Steady Enrollment and Optimal Metrics Can Become Reality: The Use of Key Enrollment Optimization Processes, Clinical Investigative Networks and eClinical Processes to Facilitate Cost Effective Clinical Trials

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Answers That Matter.

Agenda

Current Enrollment Environment

Enrollment Optimization

- Current Environment
- Investigator Sites
- Historic Enrollment Performance
- Acceleration Tools
- Site Performance and Selection

Clinical Investigative Networks

- Organizational Characteristics
- Model Efficiencies
- Analysis and Selection
- Development
- Key Elements

eClinical

- Distance Learning
- Document Repositories
- Secure Document Delivery
- eDM
- Process Efficiencies

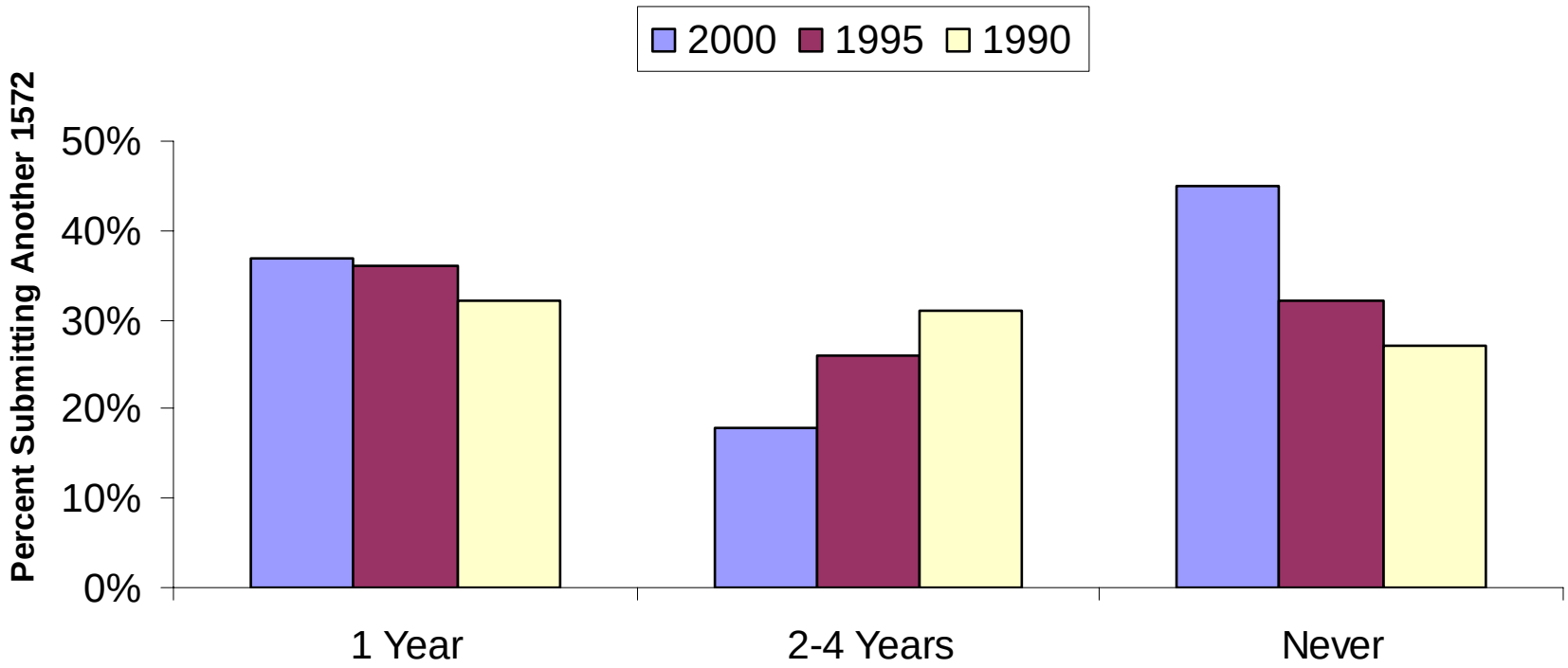
Special Considerations (Summary Points)

Q&A

Enrollment Optimization

- **Environment**
  - Increasing Development Costs
  - Limited Research Volunteers
  - Competition for Study Sites Among Study Sponsors
  - Increasing Numbers of Studies Sourced Globally
  - Decreasing Number of Investigators
  - Regulatory Expectations
    - Larger, Longer, More Complex Trials
    - Survival Data
    - Post Approval Safety Data
  - Outcomes

Decreasing Investigator Resources



***Source:** Tufts Center for the Study of Drug Development Impact Report, 7 (3) 2005*

Enrollment Projection Consideration

How do you project enrollment?

- Historic site performance
- Zero Enrolling Sites
- Comparator Studies
- External Data Sources
- Protocol Feasibility

Enrollment Projection Goals

- Avoid Straight Line Graph
- Projections represent data based decisions
- Over Enrollment Costs Prohibitive
- Under Enrollment may Jeopardize the Study and add Costs

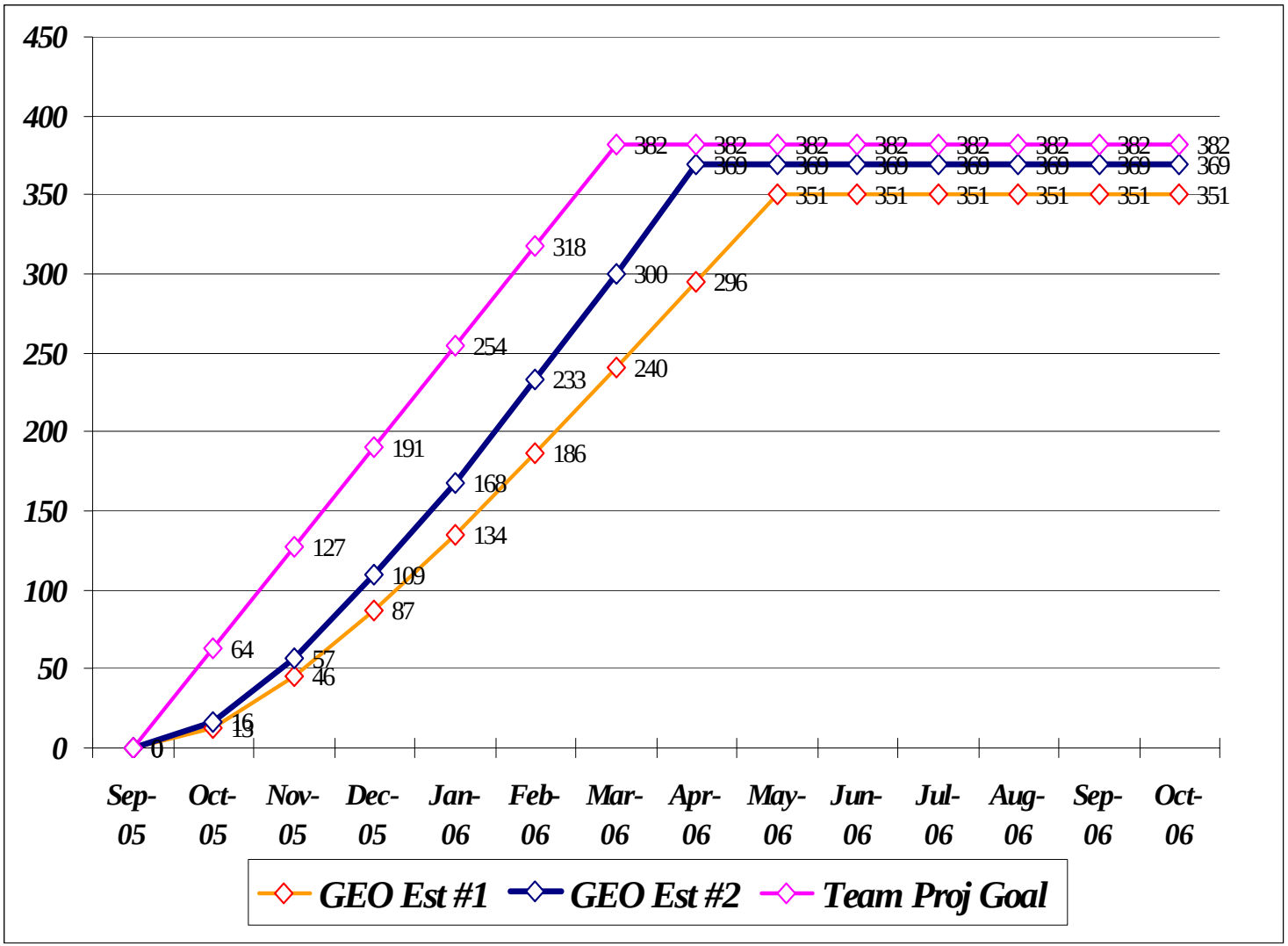
Managing Timeline Knowns

- Seasonality
  - US Thanksgiving to January 1
  - EU July and August
- Variable Site FPV
- Varying country and site FPV and patient arrival rate information

Acceleration

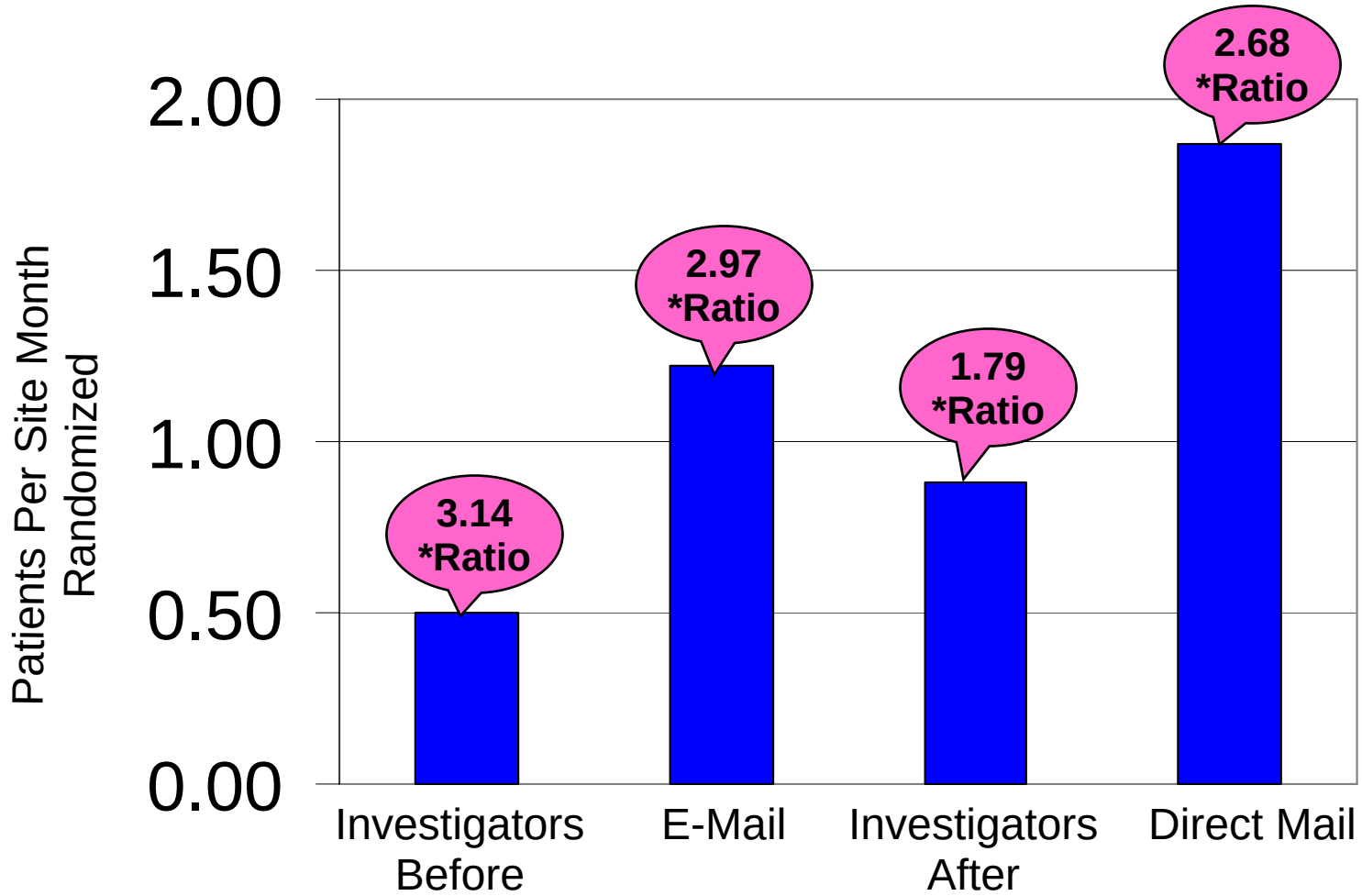
- Study Branding
- Site Collateral Materials
- Centralized Advertising
- Internet Pre-screening
- Centralized Call Center
- Site Selection Near Patient Populations

Enrollment Projection Tool



Osteoporosis Acceleration

Intervention Impact Metrics

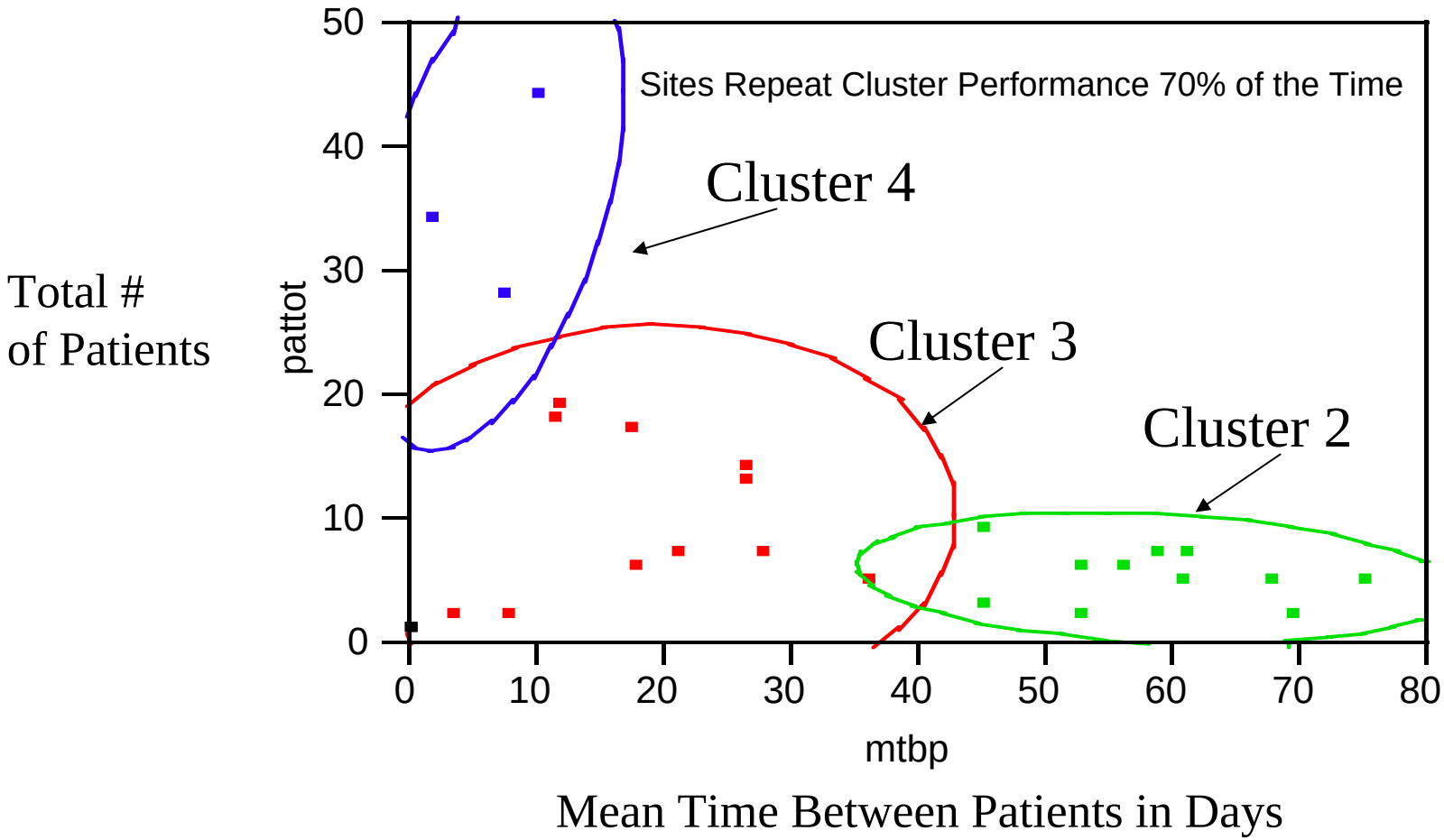


*Total screened to enroll one patient

Selecting Sites by Historic Enrollment Performance

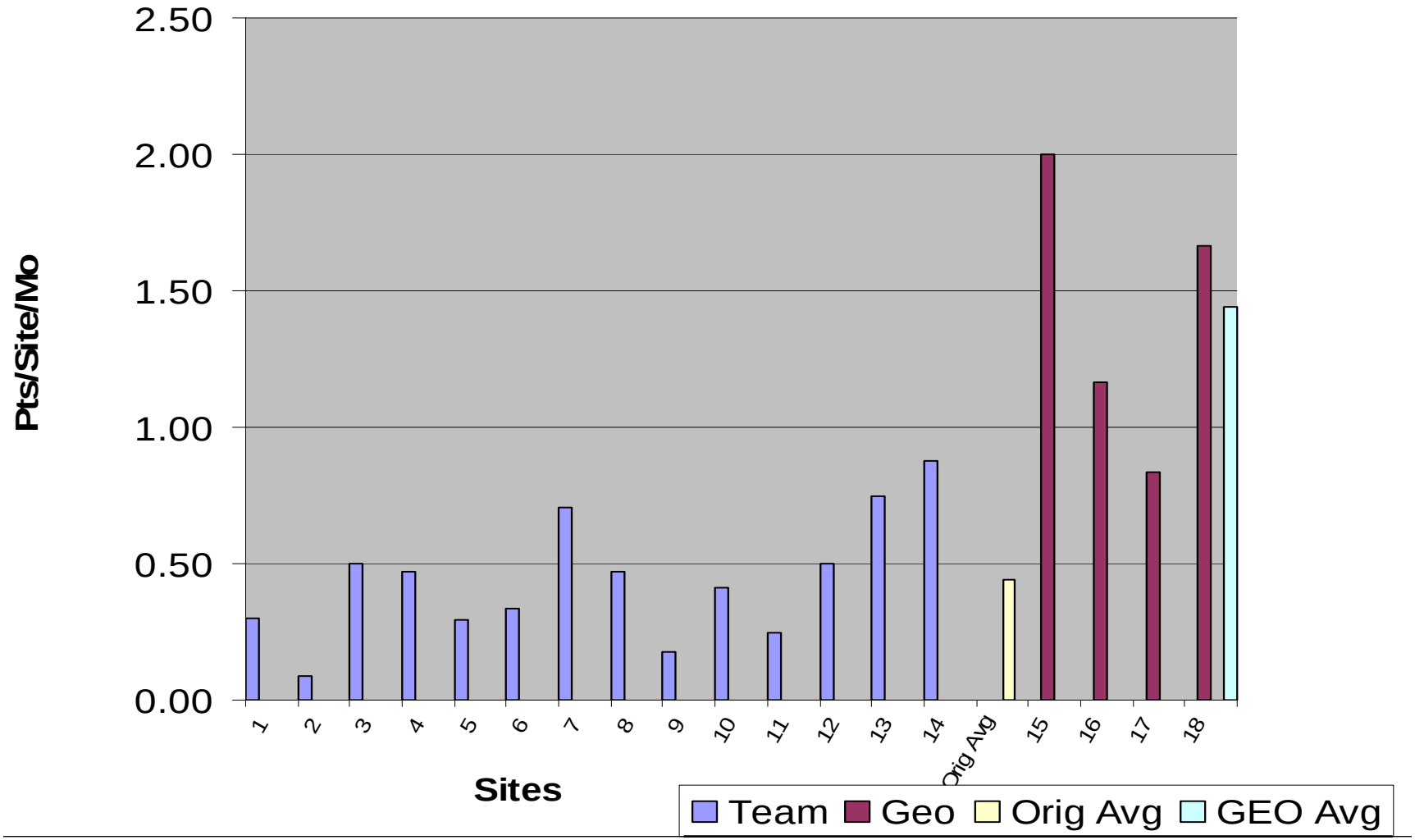
- Sites are compared to their peers within a specific Study.
- 0 Enroller Sites are not measured.
- Metrics use # of patients randomized and mean time between patients.
- Sites perform consistently across studies.
- Do you want effective sites running your studies?

Diabetes Study
Investigator Cluster Analysis



Note: Excludes 0 and 1 Enrollers

Using Internal Investigator Data for Site Selection

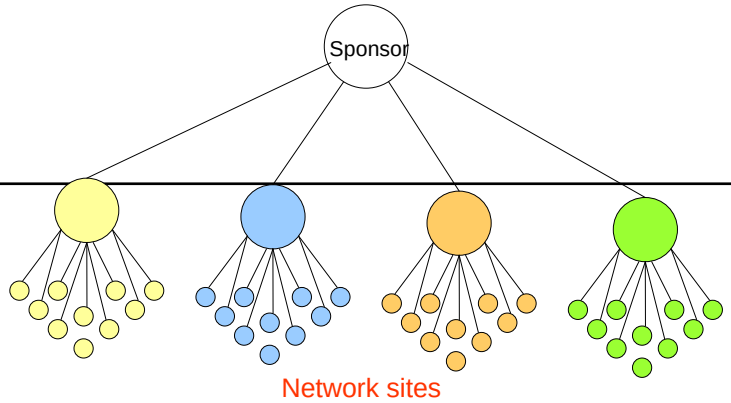


Investigator Site Selection

Selecting Sites

- Clinical Research Organization
- Site Management Organization
- Academic Research Organizations
- Sponsor Single Site
- Clinical Network Model

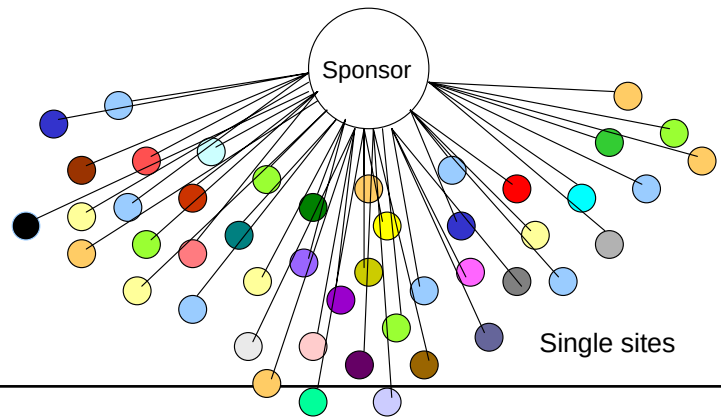
A Different Approach



Clinical Network Model

VS

Single Site Model



Clinical Investigative Networks

-Group of independent clinical research sites

-Managed/organized by central admin group

-Bound/coordinated by central/core set of network SOPs

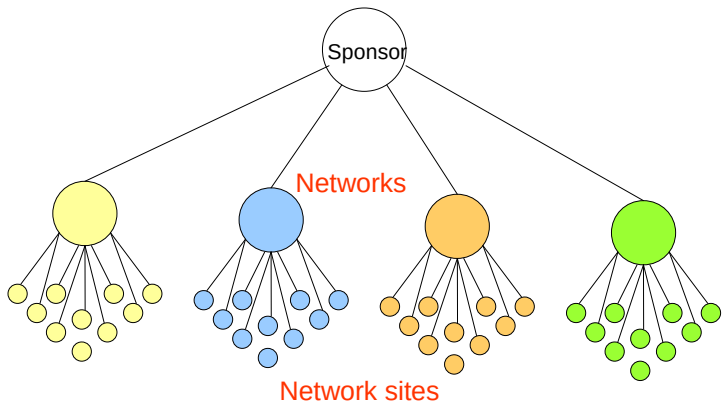
-Functions as one large clinical research entity

-SMO characteristics

- Site selection/Trial placement
- Trial feasibility surveys
- Enrollment forecasting
- Budgets & Contracts
- Site reimbursements
- Site/Project management

-CRO characteristics

- Trial initiation/start-up
- Site/Project management
- Regulatory document collection and maintenance



Clinical Investigative Networks

- Full Data Management
    - CRF design, Edit design, Data entry, Query creation, Query resolution, SAE Reconciliation/cross checks, Lab reconciliation, Patient diaries, Data Transfers, Reporting, etc…
- Statistical support services
- Medical writing services
    - Protocols
    - Final study reports
    - Abstracts/Manuscripts
- QA audit services

-Clinical research site characteristics

- Patient Recruitment
- ICD administration
- Data Collection
- Safety Reporting
- Pharmacy
- Labs

Clinical Investigative Networks

-Common organizational characteristics

- Central disease state committees
- Research advisor or Chief Medical Officer (leads/facilitates central committee)
- Regional research leader (regional representative on central disease state committee)
- Central admin staff (assists the central committees providing data, trial updates, safety updates, communication tools, consults and provides/maintains standard/consistent/streamlined processes)
    - Central Project mgmt. staff
    - Central Regulatory staff
    - Central Safety staff
    - Central Pharmacy staff
    - Central IT/Data Mgmt. staff
    - Central Financial/Legal staff
    - Central IRB

- **NOTE**: Network structures will vary with network size, disease focus and other variables
    - (ie. Oncology Committee vs. Tumor Specific Committees)
    - (ie. Community based vs. Academic based)

  The network structure is crucial to ensure that proper trial placement, proper trial oversight and communication occurs

Model Efficiencies (Level of centralization)

Example: 120 Patient, Phase II Oncology Trial

	Single Site Model	Centralized **Network Model**
IRB		
IRB Approvals (initial and annuals)	20 IRBs	1 central IRB
Pharmacy		
Study drug	20 pharmacies	1 central pharmacy
Lab kits	20 local labs /pharmacies	1 central lab/pharmacy
Project/Site Management		
Site Selection (+ depends on % acceptance)	20 + sites to research/select	1 network
Timelines/Tracking	20 timelines /contacts	1 timeline/contact
Data Collection		
Monitoring	20 sites to monitor	Centralized monitoring
Safety		
SAE Reporting & Follow-ups Medwatch forms	20 safety offices	1 centralized office
Regulatory		
Regulatory Readiness (Document collection)	20 regulatory offices	1 centralized office
ICDs	20 ICDs to review	1 ICD to review
Legal		
Contracts	20 contracts to create	1 contract to create
Finance		
Trial Budgets	20 budgets to create	1 budget to create
Trial Payments	20 sites mailing addresses	1 central office

Model Efficiencies (value model example)

Example: 120 Patient, Phase II trial Oncology Trial

Operations Productivity Impact:

Assumes centralized model:
Central IRB
Central monitoring
Central Pharmacy
Central Regulatory
Central Data Mgmt.
Central Safety Office
Central Contracts

Example

Centralized Network Model

To initiate (1) 120 patient trial:
CRA: Time – Site selection: Done by network – 1 call/email to send Fast Facts
CRA: Site selection done by network
CRA: Travel - 1 trip to initiate network x $800/trip = $800
(travel costs, food, transportation, etc…)
CRA: Time - 1 day trip for each trial = $500 (salary + benefits) = $500
CRA: 2.5 hours/SEC x 1 SEC x $50/hour = $125 ($50/hour)
CRA: no trips required for start up – start-up done virtually
CRA: start-up time: $500 = 1 day start-up time = $500
CRA: Travel - 16 monitoring visit trips/year x 2 years x $800/trip = $25,600
CRA: Time - $500/day x 1 day each visit x 16 visits/year x 2 years = $16,000
CRA: Travel – 6 trips to data clean & closeout x $800/trip = $4800
CRA: Time - $500/day x 6 days to data clean & closeout = $3000
CRA: Time – Project Mgmt. – 10 hours/month x $50/hour x 24 months = $12,000

Single Site Model (Decentralized)

To initiate (1) 120 patient trial: 6 patients/site assumed; 2 sites/CRA
CRA: Time:Site selection:6 sites contacted/research 4 hrs/site x 6 x $50/hr=$1200
CRA: Travel – 3 trips (50% of sites; others called) $800/trip x 3 = $2400
CRA: 1 selection trip/site x 20 sites x $800/trip = $16,000
(travel costs, etc…)
CRA: 1 day/site trip = $500/day x 20 trips = $10,000 (salary + benefits)
CRA: SEC/site (2.5 hours/SEC) = $50/hr. x 20 sites x 1SEC/site = $2500
CRA: no trips/travel expenses required for start up – start-up done virtually
CRA: start-up time: $500 = 1 day start-up x 10 CRAs = $5,000
CRA: Travel - 6 monitoring visit trips/year x 2years x20 sites x $800/trip=$192,000
CRA: Time - $500/day x 12 visits x 1 day each visit x 20 sites = $120,000
CRA: Travel – 40 trips (2 per site) to clean data & closeout x $800/trip = $32,000
CRA: Time - $500/day x 40 days to closeout = $20,000
CRA: Time – Project Mgmt. – 8 hours/month x $50/hour x 24 months x 10 CRAs = $96,000

NOTE: Listing above not all inclusive; several other clinical staff roles and tasks would be affected and thus affect value model (ie. Regulatory, Contracts, Legal, CT Material, IT/eDC, etc…)

Model Efficiencies (High Level Metrics)

Regulatory Readiness (Protocol receipt to study drug shipment – in working days)

	Trial A	Trial B	Trial C
Investigative Network A	63 Days (50 US network sites initiated)	55 Days (16 US network sites initiated)	62 Days (15 US network sites initiated)
Single Site (Avg.)	89 Days	180 Days	114 Days
Single Site Range	37 to 230 Days	157 to 203 Days	89 to 156 Days
	26 days faster over Single Site Avg.	**125 days faster over Single Site Avg.**	**52 days faster over Single Site Avg.**

Network average over last 11 trials: 42 working days with an average of 40 sites being initiated

CRF Query Rates (Network A vs. all other single sites participating in same trial; US only trials)

	Trial A	Trial B	Trial C
Investigative Network A	1.31 queries/CRF Visit	3.47 queries/CRF Visit	1.88 queries/CRF Visit
Single Site (Avg.)	2.12 queries/CRF Visit	8.43 queries/CRF Visit	2.32 queries/CRF Visit
	0.81 less than Single Site Avg.	**4.96 less than Single Site Avg.**	**0.44 less than Single Site Avg.**

Source: ***Scheible, Russell, Brinkman, The Clinical Investigative Site Network, Applied Clinical Trials, 14 (3) 42 (March 2005)***

Model Efficiencies (High Level Metrics)

Enrollment Rates (Network A vs. all other single sites participating in same trial; US only trials)

	Trial A	Trial B	Trial C
Investigative Network A	3 Patients/month	2.5 Patients/month	4 Patients/month
Single Site (Avg.)	0.14 Patient/month	0.34 Patient/month	0.70 Patients/month
Single Site Range	0 to 0.78 Patients/month	0 to 0.67 Patients/month	0 to 1.87 Patients/month
	2.86 higher than Single Site Avg.	**2.16 higher than Single Site Avg.**	**3.30 higher than Single Site Avg.**

Network average over last 11 trials for initial study drug shipment to FPV: 19 calendar days
Network monthly enrollment rate per trial: 3.3 patients/month/enrolling trial
Network monthly enrollment rate: 35.9 patients/month

Source: ***Scheible, Russell, Brinkman, The Clinical Investigative Site Network, Applied Clinical Trials, 14 (3) 42 (March 2005)***

Analysis and Selection

Network/Sponsor Analysis (High level structure/process analysis)

- Network identification (utilize field staff expertise, thought leaders, web, etc…)
- Network structure/process/service discussions
- Network key question list utilized for consistent/cross functional analysis
- Historical Trial Hx/Patient Population
- Sponsor key element presentation to network
- Determine initial level of interest
- Internal committee review of network/sponsor fit

Network Assessment (Detailed quality/process analysis)

- Current state determination
- Centralized vs. Decentralized
- Organizational structure and flow
- Processes, SOPs, Training
- Compliance analysis – GCPs, Privacy/HIPAA, 21CFR11, hazardous waste disposal regulations, etc…
- Clinical services
- eClinical/System capabilities
- Standard Quality/TPO checklists utilized for consistent approach

Value Model & Needs Analysis

- Sponsor and Network participate
- Needs Analysis performed (Trial types, research interests, windows of opportunity, etc...)
- Key Clinical Criteria and Goals are paired up (Best fit analysis)
- Value Model creation and analysis – based on network structure, flow and needs
- Determine final level of interest

Development

Process Review Discussions **(Detailed Process Analysis/Development)**

- Detailed Process/SOP analysis and comparison (Sponsor and Network)
    - -Topic/Area expert focused groups
    - - GPS (Safety), CDS (Labs), SDC (Study Drug), Data Mgmt.& IT, Regulatory, Stats., Medical Writing
- Identify current sponsor/network process issues/incompatibilities
- Merge processes (if possible) for optimal efficiency and to ensure compliance
- Ensure all changes are communicated to affected sponsor/network staff and training occurs
- Helps to ensure all sponsor/network staff understand both sponsor and network processes completely

Alliance Development **(Quality/Metric/Scientific Strategy contract)**

- Quality guidelines/expectations (proactive compliance approach)
- Metric goals & descriptions (collection and analysis)
    - -Regulatory Readiness
    - -Data Quality
    - -Data Timeliness
- Quarterly metric reviews (including contingency plans and triggers)
- Periodic scientific meeting schedule (engage the physicians; improve trial design/strategy)
    - -“Run the right trials at the right time”
- Service listing (ie. Data mgmt. services, Stats., Medical writing, Reg. document collection, etc…)
- Detailed Model Description (including level of centralization), expectations and change control process
- Master clinical trial agreement (standard contract wording agreements for future trial contracts)
- Monthly operational meetings
- Special focused group/topic sessions (ie. Reg. Readiness, Stats., Data mgmt., etc…)
- Agreement time length and periodic review process

Development

Periodic Scientific Strategy Meetings

- Trial strategy /Portfolio discussion
- Review of sponsor needs, network and patient population needs
- Review of recent treatment trends and strategies
- Trial design discussions
- Capacity analysis and planning
    - Set trial timelines and goals

Network Alliance Annual Year End Review

- Year end metrics review
- Voice of the Alliance surveys (sponsor and network staff)
- Determine areas for improvement/adjust metrics/plan implementation
- Trial strategy and design review
- Value model analysis
- Set new goals and metrics (if applicable)

NOTE: agreement lengths may vary (ie. 1 year vs, 2 or 3 years) depending on variables such as performance History, etc… Regardless of agreement length, annual reviews should occur.

Key Network Elements (Requirements)

IRB

-Centralized IRB vs. satellites
-Initial approvals
-Annual reapprovals
-21CFR56 compliance discussion

Regulatory

-Centralized office vs. satellites
-Regulatory readiness (electronic or paper)
-Annual reapproval process (electronic or paper)

Safety Reporting

-Central safety committee vs. satellites
- Medwatch forms
- SAE reporting

Legal/Finance

-Centralized budgets/contracts vs. satellites
-Master clinical trial agreement
-Accounts payable process

SOPs & Training

-Network-wide processes
-Site qualifications
-Audit process (see QA)

Quality Assurance

-Independent of clinical area
-Audit process and periodic schedule

Pharmacy

-Drug distribution (oral vs. IV)
-Drug accountability (Electronic or Paper)
-Drug storage and monitoring
-Drug destruction and documentation
-Drug handling and training

Lab Samples

-Lab kit distribution
-Lab sample collection capability (ie. PK, other)
-Lab sample storage, shipment and monitoring

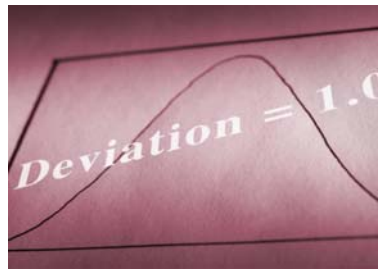
Key Network Elements (Requirements)

Project Management

-Site selection and capacity analysis
-Communication and escalation process
-Staff scheduling, timelines, facilitation and tracking
-Audit readiness and coordination

Stats / Medical Writing

-Statistical Analysis Plans
-Manuscripts, Abstracts and Posters
-Protocol development and review



Data Management

-CRF data collection process (shadow charts, eDM, satellites)
-sSource Documents
-Query process
-Communication and escalation process
-Data storage and back-up
-Data analysis
-CRF and data edit development
-Data transfers and reporting

eClinical

-Secure document repositories
-eSource Documents
-eCRF or eDC
-eQuery process
-Distance learning: secure webcasts, webconferences, CDs, DVDs
-21CFR11, HIPAA, Privacy compliance, validations

eClinical

Distance Learning

CD
DVD

Secure webcast (Live & Archived – website)

Webconference

Document Repositories

Internally developed vs. COTS vs. ASP
Area Level access

Document Level access

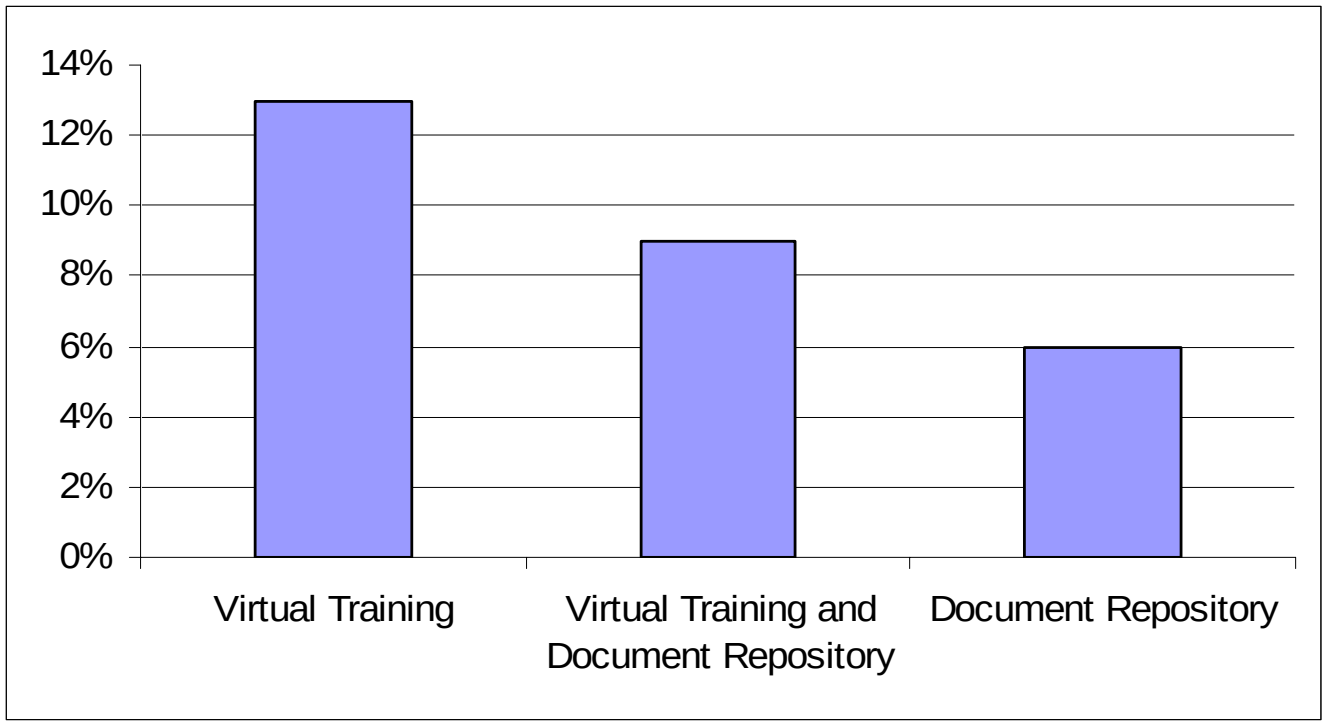
Secure Document Delivery

Fax to Repository (Hybrid)
Online (eSig.)

eDM

eDC
eSource Document

Collaboration and Virtual Training Cycle *Time Reduction



*__Protocol Approval to Regulatory Readiness__ -trial median cycle time was used to calculate the overall virtual median cycle time

Applied Clinical Trials, Volume 15, Number 7, pp 32-37

Metrics - Quality

	Live vs. Virtual: Quality Metrics CRF Queries and GCP Issues														
	Compound I											Compound II			
	Study A	Study B	Study C	Study D		Study E	Study F	Study H	Study I	Study J	Study K	Study L	Study M	Study N	Study O
Queries/Visit	1.1	0.8	0.5	0.5		0.7	0.7	0.7	0.9	0.6	0.2	1.5	2.9	2.7	14.9
GCP Issues Per Site	2.2	7.5	2.0	2.3		4.5	2.5	1.5	1.0	2.3	1.3	6.3	2.5	1.0	7.0
Studies in blue denote Distance Learning. Studies in black denote Live training.															

	Live vs. Virtual: Quality Metrics CRF Queries and GCP Issues																
	Compound III					Compound IV								Compound V			
	Study P	Study Q		Study R	Study S	Study T	Study U		Study V	Study W	Study X		Study Y	Study Z	Study AA	Study AB		Study AC	Study AD	Study AE
Queries/Visit	2.7	4.1		0.3	0.2	0.1	1.2		1.1	1.2	0.9		0.5	0.4	0.4	0.6		6.1	2.3	2.8
GCP Issues Per Site	3.9	3.2		2.5	2.7	4.8	13.6		2.6	6.4	5.6		1.6	2.2	1.9	3.8		7.3	5.0	2.0
Studies in blue denote Distance Learning. Studies in black denote Live training.																				

Applied Clinical Trials, Volume 15, Number 7, pp 32-37

Special Considerations (Summary Points)

Enrollment Optimization:

Environmental Factors

- Increasing Development Costs
- Globally Sourced Trials
- Changing Regulatory Expectations

Investigators

- Decreasing Investigators
- How do they perform?

Enrollment Projection Considerations

- Historic Comparator Studies
- Enrollment Targets
- Use Known Study Information
- Acceleration
- Centralized Support

Special Considerations (Summary Points)

Clinical Investigative Networks:

Characterizing networks

- Structure and processes
- Capabilities and capacity (ie. Community based vs. Academic; Regional vs. International)
- Strengths and weaknesses
- Well developed analysis/selection/assessment process
- Pairing up networks/networks or networks/single sites or TLs
- Consider tracking in database

Trial /Network pairing

- Phase I trials (shorter, smaller trials)
- Lab/procedure capability
- Patient population/network distribution
- Competing trials / trial timing

Initial time to initiate network alliance

- Initial identification and analysis/selection
- Initial process review sessions

First year learning curve

- implementation year; keep staff focused and motivated
- consider multiple year initial agreement (ie. 2 years)
- meaningful metrics should appear in the second year
- efficiency should appear in the second year
- steady trial stream should be in place in second year

Value model/Strategy analysis

- Periodic trial strategy / treatment trend analysis
- Periodic trial portfolio review
- Periodic network structure/process analysis (ie. Level of centralization)
- Continuous performance metrics analysis
- Fair market value (single site model vs. network model)

Special Considerations (Summary Points)

eClinical:

Developmental timeline

- Internally developed vs. COTS vs. ASP
- Build the system/tool around the process

Budget limitations

- Internally developed vs. COTS vs. ASP
- Compare to value model (based on intended use)

User functionality requirements and capacity

- Characterize end users
- streamlined computer diagnostic testing
- Validation and testing should be based on real user criteria
- Periodic review of functionality and processes
- Feedback process

Ancillary Supportive Functions are critical

- Help Desk
- Technical Support
- Contingency and Back-up Plans
- Historical Technical support files/tools
- Training

Regulations analysis

- Periodic review of the regulations