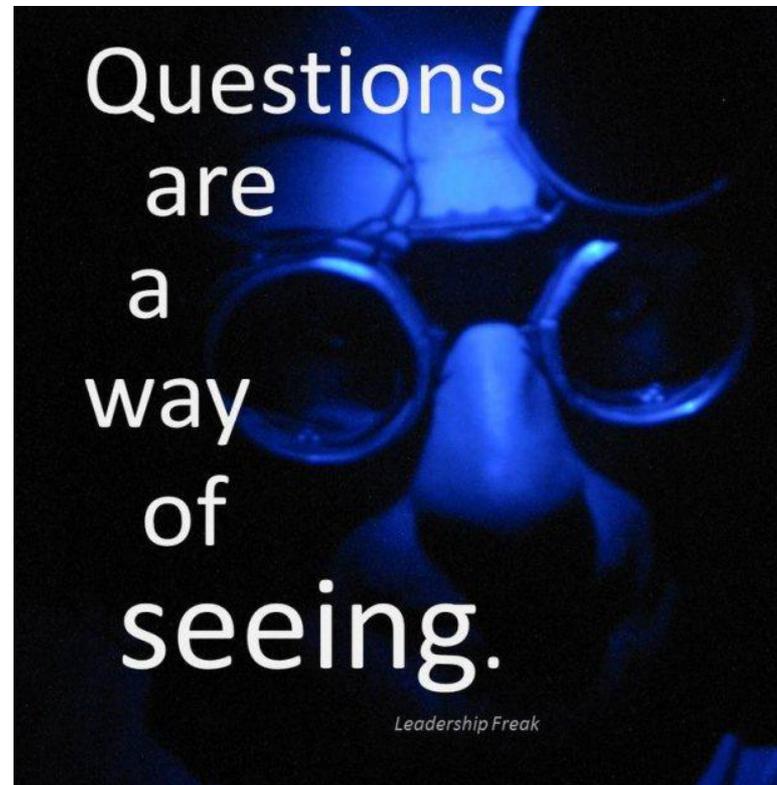


Randomized Trial to Prevent Vascular Events in HIV

NIH Team

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Questions



Q & A Back-up Slides

- Q: What is more important: doing the best science or just getting the trial done?
- A: Both are equally important: if you can't complete the trial, the science isn't done, and the results are not disseminated to the scientific and public health communities
- Q: How does milestone monitoring help manage public fund resources?
- A: Milestones allow a trial to be monitored for enrollment targets or endpoint milestones and resource usage at a frequency that allows for timely problem-solving so that:
 - (1) the trial either enrolls fully and meets its milestones in the projected timeframe or is terminated early to avoid waste of resources, and
 - (2) is ultimately published so that the findings, whether positive or negative, are available to guide future research directions

Q & A Back-up Slides

- Q: How does embedding milestones in a clinical trial Funding Opportunity Announcement (FOA) help in review?
- A: Milestones in a FOA aid all levels of application review:
 - (1) Allows for pre-review-for-responsiveness
 - (2) Enables peer review of clinical trial applications to be more rigorous by ensuring that any study section consists of appropriate clinical trial experts for trial feasibility (e.g., clinician trialists, biostatisticians, pharmacologists), as well as the basic science experts needed to evaluate the scientific rigor of any pre-clinical data provided
 - (3) Ensures that secondary review by Advisory Councils can address important NIH institute clinical research priorities.