PharmaNet/i3
Strategic Resourcing
INVENTIV HEALTH CLINICAL

Innovative Solutions Designed to Improve Operational Capacity, Efficiency and Effectiveness in Clinical Monitoring

Brett Barber, Sr. Director, Strategic Resourcing
Nicole Baker, Sr. Director, Strategic Resourcing
Lisa Rhiner, Clinical Study Lead

October 4, 2012

Objectives

- Apply innovative approaches to resourcing, study start up, and data review through standardized and centralized practices
- Describe how a standardized monitoring process can reduce cycle times and impact monitoring efficiency
- Evaluate the use of metrics to ensure project delivery, patient safety and bolster organizational performance

Site Selection - Industry Challenges

- Increasing economic pressures to deliver drugs to market faster and at less cost
- Increasing regulatory pressures to deliver with a high level of quality to ensure patient safety
- Patient enrollment and study start-up delays
- Accurately identifying a site's ability to enroll patients
- Resources are often not assigned to best leverage expertise, location, capacity or prior investigator relationships
- Workload pressures with increased focus on speed can result in CRA turnover

Site Selection-Current Industry Standard

- Site selection activities are performed by CRAs in addition to a CRA's "day job" and are often prioritized below other activities (e.g. deadlines)
- CRA therapeutic expertise and skill level for site selection activities are variable
- Cycle time is variable
- No single point of accountability for site selection delivery, work scattered across many CRAs
- Lack of coordination and ineffective communication to sponsor regarding progress
- CRAs possess valuable knowledge of local sites which should not be lost with any proposed model changes

Solution: Dedicated Site Selection Team

- Restores balance to CRA workloads
- Can bring needed expertise to the process by utilizing therapeutically aligned teams
- Provides end-to-end accountability resulting in better coordination of efforts
- Allows for single point of contact to enable proactive communications
- Model retains local knowledge as the dedicated team collaborates with local CRAs for recommendations and up-to-date information regarding site performance

Solution: Dedicated Site Selection Team, cont…

- Identify experienced, high performing CRAs that have a passion and commitment to site selection from existing CRA team
  - Resourcing depends on # sites needed and # of studies – recommend 5-10% of CRA staff
- Successful model (spanning over 3.5 years)
  - 12 Dedicated Site Selection Leads
  - Across all Therapeutic Areas
  - Experience with Pharma Industry Leader

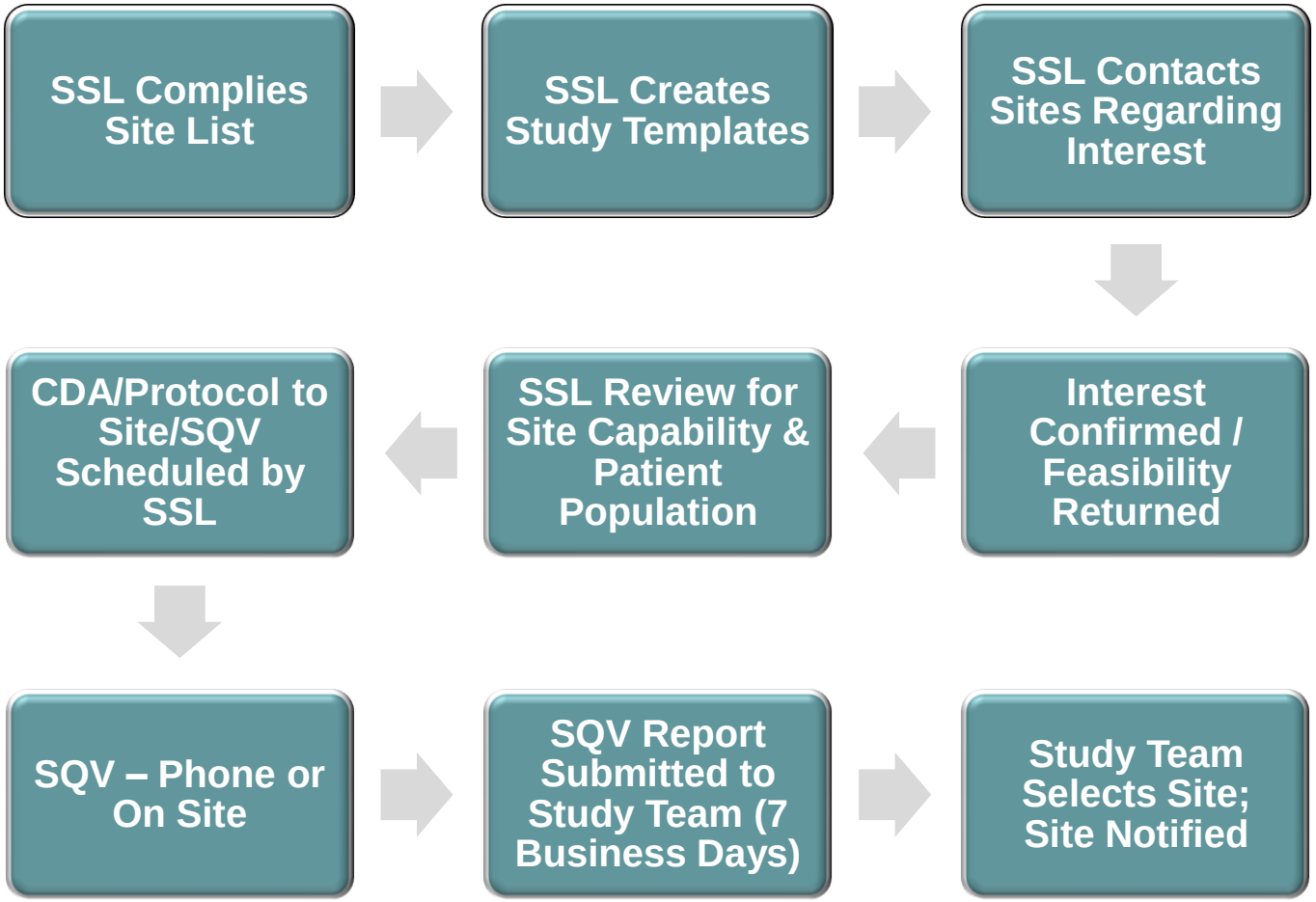
Site Selection Lead vs. CRA Responsibilities

Site Selection Lead	CRA
Create potential site list (dbase searches, prior TA experience, CRA & study team suggestions)	Provide site performance feedback to SSL
Create communication templates to be used during site selection	May assist with site contacts or follow up, if requested
Maintain regular contact with study team throughout site selection process via teleconferences and trackers	Assist with due diligence reviews, if requested
Complete due diligence review for each site	Once a qualification visit has been scheduled by SSL, CRA will confirm with site and be primary site contact at that point
Initial contact regarding interest and persistent follow up with potential sites throughout site selection process	Ensure CDA is executed prior to visit
Review any feasibility questionnaires and schedule qualification visits if site is interested and acceptable	Complete onsite qualification visits and reports
Review all qualification visit reports prior to client submission	Follow up with the site on any issues as requested by the study team
May complete telephone qualification visits, if permitted by sponsor SOPs	May complete telephone qualification visits, if permitted by sponsor SOPs
Conduct CRA training regarding the site selection process	Other site selection activities as delegated by the SSL
Other site selection activities as delegated by the Sponsor	

Dedicated Site Selection Model

- One Dedicated Site Selection Lead (SS CRA) identified to lead each SS effort
  - PoC for study team questions & overall project accountability
- SS Lead work with field CRAs to identify potential sites and obtain feedback regarding study team recommended sites
- SS Lead is responsible for all preliminary site feasibility, viability assessment, and pre-qualification activities
- SS Lead performs telephone Site Qualification Visit & write reports (if permitted)
- Local field CRAs perform on-site qualification visit & write reports
  - Knowledge transfer occurs between SS Lead and local CRA to ensure complete understanding of protocol requirements prior to conducting pre-study visit
- Sponsor makes ultimate decision regarding site selection, but through intelligent partnering this decision is founded on data

Site Selection Process Flow



PharmaNet|i3 Strategic Resourcing
INVENTIV HEALTH CLINICAL

Metrics Delivered to Client

- Cycle time metrics collected and reported:
  - Time from launch of effort by sponsor to first pre-trial qualification completed
  - Time from launch of effort to final pre-trial qualification completed
  - Number of days +/- established negotiated deadline that all requested pre-trial qualification reports with viable sites are delivered to sponsor

Built for Speed – Case Study Metrics

Decreased study start-up cycle times over 50% for current client

- Average cycle time for Oncology Studies
  - Effort Launch to 1st Site Qualification Visit*: 17 days
  - Effort Launch to Final Site Qualification Visit*: 52 days
- Average cycle time for Non-Oncology Studies
  - Effort Launch to 1st Site Qualification Visit*: 15.5 days
  - Effort Launch to Final Site Qualification Visit*: 40 days

*Site Qualification Visits considered complete upon submission of visit report

Benefits of Dedicated Site Selection

- Reduces cycle times
- Improves quality of site qualification and reports
- Provides end-to-end accountability
- Allows for single point of contact to enable proactive communication to sponsor
- Restores balance to CRA workloads
- Retains field knowledge regarding site performance
  - collaborate with local CRAs for recommendations and up-to-date information regarding site performance
- Quality reviews built into processes

Process Initiative (CMMI)

- Clinical Monitoring Management Initiative

  Six Sigma Analysis

  - Recruitment
    - Sites default to maximum enrollment period
    - Limited CRA and site strategy

  - Monitoring Visit Process
    - Site visits lacked rationale
    - Monitoring content varied radically between CRAs

Process Initiative (CMMI), cont…

- CMMI

  Six Sigma Analysis, cont…

  - Demand and Capacity Management
    - Management team lacked capacity visibility
    - No transparent metrics to quantify CRA site visit activities

  - Protocol Pilot
    - OAB Trial, 28 Monitors, 73 sites, 1220 subjects

Protocol Pilot

- Recruitment and Enrollment
  - Setting expectations for CRAs and sites
    - > Bridging the ‘planned’ to the ‘actuals’ by forecasting
  - Deficit threshold of ‘2’ established
  - Recruitment discussion guidance document

CRSM	RM
Name	Name

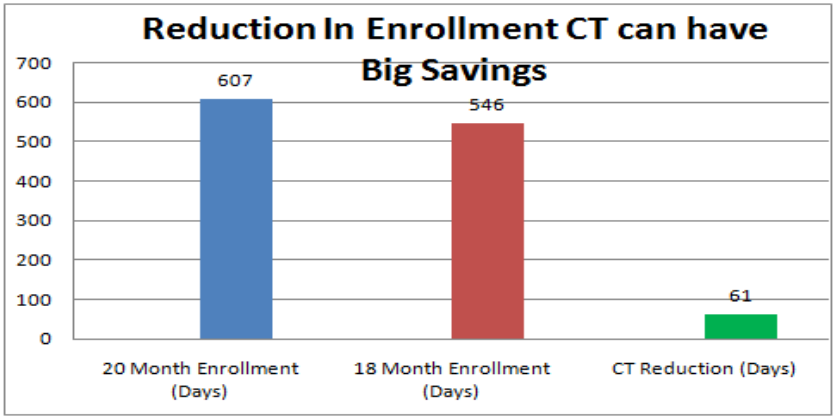
June 4, 2010

CRSM Planning Tool Summary

						Protocol A0221049 Screening Metrics to Date					
Error Check	Error Check 2	Last Data Entry	Site Number	PI Name		Actual # Screened to Date	# Actual Screen Failures to Date	Screen Fail Rate % to Date	# Planned Enrolments to date	Actual # Enrolled to date	More Than 2 Behind Enrolment Plan
		3-May-10	1002	Rankin		17	2	11.76%	15	13	-2

Protocol Pilot

- Recruitment and Enrollment, cont…
  - At the initiation of the pilot, 26 sites were taking in excess of 19 months to enroll subjects in the study. The pilot team decreased that to 14 sites.
    - > Improved enrollment rates at 12 sites
  - Pilot data was so compelling it prompted the ST to re-draft the site selection criteria and close non-performers



10 % CT Reduction	
20 Month Enrollment (Days)	607
18 Month Enrollment (Days)	546
CT Reduction (Days)	61
New drug dev costs / day	$ 1,000,000
Potential saving to Sponsor	**$ 61,000,000**

Protocol Pilot, cont…

- Monitoring Visit Process
  - Based on SMP requirements ‘push’
    - Site visits occurred per a time interval – typically every 4-6 weeks – and were loosely based on the SMP regardless of necessity
  - Lean process based on the ‘pull-system’
    - Metrics calculate and forecast the actual work demand at each site and this drives the monitoring visit and estimates the time required for future site visits

Monitoring Visit Process

- Forecasting Milestones
  - Cumulative Weekly
- Page Verification
  - Enrolled vs. S/F
  - On-site vs. Remote
  - Logs

Site Volume Drivers	
Tot N monitoring pages per patient	65
Tot N pages from Logs per patient	10
N of visits in trial	5
Subject visit frequency weeks	3.6
Wks screening duration	2
Wks trial duration	12
CRA Data Verification Forecast Drivers	
TOT No of Screening Data Pages	16
No of Onsite Monitoring Pages per visit	6.5
No of Remote Monitoring Only Pages per visit	3.33
No of Logs Pages per visit	2
No of screen Page fails per visit	2
Monitoring frequency weeks	4.0
Screening Page time including consent (min)	1.2166667
Onsite Monitoring Page time (min	1.1048333
Remote Monitoring Only Page Time (Min)	1.3
Log Page time (min)	1.5
Screen Fail Page time (min)	0.8
Data Pull Hours	3

Monitoring Visit Process, cont…

- Validating the Data Pull-System
  - Calibrated drivers on 1/29. Planning tool forecasted 2.6 hr's of data. CRA worked 3.0 hours on data. 2 diary entries required detailed explanation that took 15 – 20 min's

Enter Start screening Date	19			20			21			22			23			24			25			26			27		
CRSM Weekly forecast	1/18/10			1/25/10			2/1/10			2/8/10			2/15/10			2/22/10			3/1/10			3/8/10			3/15/10		
	P	F	A	P	F	A	P	F	A	P	F	A	P	F	A	P	F	A	P	F	A	P	F	A	P	F	A
Milestones																											
Enter comments				3rd MV																		As Is MV 4					
Subjects																											
No of Subjects Screen - cumulate	8		10	8	11	10	10	10		10			10			10			12			12			12		
No of Screen Fails - this week	1		0		1	1		0					1												1		
No of Subjects Randomised - this week	1		0	0	0	0		0					1												1		
No of Subjects Randomised ACTIVE - cumulate	3		4	3	4	4	3	4		3			3			3			3			3			3		
No of Subjects Complete - cumulate	1		0	1	0	0	1	0		1			2			2			2			2			3		
No of Subjects discontinued - cumulate			1			1		1																			
Total Pages not locked (includes logs)			221			227																					
Total log pages			21			22																					
Pages added - this week			92			6			-227			0			0			0			0			0			0
Log pages added - this week			10			1			-22			0			0			0			0			0			0
Pages Verification																											
Tot verification on Site Hrs required	2.5	0.5	0.9	2.6	2.5	2.5	0.1	0.3	-0.4	0.3	-4.3	-4.3	0.8	-4.3	-4.3	1.0	-4.3	-4.3	1.2	-4.3	-4.3	1.3	-4.3	-4.3	1.8	-4.3	-4.3
Tot verification time at site (hrs)				2.6		3.0																					
Tot pages verified (Not Logs)				127		88																					
Total Log Pages Verified				12		11																					
Total Pages Remote verified (Not logs)						20																					
Pages left for following week	130		119	0		6	9		221	18		-221	44		-221	53		-221	62		-221	71		-221	98		-221
Log Pages (Agg)	11		16	0		6	2		-16	3		-16	5		-16	6		-16	8		-16	9		-16	11		-16

Calibrated drivers forecast 2.6 hours of data

Actual time to monitor data = 3.0 hours

Monitoring Visit Process, cont…

- Validating The Data Pull-System, cont…

Enter Start screening Date	19			20			21			22			23			24			25			26			27		
CRSM Weekly forecast	1/18/10			1/25/10			2/1/10			2/8/10			2/15/10			2/22/10			3/1/10			3/8/10			3/15/10		
	P	F	A	P	F	A	P	F	A	P	F	A	P	F	A	P	F	A	P	F	A	P	F	A	P	F	A
Milestones																											
Enter comments					3rd MV																		As Is MV 4				
Subjects																											
No of Subjects Screen - cumulate	8		10	8	11	10	10	10		10			10			10			12			12			12		
No of Screen Fails - this week	1		0		1	1		0					1												1		
No of Subjects Randomised - this week	1		0	0	0	0		0					1												1		
No of Subjects Randomised ACTIVE - cumulate	3		4	3	4	4	3	4		3			3			3			3			3			3		
No of Subjects Complete - cumulate	1		0	1	0	0	1	0		1			2			2			2			2			3		
No of Subjects discontinued - cumulate			1			1		1																			
Total Pages not locked (includes logs)			221			227																					
Total log pages			21			22																					
Pages added - this week			92			6			-227			0			0			0			0			0			0
Log pages added - this week			10			1			-22			0			0			0			0			0			0
Pages Verification																											
Tot verification on Site Hrs required	**2.5**	**0.5**	**0.9**	**2.6**	**2.5**	**2.5**	**0.1**	**0.3**	**-0.4**	**0.3**	**-4.3**	**-4.3**	**0.8**	**-4.3**	**-4.3**	**1.0**	**-4.3**	**-4.3**	**1.2**	**-4.3**	**-4.3**	**1.3**	**-4.3**	**-4.3**	**1.8**	**-4.3**	**-4.3**
Tot verification time at site (hrs)				2.6		3.0																					
Tot pages verified (Not Logs)				127		68																					
Total Log Pages Verified				12		11																					
Total Pages Remote verified (Not logs)						20																					
Pages left for following week	130		119	0		6	9		-221	18		-221	44		-221	53		-221	62		-221	71		-221	98		-221
Log Pages (Agg)	11		16	0		6	2		-16	3		-16	5		-16	6		-16	8		-16	9		-16	11		-16

Enter Start screening Date	28			29			30			31			32		
CRSM Weekly forecast	3/22/10			3/29/10			4/5/10			4/12/10			4/19/10		
	P	F	A	P	F	A	P	F	A	P	F	A	P	F	A
Milestones															
Enter comments										Pull System MV 4					
Subjects															
No of Subjects Screen - cumulate	12			14			14			14			14		
No of Screen Fails - this week										1					
No of Subjects Randomised - this week										1					
No of Subjects Randomised ACTIVE - cumulate	3			3			3			3			3		
No of Subjects Complete - cumulate	3			3			3			4			4		
No of Subjects discontinued - cumulate															
Total Pages not locked (includes logs)															
Total log pages															
Pages added - this week			0			0			0			0			0
Log pages added - this week			0			0			0			0			0
Pages Verification															
Tot verification on Site Hrs required	**2.0**	**-4.3**	**-4.3**	**2.2**	**-4.3**	**-4.3**	**2.4**	**-4.3**	**-4.3**	**2.9**	**-4.3**	**-4.3**	**0.1**	**-4.3**	**-4.3**
Tot verification time at site (hrs)										2.9					
Tot pages verified (Not Logs)										134					
Total Log Pages Verified										17					
Total Pages Remote verified (Not logs)															
Pages left for following week	107		-221	116		-221	125		-221	0		-221	9		-221
Log Pages (Agg)	12		-16	14		-16	15		-16	-1		-16	1		-16

- 'As-Is' MV March 8th forecast would yield 1.3 hours of SDV
- Pull-system MV April 12th would yield the pilot target of ~3 hours SDV

…a difference in five weeks

Monitoring Visit Process, cont…

- Pull-System vs. 'As-Is' Process
  - Expenditure analysis
    - > Speculation based on 1948 active sites

Summary table PO Pilot	'As-Is' every 4 weeks	3 Hour Data Pull	Difference	Reduction
Number of MVs	541	186	356	66%
Mileage Expense	$47,969.00	$16,282.00	$31,687.00	66%
Time in Car	1919	651	1267	66%
Hotel and Meal Allowance Cost	$24,180.00	$8,016.00	$16,164.00	67%
Time Spent Writing MV Reports	677	232	444	66%
Time at Site	3025	1038	1987	66%
Total Time for Site	5621	1922	3699	66%
FTE Required	703	240	462	66%
FTE $	$183,127.00	$62,605.00	$120,522.00	66%
$ Savings for (41 Weeks)	$255,276.00	$86,903.00	$168,373.00	66%
$ Savings Annulaized (52 Weeks)	$323,764.00	$110,218.00	$213,546.00	66%
Average/Site	$6,348.00	$2,161.00	$4,187.00	66%
Active Sites	12,366,532.00	4,209,912.00	$8,156,620	66%

CMMI and Protocol Pilot Lessons Learned

- Trends across functional lines emerged
- Recruitment and Enrollment
  - Improved accuracy in forecasting patient recruitment
    - > Model empowered CRAs and sites
    - > Earlier transparency in enrollment feasibility
- Monitoring Process
    - > Transparency across the organization
    - > Pull-system influenced a revised SMP
    - > Pilot recalibrated to two-hour pull

Operational Excellence Goals

- Process Transformation
  - Concept integration into an IT platform
- Standardization with flexibility
  - More predictive monitoring visit method
- Design metrics to compel capacity management
  - Utilization and resourcing rationale
- Continuous improvement

FDA Guidance – Risk-Based Monitoring

- FDA Aug 2011 Draft Guidance for Industry on Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring encourages the utilization of centralized monitoring.
  - "Effective monitoring by sponsors is critical to the protection of human subjects and the conduct of high-quality studies" (Section II)
  - "Incorporation of centralized monitoring practices, where appropriate, should improve a sponsor's ability to ensure the quality and integrity of clinical trial data" (Section II.C)
  - Allows for targeting "on-site monitoring by identifying higher risk clinical sites" (Section IV.A.2)

Centralized Data Review Team Defined

- What is it?
  - Team of protocol trained, experienced CRAs focused on remote data review
  - Big picture review and visit-by-visit review per subject
  - Identify study-wide safety & eligibility issues early
  - Allows for proactive trending & analysis across subjects
  - Identify need for additional site or CRA training

Centralized Data Review Process

- Develop centralized data review plan:
  - Includes Communication Plan
  - Based on protocol, Study Monitoring & Data Management Plans
    - Focused/risk-based monitoring
    - Data Review Timeframes
    - Eligibility / Safety / Critical endpoints
  - Example line listing reviews
    - Eligibility
    - AE to Con Med
    - Con Med to AE
    - AE to Dosing
    - Labs (if available)
    - Efficacy / End Points

Centralized Data Review Team Actions

- Patient Profile review
  - Review patient's entire data module to ensure consistency and accuracy
  - Ensure patient's data 'paints' a feasible and logical clinical picture
- Large Listings review
  - Correlate data fields and review accuracy for **all** study patients (protocol level review)
  - Interpretive review
  - Trends and transparency to help mitigate safety, feasibility, efficacy warning signs early in the study

Centralized Data Review Communication

- CRA communication plan includes:
  - Query resolution responsibility
  - Handling of potential safety issues identified by CDRT CRA
  - Communication of issues/trends to CRAs (CDRT & Site) and ST
  - Handling of CDRT CRA data questions directly to site personnel
  - Communications with ST and DM (defined by project)
- CDRT CRA communicates in writing to site CRA:
  - Potential protocol deviations
  - Potential safety issues not addressed elsewhere
  - CRFs reviewed
  - Open query list
  - Trends identified or suggestions for site training

How does CDRT *differ* from Data Mgmt?

- As therapeutically trained monitors, CDRT members are able to:
  - Review data from a clinical perspective
  - Generate queries with site level perspective in mind
  - Identify clinically-based deviations and violations
  - Earlier “eyes on data”
  - Identification and *resolution* of queries prior to DM review

Centralized Data Review Resourcing

- Resourcing model algorithm build based on:
  - Number of CRF pages
  - Protocol complexity
  - Time/CRF page review
  - Time/line listing review
- Factors affecting resourcing
  - Protocol complexity
  - CRF complexity
  - Enrollment rates
  - Site performance

Centralized Data Review Resourcing

- Resourcing model algorithm build based on:
  - Number of CRF pages
  - Protocol complexity
  - Time/CRF page review
  - Time/line listing review
- Factors affecting resourcing
  - Protocol complexity
  - CRF complexity
  - Enrollment rates
  - Site performance

Centralized Data Review Team Experience

- Oncology Focused Remote Data Review
  - Began as retroactive review in preparation for database lock and NDA filing
  - Evolved into dedicated team remotely reviewing data in parallel with CRA and data management reviews
  - Remote CRAs work very closely with clinicians, CRAs, and data management
- Integrated Centralized Data Review
  - Studies selected to use centralized data based on complexity
    - Some studies utilize traditional monitoring process
    - Some studies utilize combination of centralized data review and traditional monitoring process
    - Some studies utilize centralized data review only (i.e., long-term follow-up)
- "Carved-out" Centralized Data Review
  - CRAs with available capacity handle remote data review for high enrolling or complex studies

CDRT Pilot Study

- Pilot Study Parameters
  - Phase IV (enrollment ongoing)
  - 12 US Sites
  - 350 US Subjects
  - Metrics collected for 3 Month Time Period

Group 1

- **1.0 FTE Central CRA + 4 Regional CRAs**
- **6 Sites**

Group 2

- **6 Regional CRAs**
- **6 Sites**
- **CRAs Following Standard Data Review & Monitor Process**

CDRT Pilot Study – Volume Metrics

	Group 1		Group 2
	Central CRA	Site CRA w/ SDV	Standard CRA Process
Sites	6		6
Active Randomized Subjects	111		91
CRFs Reviewed (#)	7826	997	5524
Initial review within 15 Days of Data Entry ("eyes on data")	63%*	8%	56%

*Central CRA responsible for addressing data review backlog at start of pilot.

CDRT Pilot Study – Quality Metrics

Query Category	Group 1 Central CRA &Site CRA w/ SDV	Group 2 Standard CRA Process
Missing Data	277	27
Inconsistent Data	304	75
Safety Queries – AE	18	5
Safety Queries – Deviations	16	0
Source Clarification	44	3
Eligibility	5	0
CRF Completion Errors	185	12
Total Queries	849	122

Central Data Review Team Implementation

- Implemented CDRT on a larger scale in March 2012
  - Volume of data reviewed:
    - > 11 protocols as mid-March 2012
    - > 44 studies as of mid-May 2012
    - > 83 protocols as of July 2012
  - Data review expected within 15 days of data entry
  - Reviewing data across multiple trial phases and TAs
  - 30 experienced CRAs dedicated to data review (no assigned sites)
  - 6 CRAs coordinating efforts, assigning work, and helping with review as time allows

Central Data Review Team Metrics

- Metrics for data review within 15 days of data entry:

Month	Compliance Metric
January 2012	84%
February 2012	84%
March 2012	95%
April 2012	97%
May 2012	96%
June 2012	97%
July 2012	98%

Central Data Review Team Benefits

- Proactive review of patient eligibility & safety
- Real time identification of site data issue trends
- Inaccurate or missing data identified promptly
- Facilitates identification of:
  - Need for protocol clarification/amendments
  - Need for additional site training
  - Monitoring best practices
- Strengthens data integrity throughout study life cycle
- Faster review + more data reviewed = cleaner data in the database

Impact of a Centralized Model On Resourcing

- More predictive and measureable for demand and capacity management
- Improved forecasting
- Strategic ‘metrics driven’ model provides operational rationale
- Improved workflow
- Drives performance by leveraging individuals to their aspirations and abilities

Questions?

Thank you

Name Debra Santolini

Email dsantolini@pharmanet-i3.com

Phone **609-580-8209**

PharmaNet|i3 Strategic Resourcing
INVENTIV HEALTH CLINICAL