Evaluation of Clinical Trials Process and Recommendations for Speeding the Clinical Trial Process

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February NCAB 2009

About the Collaborators

- **The Center for Management Research in Healthcare**
  - Co-Directors: David M. Dilts, PhD and Alan B. Sandler, MD
  - Researchers: Josh Crites PhD, Steven Cheng BE, Lori Ferranti MSN, MBA, and Amy Wu, B.Mus

- **Dr. Dilts has led analysis of several cooperative group and Cancer Center clinical trial processes**
  - The steps and time to process phase III clinical trials at the Cancer Therapy Evaluation Program (J Clin Onc in press)
  - Development of clinical trials in a cooperative group setting: The Eastern Cooperative Oncology Group (Clin Ca Res, 14:3427-3433, 2008)
  - A timing and process flow analysis of opening clinical trials within an oncology cooperative group setting: The case of the CALGB (J Clin Onc, 24:304S-304S, 2006)
  - Processes to activate phase III clinical trials in a cooperative oncology group: The case of Cancer and Leukemia Group B (J Clin Onc 24:4553-4557, 2006)

Outline

- **The Question**
- **Timeline and Evaluation Process**
- **Evaluation Results and Report**
- **The Recommendations**
- **Implementation**

The Question

- **Can the Timeline for Development and Execution of Clinical Trials at the NCI Intramural Clinical Program be Improved and Accelerated?**

David Dilts, PhD

- **Expert in the evaluation of systems process**
- **Has evaluated clinical trials process at several Cancer Centers**
- **Has evaluated CTEP processes**
- **Was engaged to evaluate processes of the NCI Clinical Program**

- ***Goal: To accelerate time from protocol submission to patients on trial***
  - *specifically, cut time by half*

Timeline and Evaluation Process

Dec 2007
Interviews with clinical Branches and Staff

April 2008
Round 2 of Interviews

Aug 2008
Presentation of Key Findings to subset of Clinical Branch Chiefs: Discuss Retreat Agenda

September 2008
Retreat to discuss results and recommendations with Focus group discussions

October 2008
Begin Implementation

- **Major stakeholder input was elicited**
- **Factors considered:**
  - Overall development time
  - Trial phase
  - Branch characteristics (# of trials, size of branch, etc..)

Process Map

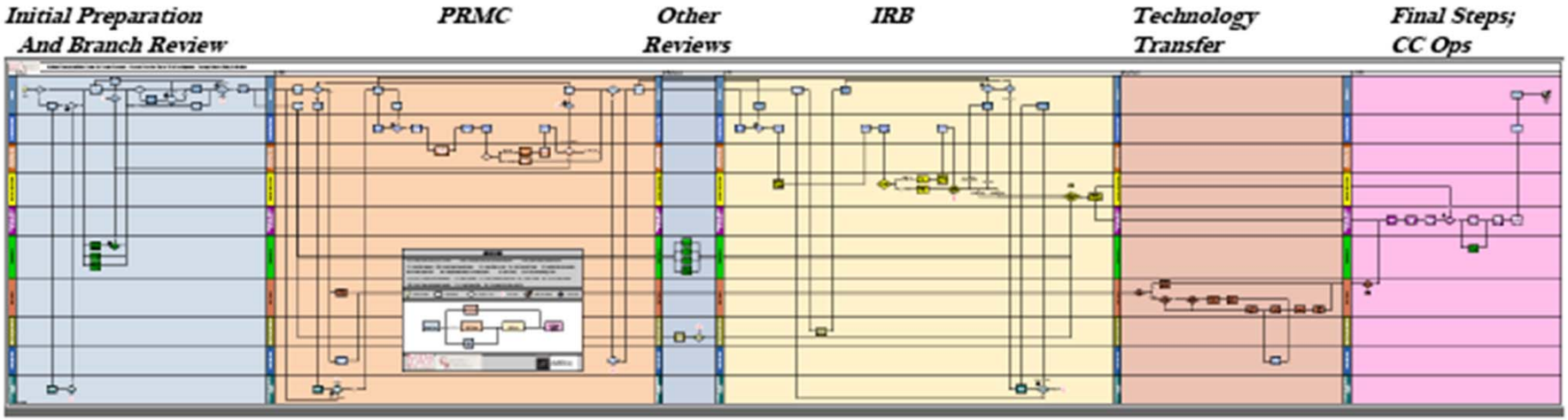


Figure B2: CCR Process Map with Section and Swim Lane Definitions

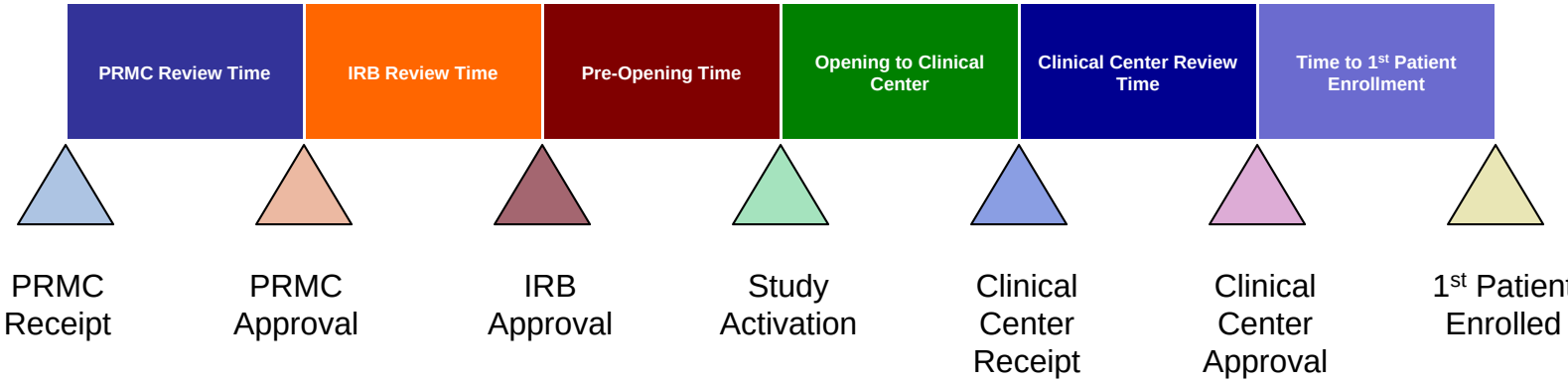
Swim Lanes (horizontal rows) representing process steps enacted by:

- PI / Branch
- Protocol Review Office
- Protocol Review and Monitoring Committee (PRMC)
- Institutional Review Board (IRB)
- Clinical Center office of Protocol Services
- Support Teams
- Technology Transfer
- Food and Drug Administration
- Industry Sponsor
- Cancer Therapy Evaluation Program

Some Data and Observations

- **Study period: 1/2000 – 12/2007**
- **No differences detected by:**
  - Phase
  - Low- or high- throughput Branches
- **Experienced PIs can open trials approximately 2.5 months faster**
  - Mentoring and training is important
- **A total of 12.6% of all trials opened and closed with no accrual**
- **A total of 30.4% of studies did not achieve at least 20% of stated maximum accrual goals** (minimal accrual goal data was not available so maximum was used)
- **Phase I and I/II studies achieved 56% of max. accrual goals with Ph II having less accrual success (35.2% and 29%, respectively)**

Clinical Trials Development Timeline



Overall Development Time	n	Median	IQR*	Min/Max
PRMC Review Time / IRB Review Time / Pre-Opening Time / Opening to Clinical Center / Clinical Center Review Time / Time to 1st Patient Enrollment	263	208	142-308	47-1435

* interquartile range: The IQR is the width of an interval which contains the middle 50% of the sample, so it is smaller than the range and its value is less affected by outliers

Development Time by Stage

Overall Development Time						n	Median	IQR
PRMC Review Time	IRB Review Time	Pre-Opening Time	Opening to Clinical Center	Clinical Center Review Time	Time to 1st Patient Enrollment	261	64	39-115
PRMC Review Time	IRB Review Time	Pre-Opening Time	Opening to Clinical Center	Clinical Center Review Time	Time to 1st Patient Enrollment	168	96	51-160
PRMC Review Time	IRB Review Time	Pre-Opening Time	Opening to Clinical Center	Clinical Center Review Time	Time to 1st Patient Enrollment	172	1	1-2
PRMC Review Time	IRB Review Time	Pre-Opening Time	Opening to Clinical Center	Clinical Center Review Time	Time to 1st Patient Enrollment	169	1	1-1
PRMC Review Time	IRB Review Time	Pre-Opening Time	Opening to Clinical Center	Clinical Center Review Time	Time to 1st Patient Enrollment	270	4	2-8
PRMC Review Time	IRB Review Time	Pre-Opening Time	Opening to Clinical Center	Clinical Center Review Time	Time to 1st Patient Enrollment	229	50	18-140

Development time is not different among branches with high throughput of trials

Branches with >45 studies between 2000 – 2007*	No. of Trials	Overall Development Time, *days* (Median, IQR)	min – max, *days*	Comparison	P Value *
SB	56	183 (149-257)	68 - 1107	vs. POB	P=0.909
				vs. MOB	P=0.132
POB	49	175 (129-402)	81 – 1023	vs. SB	P=0.909
				vs. MOB	P=0.361
MOB	49	225 (139-323)	47 - 1435	vs. SB	P=0.132
				vs. POB	P=0.361

- SB – Surgical branch, POB – Pediatric Oncology Branch, MOB – Medical Oncology Branch
- SB, POB, and MOB had 1 study each with incomplete development timing data
- Overall Development Time is presented in calendar days and is calculated from the receipt of the protocol at PRMC to the time the study is open to accrual at the CC
- Test for significance calculated using Mann-Whitney Test

Experience Matters

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	Principle Investigators Stratified by Number of Opened Studies between 2000 - 2007			
	1-4 Studies	5-10 Studies	Greater than 10 Studies	Total
No. of Unique Pis	43	13	5	61
Overall Development Time *				
Median Development Time, d (IQR)	241 (176 - 372)	210 (136 - 299)	177 (133 - 238)	206 (141 - 307)
No. of Trials	88	90	89	267
PRMC Review Time **				
Median PRMC Time, d (IQR)	71 (39 - 124)	75 (45 - 128)	44 (31 - 84)	64 (39 - 114)
No. of Trials	88	89	88	265
IRB Review Time ***				
Median IRB Time, d (IQR)	108 (54 - 184)	87 (52 - 160)	99 (47 - 145)	96 (51 - 160)
No. of Trials	49	62	60	171

Overall Development Time:: “1-4” vs “>10”, p<0.001;
“1-4” vs “5-10”, p=0.026
PRMC Review Time:: “5-15 vs “>10”, p<0.001;
“1-4” vs “>10”, p=0.011
IRB Review Time:: No significant differences observed

* 7 studies (2.6%) did not have avaiable PRMC receipt date or Activation Date
** 9 studies (3.3%) did not have available PRMC receipt or PRMC approval dates
*** 103 studies (37.6%) did not have avaiable IRB receipt or IRB approval dates
**** Mann-Whitney U non-parametric significance test

Recommendations

1. **Scientific quality of a protocol should be the responsibility of the Branch**
2. **The number of redundant Review Committees should be minimized**
3. **Quality assurance should be practiced instead of quality control**
4. **CCR Branch Chiefs are collectively responsible for:**
   - Assuring non-competing studies
   - Assuring consistent quality across branches
   - Developing and maintaining the vision, portfolio and priorities of trials at CCR
5. **Protocols should be generated both bottom-up and top-down**
   - Bottom-up – from the investigators
   - Top-down – from the leadership of CCR
6. **Create critical items for assisting in the achievement of goals:**
   - Visibility
   - Metrics / Standards
   - Education

Implementation

- ***Goal Stated to community:*** **60-days from scientific protocol review to opening for patient accrual**

- ***PRMC disbanded-scientific review now at Branch level***

- ***Establishment of Implementation Teams:***
  - *CCR Protocol Concept Review – focused on how concepts will be vetted across CCR (workgroup is finalizing recommendations)*
  - *Lab/Branch Scientific Reviews – focused on recommending standard operating procedures, expectations, best practices, continuity across clinical program (workgroup has formed and held first meeting)*
  - *Process and Metrics – focused on identifying what needs to be measured and how data will be collected; time frames necessary to meet 60 day goal; common categorizing of stipulations (administrative, regulatory, safety,scientific etc.)*

Implementation

- ***Potential Additional Implementation Teams:***
  - ***Protocol Support Service*** *– Writing support, administrative processing, common templates*
  - ***Training & Mentoring*** *– Protocol writing and mentoring, IRB members*
  - ***Continual Evaluation*** *– Are the metrics measuring what they were intended to measure? Evaluate metrics, including feedback from stakeholders, refine training and processes based on lessons learned*
  - ***Patient Recruitment*** *– Establishing effective outreach to accrue patients to clinical studies including community physicians and advocates; Establish stronger ties with community physicians through CME events*
  - ***Collaboration with External Sponsors*** *– Build relationships with CTEP, pharma to assure simultaneous review*
  - ***Portfolio Evaluation*** *– Regular review and evaluation of clinical trials portfolio; encourage studies both from top-down and bottom-up aligned with clinical vision and priorities*

- ***Steering Committee will be formed composed of Implementation Team Chairs for overall coordination***