Clinical Data Mining as a basis for an Information-Based Clinical QA Program

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The case for change

- More studies, more patients and more countries are involved in our clinical programs than at any time in the past

- Regulatory scrutiny is as high as ever

- Traditional audit (e.g., 10% of sites) is impractical and may be of lower value-added than other options

These factors either mean we either broaden our overview, focus resource on the high impact and high risk areas, innovate new solutions and explore new models for the lower impact and lower risk areas; OR we could exponentially expand our QA staff…..

The case for change

The increasing volume of trials and reality of resource constraints mean that a traditional approach to clinical auditing is no longer feasible, and the knowledge-based approach (further enhances a risk-based approach) is key to implementing an effective and value-added QA and Quality Management Program.

- Novartis Clinical Quality Assurance (CQA) determined that some types of clinical data and clinical trial management metrics were good indicators of potential issues at Clinical Investigator Sites (CISs). These same data also often were good predictors of sites which might be chosen for pre-approval inspections by health authorities.
- In the past we manually reviewed reports and listings from the clinical data and clinical trial management systems. This was time- and resource-intensive.

The case for change

- Thus it was determined we had a need for an automated process of identifying programs and sites that were potentially “interesting”. Then one of several courses of action may follow:
  - selecting potential audit sites based on predefined risk criteria, which replaces manual review, eliminates errors and increases the scope of sites that are reviewed. The benefits of this broadening of scope cannot be over-emphasized!*
  - some potential issues can be addressed via the Clinical Research Team and/or CRA before they become real issues, without need for CQA audit of the CIS. “A win-win”.
  - In addition, if there were also a way to be notified of sites which had potential “signals” to be evaluated in the *programs that we did not plan to audit (lower priority projects, non-pivotal studies, CISs not selected for onsite audits), we could thereby increase our overview without a dramatic rise in headcount.

The case for change

- The focus had to be on data generated out of operational activities, potentially supplemented by risk questionnaires, but relying on real operational data to the greatest extent possible (and understanding the limitations on availability and reliability)

The result: TAPAS, the Trend and Pattern Alert System!

- New version of system – under development now:
  - Identified new user groups (CRAs and Trial Management) to define new risk factors – promote idea of leading indicators

TAPAS Application

TAPAS Application views

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Risk Factor Maintenance

TAPAS Risk Factor Maintenance

Factor Number	Factor Name	Factor Short Name	Factor Description	Top M		Next N		Rest O	
				Counts	Weightage	Counts	Weightage	Counts	Weightage
01	PROJECT PRIORITY STATUS	PrjPrty	List activities sorting by Heavy-weight=3, Key=2,Foundation=1	-	3	-	2	-	1
02	SUBMISSION TARGET DATE	SubmDate	Submission date within the next 1 year = 3, next 1 - 2 years = 2, greater than 2 years = 1	12	3	12	2	-	0
03	COUNTRY	Country	Top tier to be identified by risk model get a score of 3, Middle tier to be identified by risk model get a score of, 2 Bottom Tier gets a score of 1, All others get a score of 0	-	3	-	2	-	1
04	HIGH ENROLLERS	HiEnroll	Top 5 sites get score of 3, next 5 get a score of 2, the rest get a score of 0	5	3	5	2	-	-
05	MULTIPLE NOVARTIS TRIALS	MultTrls	Investigators with number of trials >7 get a score of 3; investigators with 5-6 trials get a score of 2; all others get a score of 0	7	3	5	2	-	-
06	PROTOCOL VIOLATIONS	ProtDev	Top 5 sites get score of 3, next 5 get a score of 2, the rest get a score of 0.	5	3	5	2	-	-
07	LOW AE REPORTING	LoAERptg	% pts with no AEs >90% and number enrolled > 10 get a score of 3; %pts with no AEs > 90 and number enrolled <10 get a score of 1; all others get a score of 0.	10	3	10	2	-	-
08	HIGH ENROLLMENT RATE	HiEnrlRt	Find maximum monthly enrollment for each site. Calculate the % of total enrollment at the site that this monthly maximum accounts for (max for site n / total enrollment for site n). Across all sites, consider only those where this percentage is > 50%. Sort by descending total max monthly figure. Top 5 get a score of 3, all others get 0	5	3	-	-	-	-
09	RE-ENROLLED PATIENTS	ReEnroll	Sites with such a patient get a score of 3, all others get a score of 0	10	3	10	0	-	-
10	HIGH DROPOUT RATE	Dropouts	Calculate the % of total enrollment at the site that early terminations account for (# early term for site n / total enrollment for site n). Across all sites, for those where this percentage is > 75, sort by descending total # early terms. Top 5 get a score of 3 (if total enrolled is 10 or more)	5	3	-	-	-	-
10b	LOW DROPOUT RATE	Dropouts	Calculate % of total enrollment at the site that early terminations account for (# early term for site n / total enrollment for site n). Across all sites, for those where this percentage is < 10, sort by descending total # enrolled. Top 5 also get a score of 3 (if total enrolled is 10 or more). All others get 0.	5	3	-	-	-	-

Return

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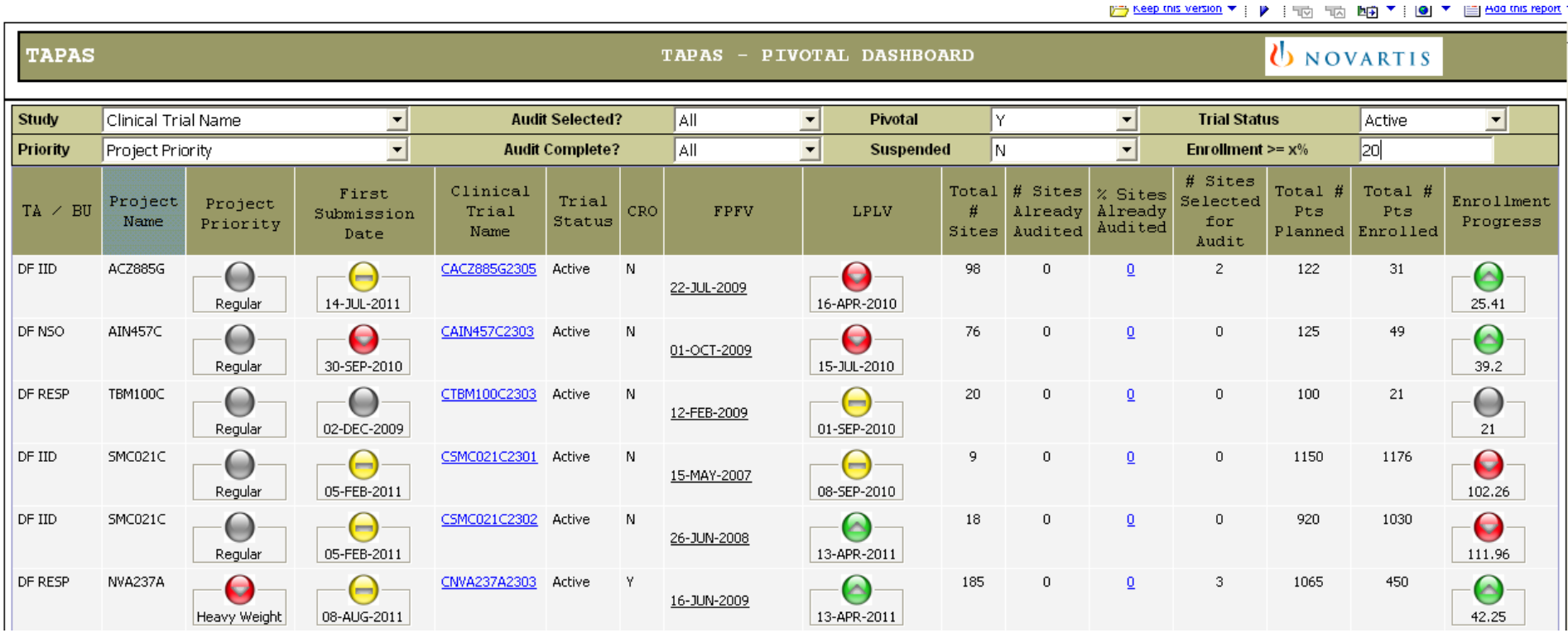
Program View



TAPAS — TAPAS – PIVOTAL DASHBOARD — NOVARTIS

Study	Clinical Trial Name	Audit Selected?	All	Pivotal	Y	Trial Status	Active
Priority	Project Priority	Audit Complete?	All	Suspended	N	Enrollment >= x%	20

TA / BU	Project Name	Project Priority	First Submission Date	Clinical Trial Name	Trial Status	CRO	FPFV	LPLV	Total # Sites	# Sites Already Audited	% Sites Already Audited	# Sites Selected for Audit	Total # Pts Planned	Total # Pts Enrolled	Enrollment Progress
DF IID	ACZ885G	Regular	14-JUL-2011	CACZ885G2305	Active	N	22-JUL-2009	16-APR-2010	98	0	0	2	122	31	25.41
DF NSO	AIN457C	Regular	30-SEP-2010	CAIN457C2303	Active	N	01-OCT-2009	15-JUL-2010	76	0	0	0	125	49	39.2
DF RESP	TBM100C	Regular	02-DEC-2009	CTBM100C2303	Active	N	12-FEB-2009	01-SEP-2010	20	0	0	0	100	21	21
DF IID	SMC021C	Regular	05-FEB-2011	CSMC021C2301	Active	N	15-MAY-2007	08-SEP-2010	9	0	0	0	1150	1176	102.26
DF IID	SMC021C	Regular	05-FEB-2011	CSMC021C2302	Active	N	26-JUN-2008	13-APR-2011	18	0	0	0	920	1030	111.96
DF RESP	NVA237A	Heavy Weight	08-AUG-2011	CNVA237A2303	Active	Y	16-JUN-2009	13-APR-2011	185	0	0	3	1065	450	42.25

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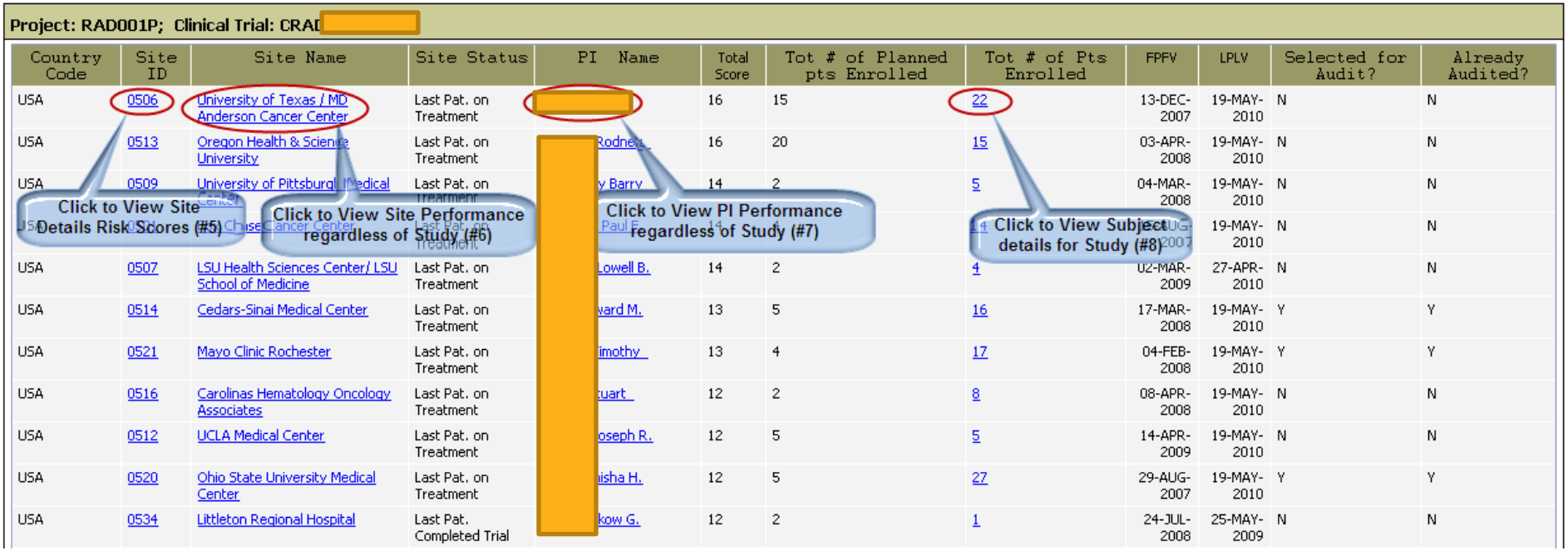
Factor Score



Country Code	Site ID	Site Name	Site Status	PI Name	Total Score	Tot # of Planned pts Enrolled	Tot # of Pts Enrolled	FPFV	LPLV	Selected for Audit?	Already Audited?
USA	0506	University of Texas / MD Anderson Cancer Center	Last Pat. on Treatment		16	15	22	13-DEC-2007	19-MAY-2010	N	N
USA	0513	Oregon Health & Science University	Last Pat. on Treatment	Rodney	16	20	15	03-APR-2008	19-MAY-2010	N	N
USA	0509	University of Pittsburgh Medical Center	Last Pat. on Treatment	y Barry	14	2	5	04-MAR-2008	19-MAY-2010	N	N
USA	0508	Case Comprehensive Cancer Center	Last Pat. on Treatment	Paul F.	14	4	11	02-AUG-2007	19-MAY-2010	N	N
USA	0507	LSU Health Sciences Center/ LSU School of Medicine	Last Pat. on Treatment	Lowell B.	14	2	4	02-MAR-2009	27-APR-2010	N	N
USA	0514	Cedars-Sinai Medical Center	Last Pat. on Treatment	ward M.	13	5	16	17-MAR-2008	19-MAY-2010	Y	Y
USA	0521	Mayo Clinic Rochester	Last Pat. on Treatment	imothy	13	4	17	04-FEB-2008	19-MAY-2010	Y	Y
USA	0516	Carolinas Hematology Oncology Associates	Last Pat. on Treatment	uart	12	2	8	08-APR-2008	19-MAY-2010	N	N
USA	0512	UCLA Medical Center	Last Pat. on Treatment	oseph R.	12	5	5	14-APR-2009	19-MAY-2010	N	N
USA	0520	Ohio State University Medical Center	Last Pat. on Treatment	isha H.	12	5	27	29-AUG-2007	19-MAY-2010	Y	Y
USA	0534	Littleton Regional Hospital	Last Pat. Completed Trial	kow G.	12	2	1	24-JUL-2008	25-MAY-2009	N	N

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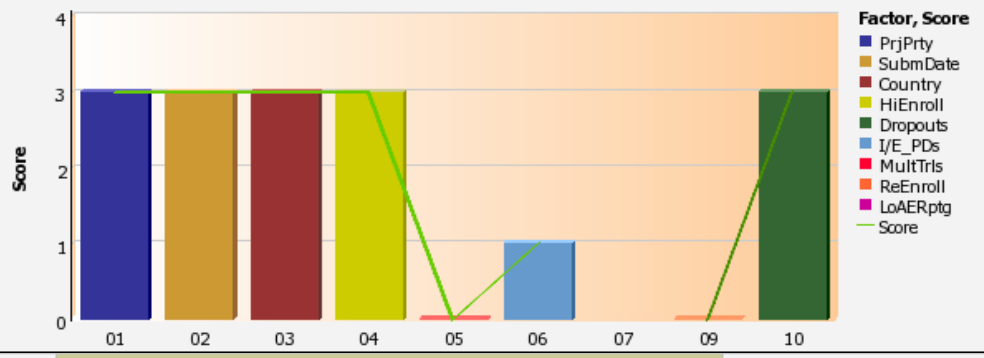
Factor Calculation

Clinical Trial: CRA[redacted] **Country :**USA **Site ID:**0506 **Principal Investigator Name:**[redacted] **Total Score:**16

Site Address: [redacted]

FPFV	17-Apr-2008
LPLV	19-May-2010
Selected for Audit?	N
Already Audited?	N
[redacted] Project Priority	Heavy Weight
[redacted] First Submission Date	12-02-10
Site Status	Last Pat. on Treatment
Total Number of Patients Planned	6



F01 CQA flagged Pivotal	Heavy Weight	F08 Max Enrolled Percentage	14.29
F02 Study Protocol Finalized	12-02-10	F09 Patients Pair Count	0
F03 Tier Level	Middle	F10 Percentage Early Termination	42.86
F04 Total Number of Patients Enrolled	14	F10 Total Number Patients Early Termination	6
F04 Percentage Patients Enrolled	3.42	F11	
F05 Investigator Active Trial Counts	2	F11	
F06 Percentage Patients in VIOPT	0	F12	
F07 Total Number of Patients Nil Aes	0		
F08 Max Enrolled Patients in Month	2		
F08 Max Enrolled Patients Month Name	01-Oct-2008		

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Summary

- Need for an aggregated data store (warehouse)
- Talk up the “leading indicator” concept in defining risk factors; make use of statistically based algorithms for identifying outliers and clusters
- Make your factors and evaluations data-driven!
- Build in configurable thresholds
- Retain risk results over time (watch emerging trends and see improvements)
- Active alerting (reeeeeally nice to have if you can get it)