Clinical Trials Infrastructure Workshop # 3

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Objectives

- To discuss the infrastructure needed to conduct clinical trials ?
- To discuss the challenges of conducting clinical research in the current environment ?
- To discuss opportunities to improve how we conduct clinical trials in Canada?

Clinical Research – Scenario # 1

- You have just starting working as a staff oncologist at a large cancer center in Canada
- You are approached by a pharmaceutical company with regards to your interest in participating in a phase III RCT in breast cancer
- You sign the CDA and eagerly await the full protocol and contract
- You promise the company your center will accrue well to this trial

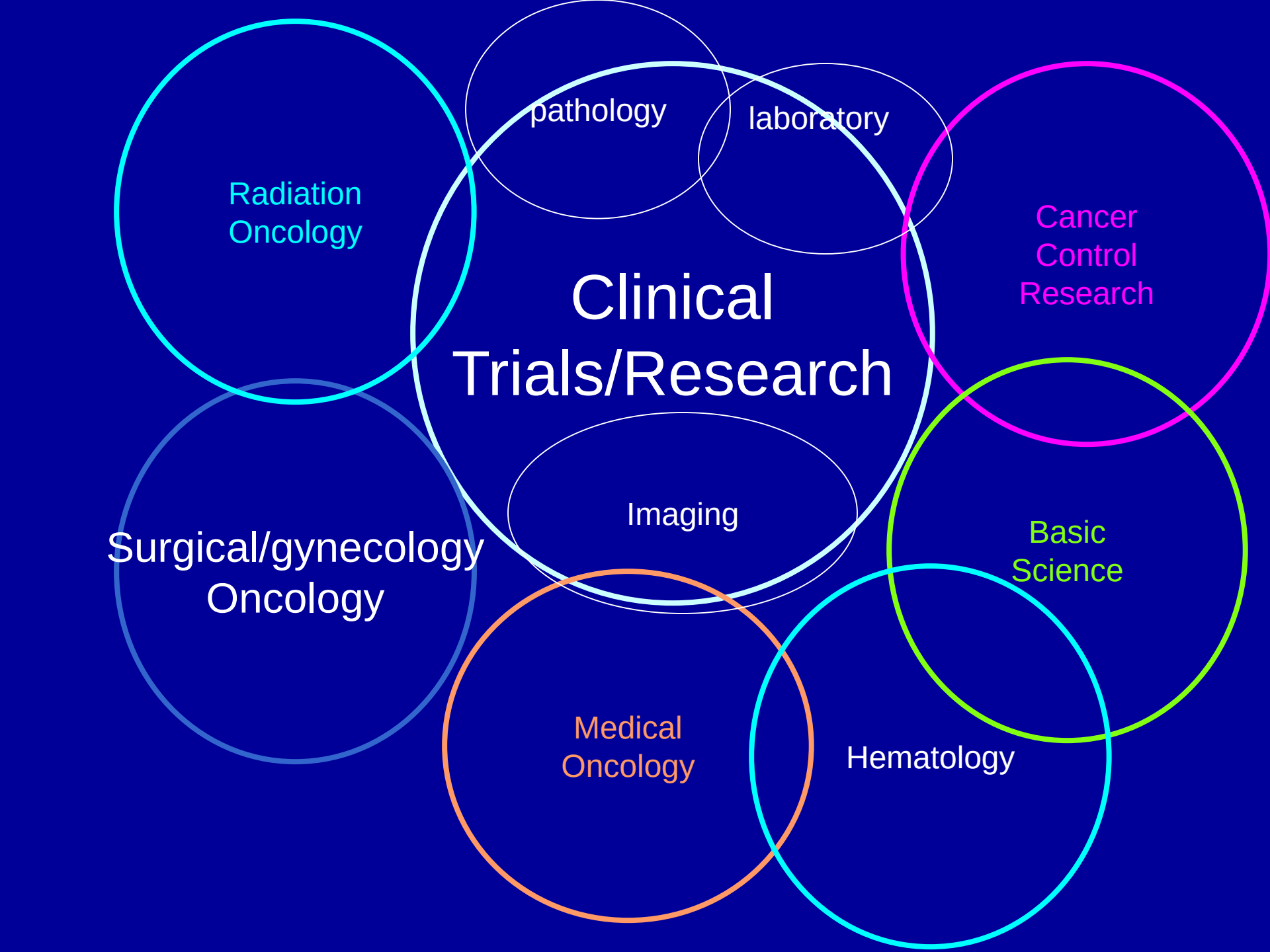
Clinical Research – Scenario # 1

- You receive the protocol and send it to your local REB for approval
- You inform your clinical trials manager that you have an exciting protocol that you will be opening in the center shortly
- You request a clinical research associate be assigned to the study
- Your clinical trials manager has significant concerns. Why ?

What are the problems with this scenario !

- Liability – CDA, contract
- Feasibility – patients, infrastructure
- Resources – budget, clinical trials staff

Landscape is changing !


pathology
laboratory
Radiation Oncology
Clinical Trials/Research
Cancer Control Research
Imaging
Basic Science
Surgical/gynecology Oncology
Medical Oncology
Hematology

Clinical Trials Mosaic

Resources

Staff

Finances

Physical Space

Protocol Review

Productivity

Clinical Trials Office

Research ethics board

Education

Pharmacology

Policy and Procedures

Communication

Quality Assurance

Disease Site Committees

Regulatory Changes

- Greater demands by Health Canada/FDA
- Privacy legislation (implications REB submissions > 6 months to activate studies)
- Increased regulatory requirements for trials outstripped available resources
- Increased costs of studies in Canada
- Less competitive with other countries

The Regulatory Traffic Jam

www.houstonfreeways.com/images/other_pages/retrospective/traffic_jam_rita.jpg

Cancer Report Card 2010/11

Fighting cancer is hard enough–
your government should not make it worse.

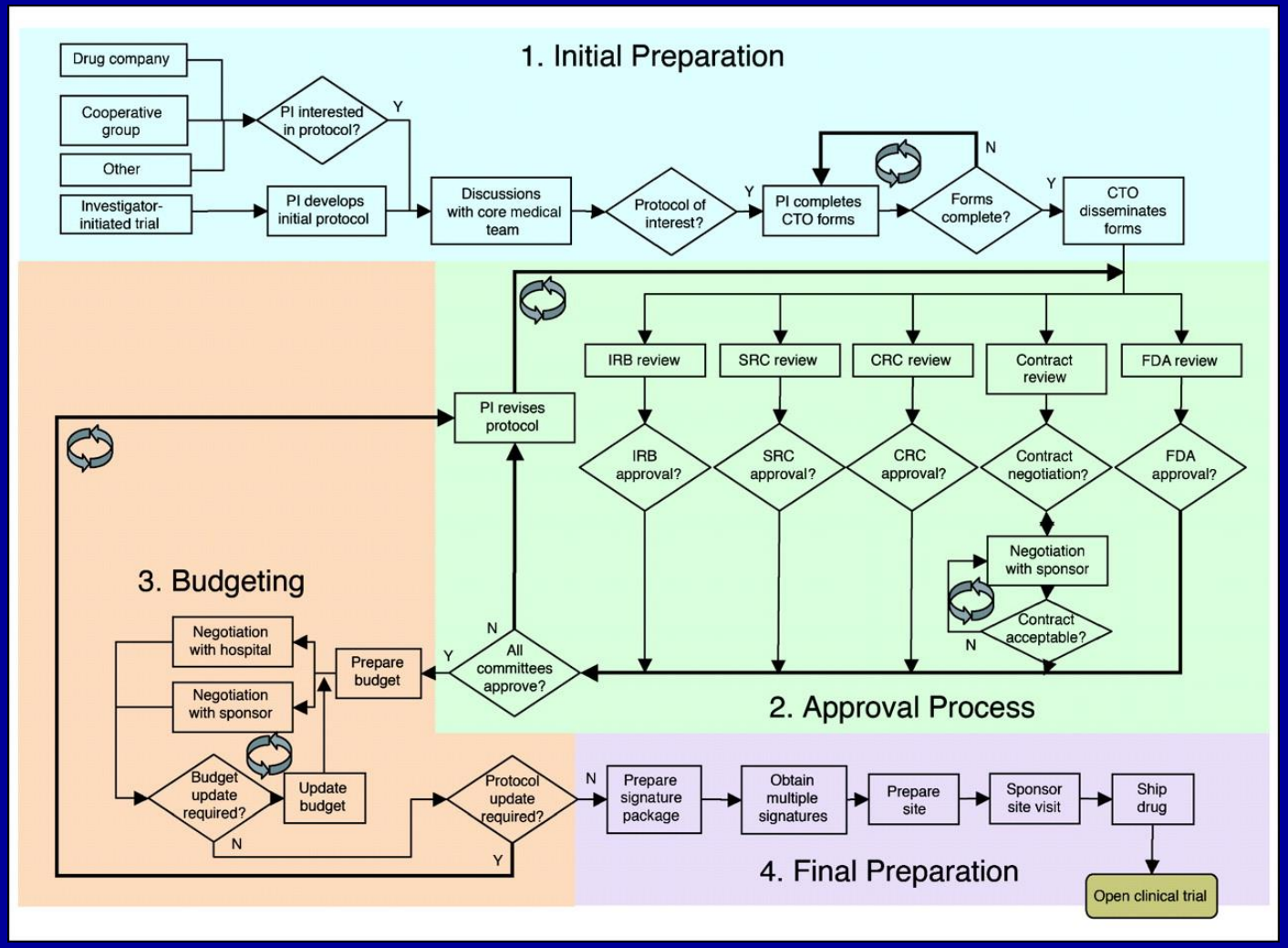
Cancer Advocacy Coalition of Canada, 2010

Invisible barriers to clinical trials: the impact of structural, infrastructural, and procedural barriers to opening oncology clinical trials

- up to 110 process steps in trial activation
- (50% non value added)
- 27 groups involved
- Median time for contract negotiations = 78.5 days
- Median time to trial activation = 171 days

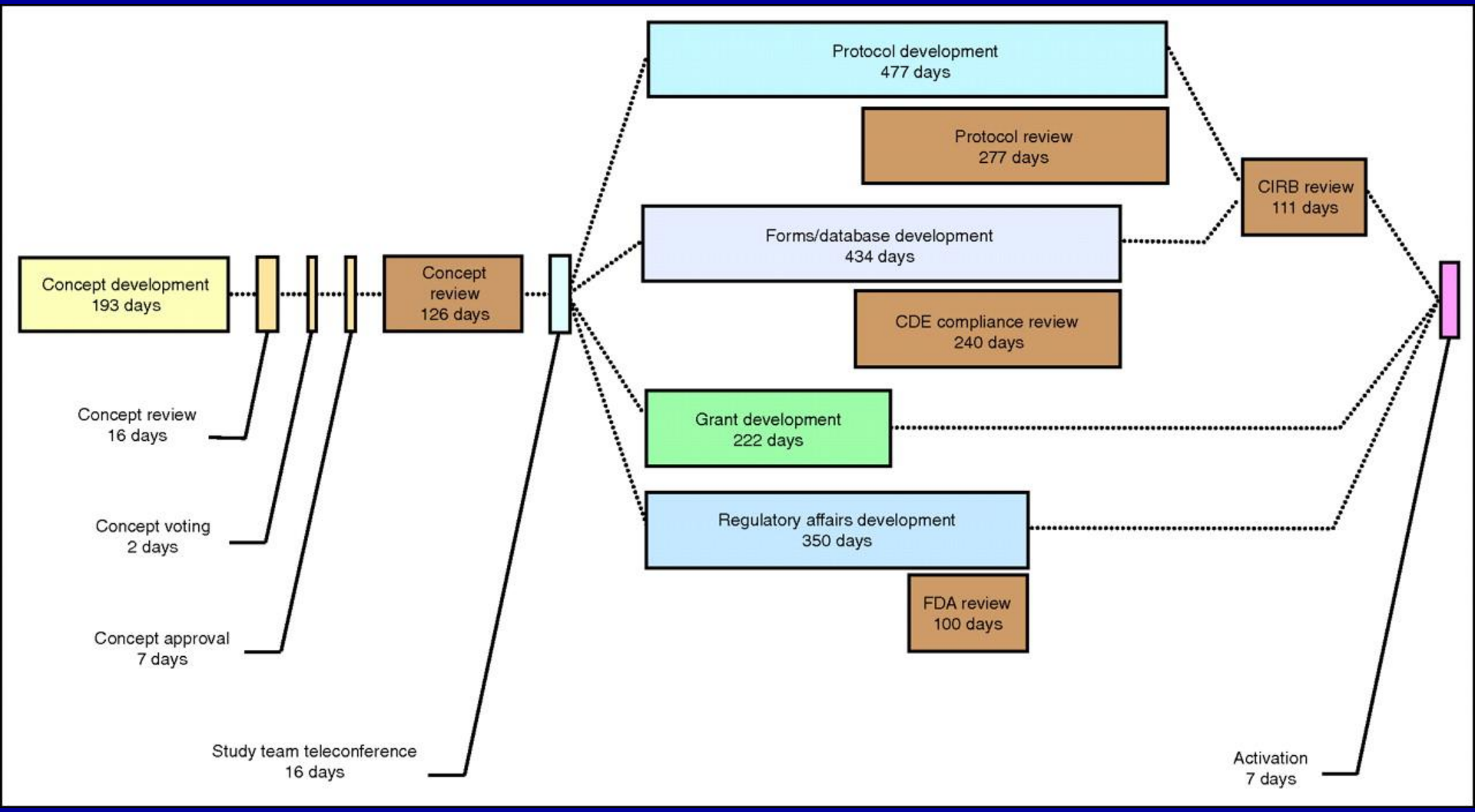
Dilts et al. JCO, 2006

Steps needed to Open a Clinical Trial.



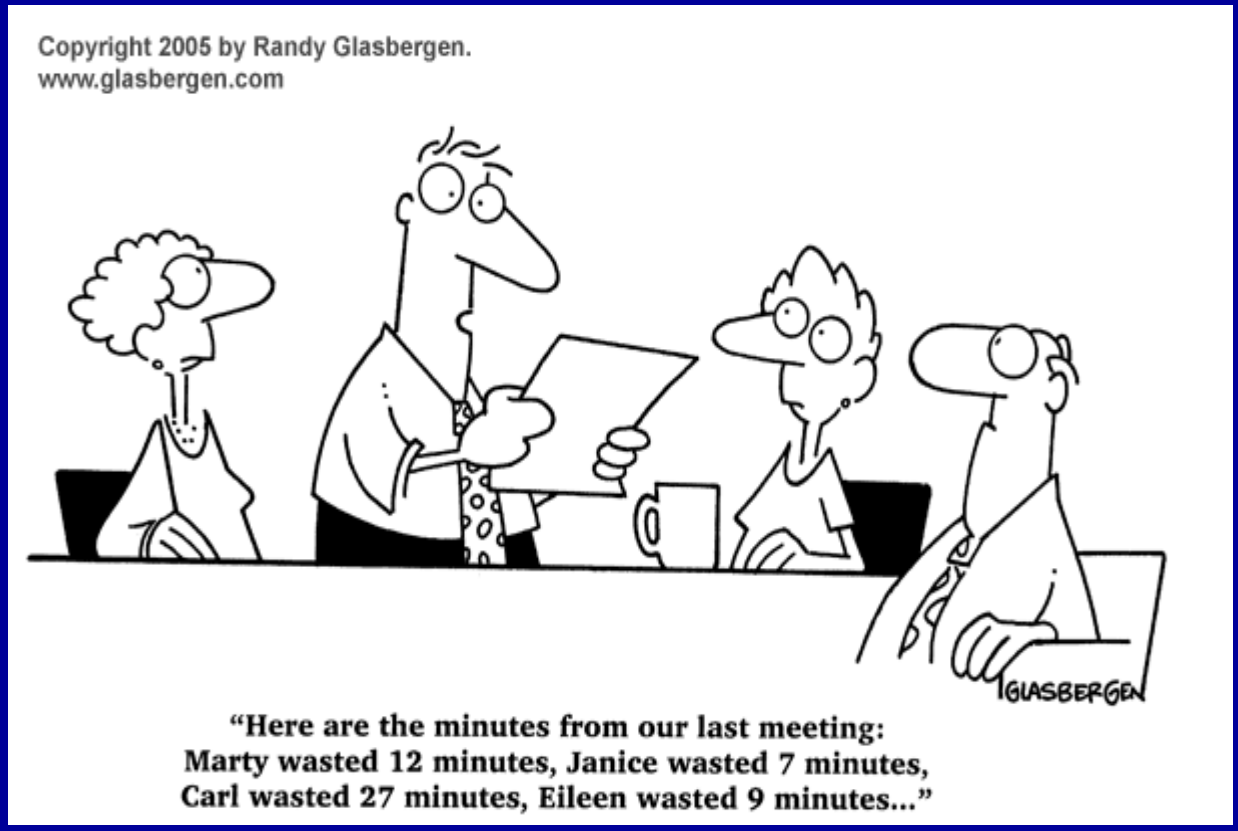
Dilts D M , and Sandler A B JCO 2006;24:4545-4552

Steps to activate a CALGB clinical trial



Dilts, et al JCO 2006

Clinical Trial Resources

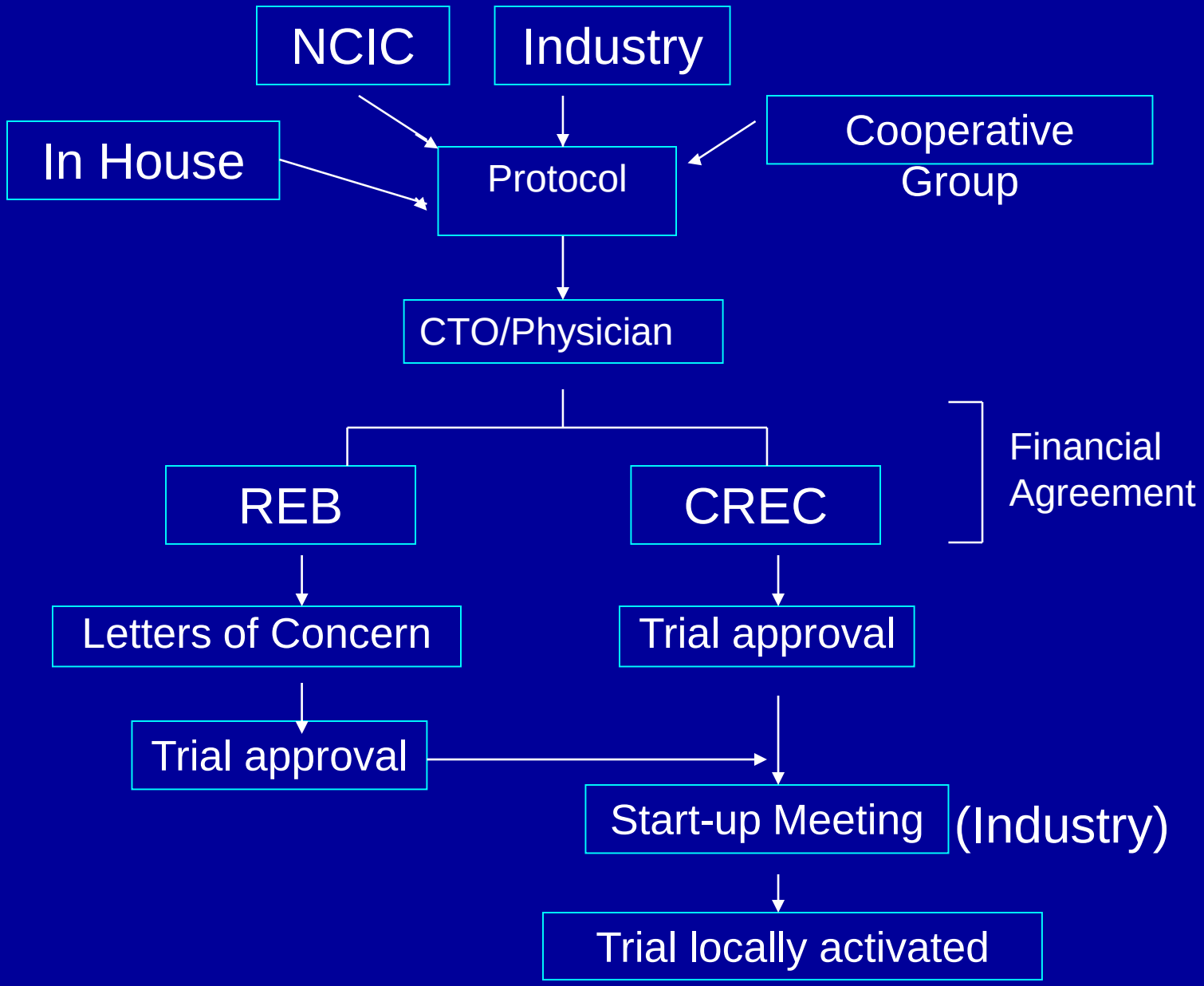


Lessons Learned

Overview of Clinical Trials in Ottawa (2001)

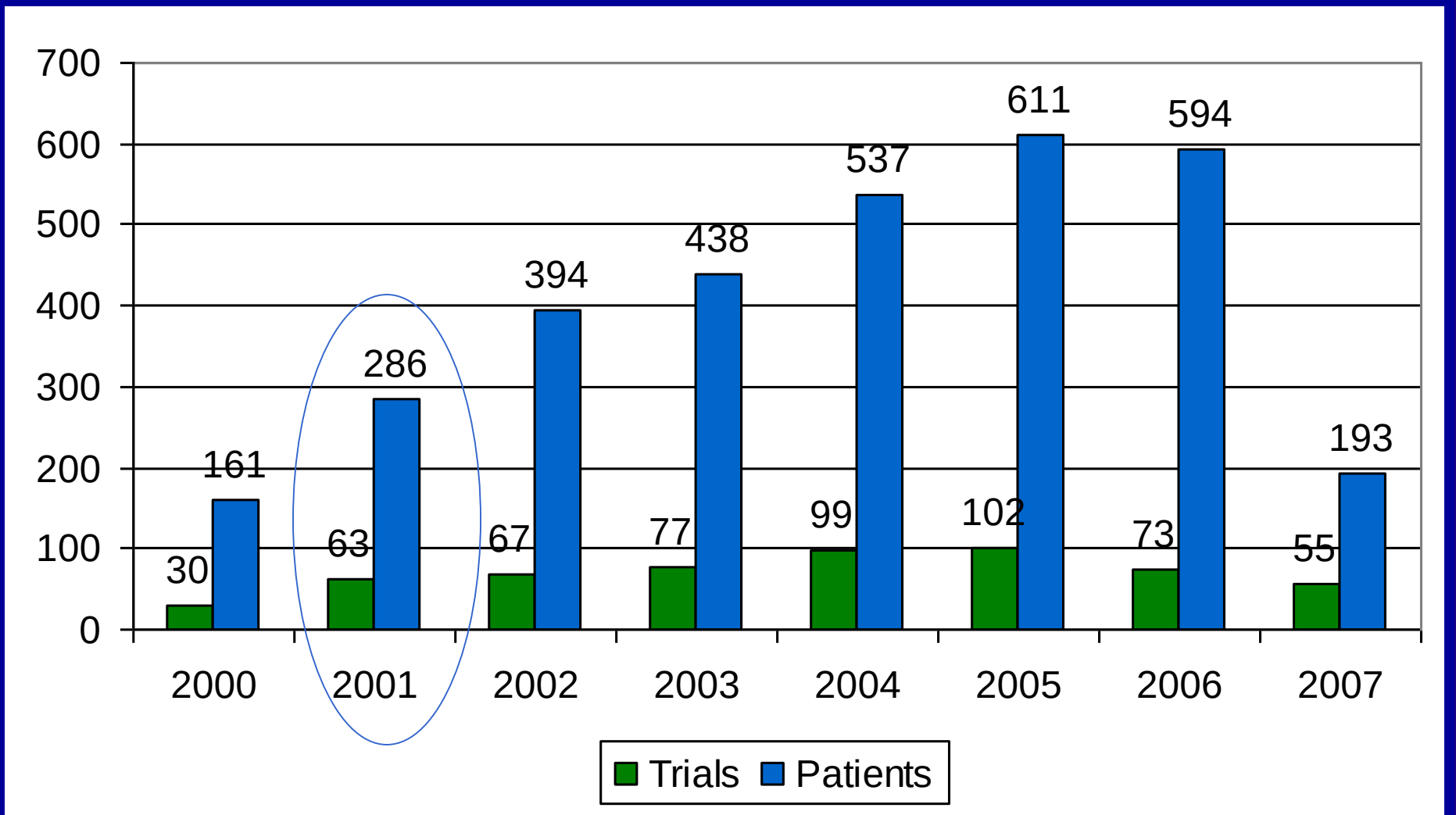
- multiple protocols submitted by individual investigators to REB simultaneously
- little communication between investigators and physicians within a disease site
- no impact analysis performed prior to submission of trial to Ethics
- Trials approved by REB but not activated due to inadequate CTO resources

Protocol Review Process (2001)



Accrual and number of trials

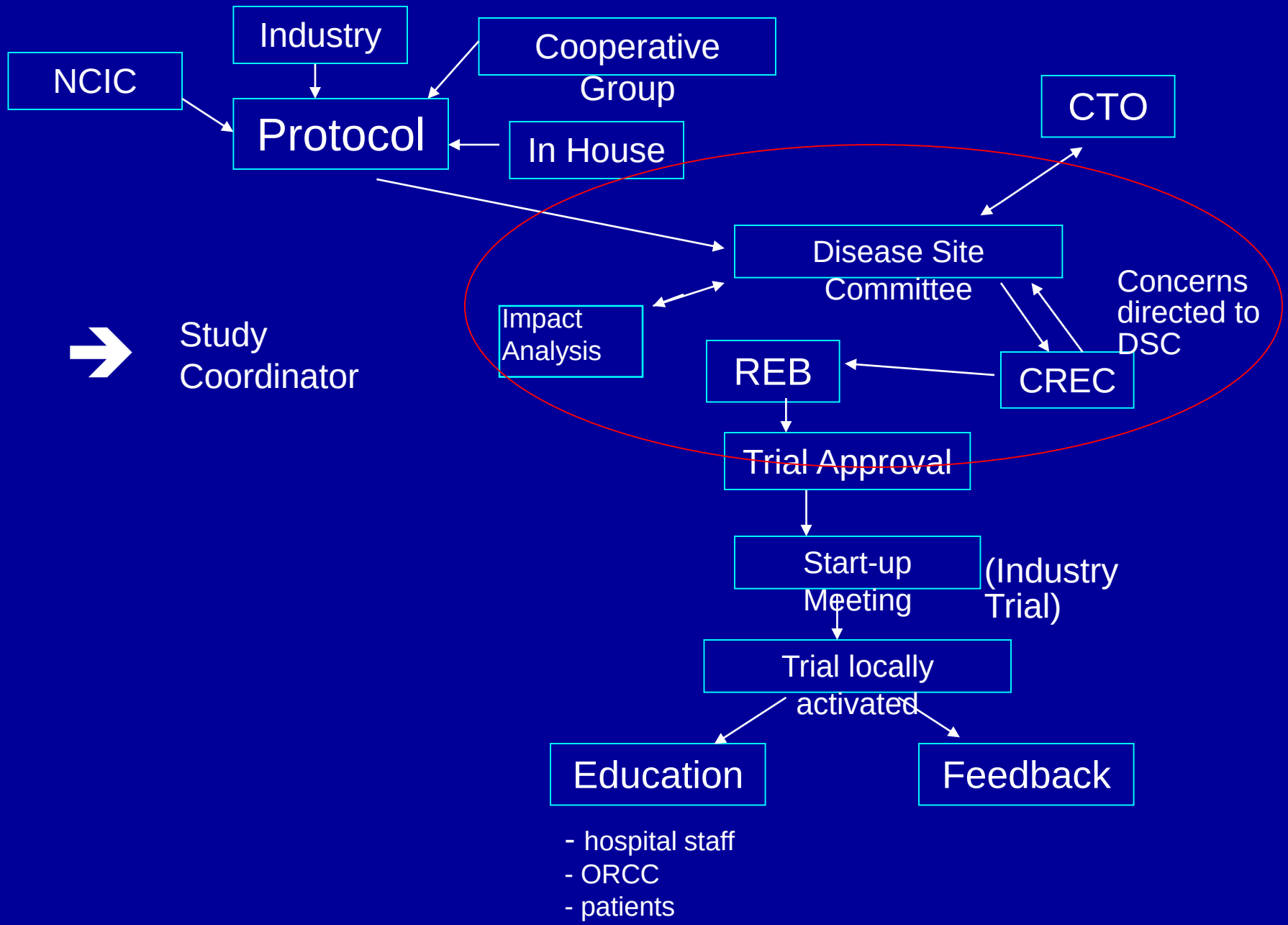
(2000-2007)



Consequences of CTO model

- Late submission of amendments
- Missing protocol amendment approvals
- Submission of SAE's not within timelines
- Insufficient source documentation
- Missing elements in consent forms
- Late submission of data (e.g form 1)

Protocol Review Process-after 2001



Protocol Review Process

- Advantages
  - Disease Site Committees prioritize protocols
  - Young investigators have the opportunity to act as principal investigator
  - CREC has the opportunity to review the impact of proposed trials prior to submission to REB
- Disadvantages
  - Another “step” in the approval process

Clinical Scenario # 2

- You have been approached by a cooperative group to be the local PI of a study in pancreatic cancer
- Your protocol was submitted and approved by the local REB and the budget is satisfactory
- You ask the clinical trials manager to assign a CRA to this trial but….she has concerns
- There are currently two other protocols open to accrual in the same patient population.
- Now what ?

Prioritization of Clinical Trials

Prioritization of Clinical Trials

1. **Total number of trials** (active and pending)
   -how many clinical trials can your CTO support ?
2. **Clinical Research Priorities**:

   - investigator initiated, peer grant-funded trials, phase I trials, biologic and targeted agents, novel radiation techniques/ approaches

Target number of studies by disesase site

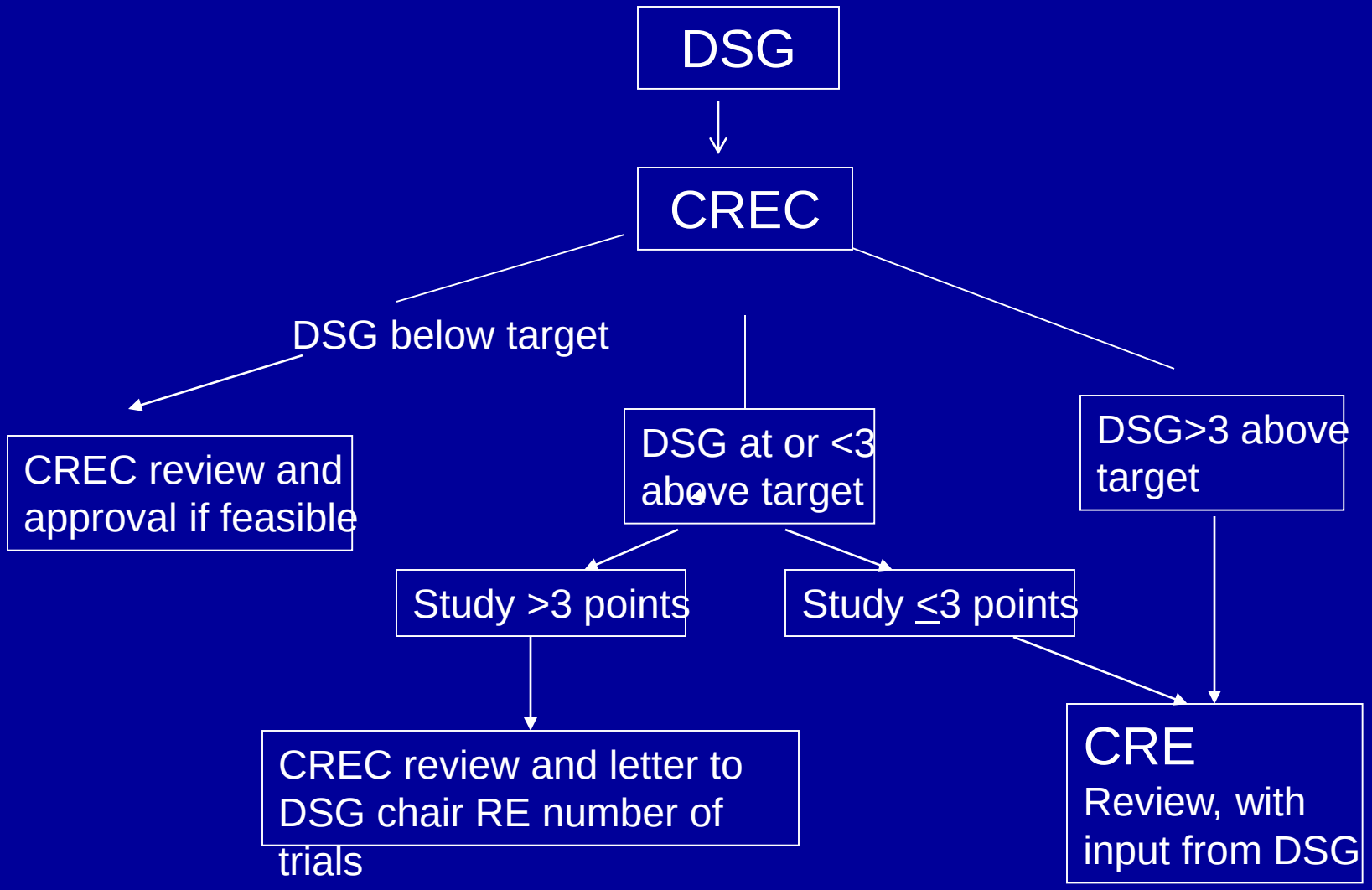
Site	Target # of active/pending trials
Breast	18
GI	18
Lung	18
GU	12
H&Neck/CNS	7
Melanoma/sarcoma	5
Phase I/IND	12
Gyne	6
Radiation without site	4
TOTAL	**Total 100**

Investigator initiated study	Points
Being a TOHRCC investigator initiated trial	1
Funded by peer-reviewed grant (CIHR/NCIC/OCRN/CBCF etc...)	3
Funded by other grants	2
Significant publication contribution	2
Accrual > 10 ; 5-10; <5	3 ; 2 ; 1
Peer-reviewed cooperative large phase II/III trials (NCIC RTOG NSABP)	**Points**
Led by TOHRCC PI	3
Expected significant publication contribution	2
Accrual > 10 ; 5-10; <5	3 ; 2 ; 1
Industry sponsored large phase II/III trials	**Points**
Led by TOHRCC PI	3
Significant publication contribution	2
Accrual > 10 ; 5-10; <5	3 ; 2 ; 1
Generous budget	1-2

Phase I / small phase II trials	Points
Being a phase I/small II trial	1
Led by TOHRCC PI	3
Significant publication contribution	2
Accrual > 10 ; 5-10; <5	3 ; 2 ; 1
Involving novel targeted single or combined anticancer therapy demonstrating a clear biological rationale and with which TOHRCC investigators have already acquired a significant expertise through collaboration with translational research scientists from the Centre for Cancer Therapeutics	2
Generous budget (if Industry sponsored)	1-2

Point system to determine priority of trials

Process of prioritizing clinical trials



Closure of Non Accruing Trials

- Trials with no accrual within 9-12 months of REB approval should be closed

- PI/DSG chair is given the opportunity to inform the Clinical Research Executive Committee if there is a compelling reason to keep trial open

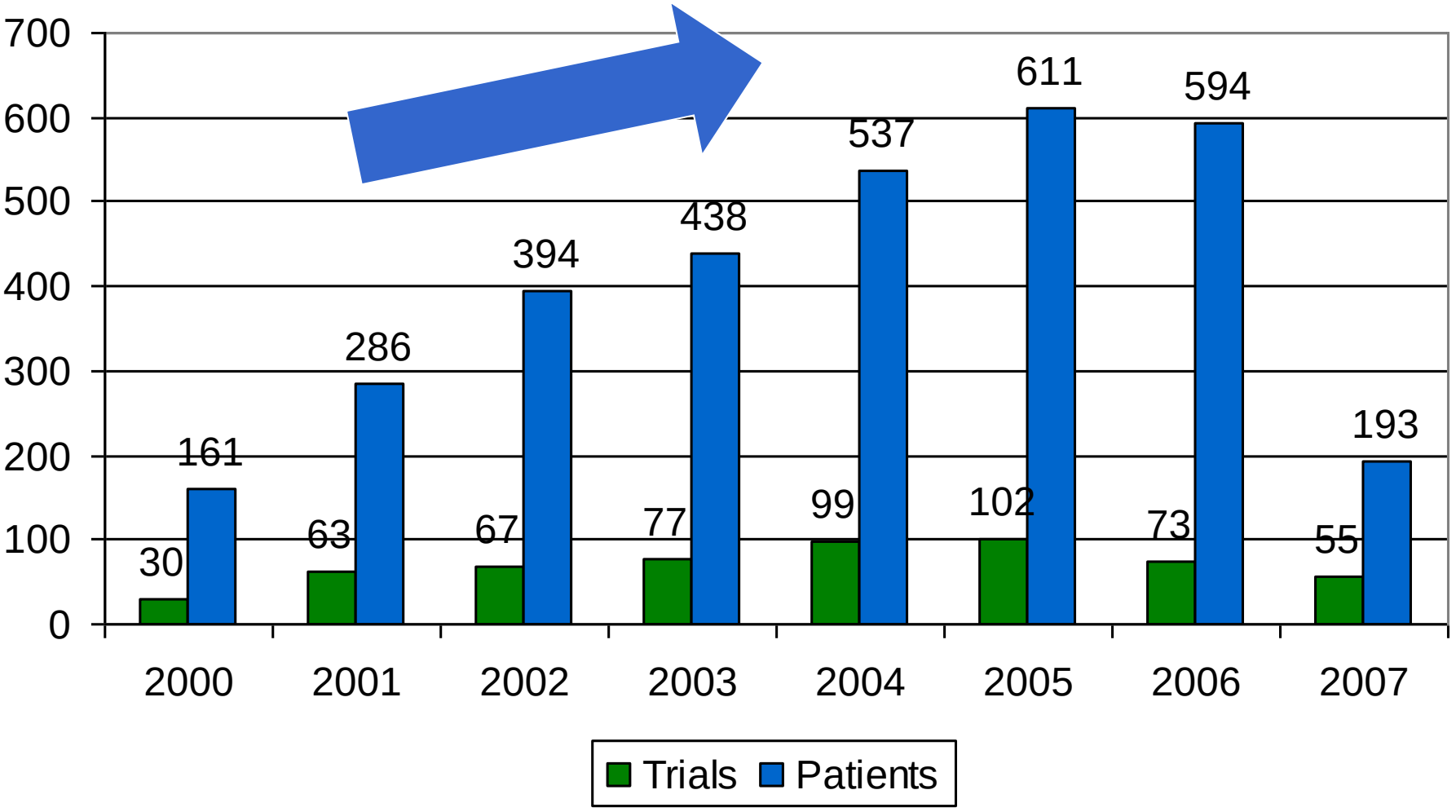
Clinical Trial Activity in Ottawa post 2001 review

- Results:
  - Total # of active trials reduced by 28%
  - Industry sponsored trials increased by 64%
  - Overall enrollment increased by 36%

Dent S. Clinical Trials Review, 2002

Accrual and number of trials

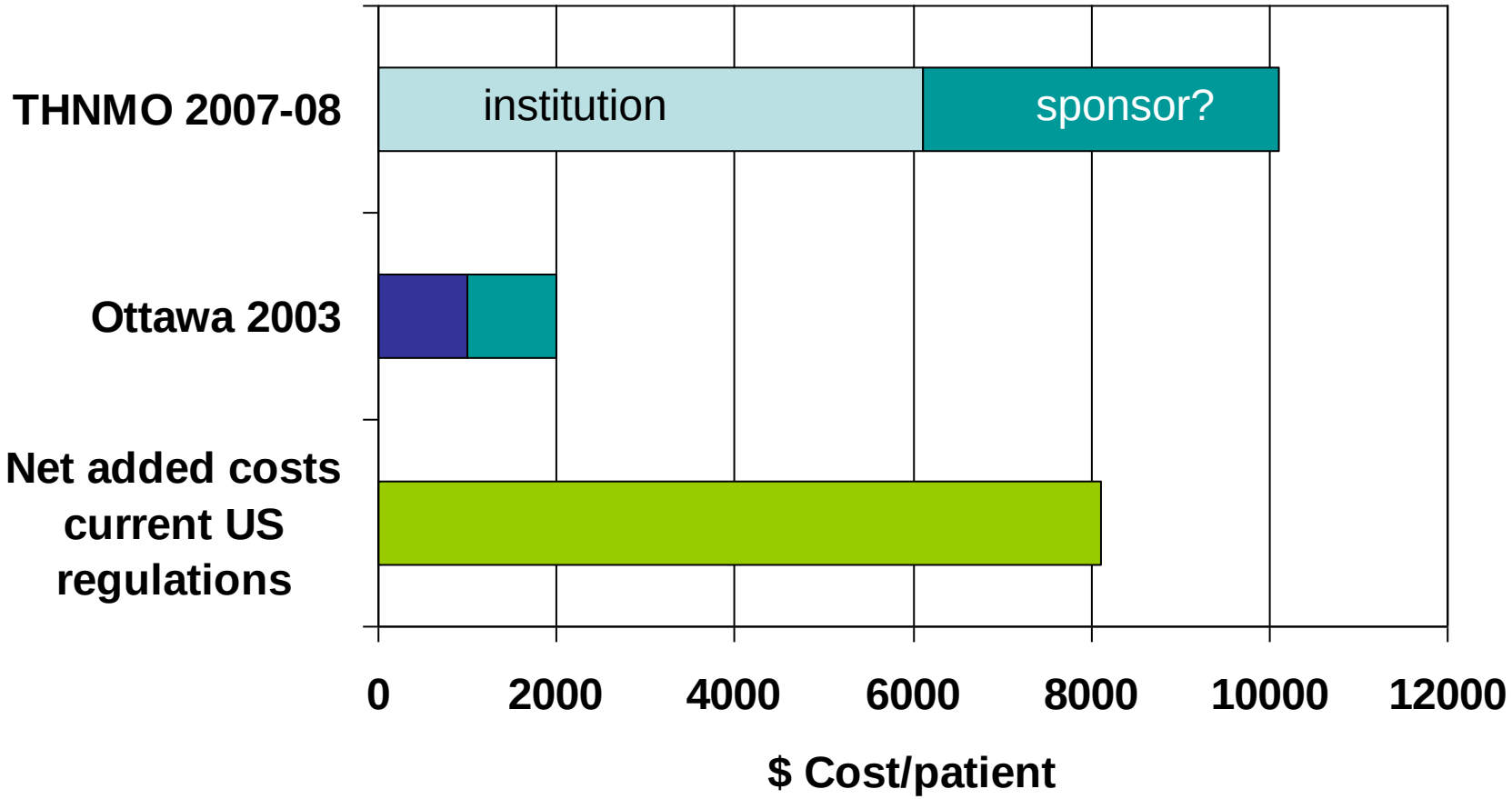
(2000-2007)



Clinical Scenario # 3

- You have been approached by another colleague to take part in a investigator initiated study in lung cancer
- All the regulatory issues have been addressed and you have REB approval
- You are informed the per case funding is $2,000
- Your clinical trials manager has significant concerns !

Regulatory, research nurse, data management cost/patient MDACC 2008 vs Ottawa, Canada 2003



Budget

- On average $9,800 to enroll a patient in a clinical trial in 2013

Sample Budget

Per Patient Costs		Cycle=28d																	
Procedure	COST	Screening	Cycle 1		Cycle 2		Cycle 3		Cycle 4	Cycle 5	Cycle 6		Cycle 7+	End of study tx	Follow-up after tx stop			TOTAL	
			1	15	1	15	1	15			1	15			4 wks	12 wks	6 mos		
Signed Informed Consent	$150.00	$150.00																$150.00	
Medical history	$100.00	X																$0.00	
Physical exam (including HEENT, vital signs, height, weight, interval medical hx)	$200.00	X	X	X	X	X	X		X	X	X		X	X	X			$0.00	
Anal and gyne exam (by investigator)	SOC	X												X			X	$0.00	
Pregnancy test (& FSH)	$40.00	$40.00																$40.00	
CBC (hematology)	$50.00	X	X		X		X		X	X	X		X					$0.00	
Serum chemistry & LFTs	$75.00	X	X	X	X	X	X	X	X	X	X		X					$0.00	
Fasting blood glucose & lipid panel	TBD	X																$0.00	
DI: CT brain (includes CD copy)	$527.93	SOC																$0.00	
DI: CT - chest (with contrast - industry- includes CD copy)	$650.00	SOC					SOC			SOC			SOC				$650.00	$650.00	
DI: CT - abdo (with contrast - industry; includes CD copy)	$650.00	SOC					SOC			SOC			SOC					$0.00	
DI: CT - pelvis (with contrast industry; includes CD copy)	$650.00	SOC					SOC			SOC			SOC					$0.00	
DI: Contrast ($41 per body part)	$123.00	$123.00					$123.00			$123.00			$123.00					$492.00	
DI: Lossless compression for CD copies	$17.00	$17.00					$17.00			$17.00			$17.00					$68.00	
DI: CD copies - CRA Shipping Time	$50.00	$50.00					$50.00			$50.00			$50.00					$200.00	
Medical Oncology: Colour photographs of superficial lesions	SOC	X					SOC			SOC			SOC					$0.00	
Cardio: EKG - 12 lead (STAT)	$16.65	$16.65		$33.30		$16.50		$16.50				$16.50	$16.50					$115.95	
Cardio: Echocardiogram of the heart (routine)	$324.00	$324.00			$324.00					$324.00			$324.00	$324.00				$1,620.00	
Cardio: CD copies (for Echo) (each)	$110.00	$110.00			$110.00					$110.00			$110.00	$110.00				$550.00	
Cardio: CD copies (for Echo) - CRA time (each)	$50.00	$50.00			$50.00					$50.00			$50.00	$50.00				$250.00	
Path: Archival tumour sample release	$100.00	$100.00																$100.00	
Eye Institute: Ophthalmology Assessment	$200.00	$200.00			$200.00					$200.00			$200.00	$200.00				$1,000.00	
Dermatology: Dermatology Exam	$140.00	$140.00			$140.00					$140.00				$140.00			$140.00	$700.00	
Dermatology: Tumour biopsy for biomarker analyses	$60.00	$60.00				$60.00								$60.00			$60.00	$240.00	
Dermatology: Cutaneous SCC tumour tissue or suspicious neoplasms	$190.00	$190.00																$190.00	
Pharmacology: Genetic blood sample (optional sample for RCR)	$100.00		$100.00															$100.00	
Pharmacology: Mandatory whole blood sample for genotyping	$100.00		X															$0.00	
Pharmacology: PK assessments (per hour)	$100.00		X	$200.00		$100.00												$300.00	
Pharmacology: Plasma biomarkers (mandatory whole blood biomarker sample)	$100.00		X				$100.00			$100.00			$100.00	$100.00				$400.00	
Pharmacology: Dry ice (per shipment)	$22.00		$22.00	$22.00		$22.00	$22.00			$22.00			$22.00	$22.00				$154.00	
Pharmacology: Shipping costs	$50.00		$50.00	$50.00		$50.00	$50.00			$50.00			$50.00	$50.00				$350.00	
Pharmacy: Drug (oral, $15 each, vemurafinib & GDC-0973/placebo)	$30.00		$30.00	$30.00	$30.00	$30.00	$30.00	$30.00	$30.00	$30.00	$30.00	$30.00	$30.00					$330.00	
CRA: QOL questionnaire (EORTC QLQ-C30 & EQ-5D, $25 each)	$50.00		$50.00	$50.00	$50.00	$50.00			$50.00		$50.00		$50.00	$50.00	$50.00			$450.00	
CRA: time (per hour)	$50.00	$200.00	$200.00	$200.00	$100.00	$100.00	$200.00	$100.00	$100.00	$200.00	$100.00	$100.00	$200.00	$200.00	$50.00	$50.00	$50.00	$2,150.00	
CRA: eCRF time (per hour)	$50.00	$200.00	$200.00	$200.00	$100.00	$100.00	$200.00	$100.00	$100.00	$200.00	$100.00	$100.00	$200.00	$200.00	$50.00	$50.00	$50.00	$2,150.00	
TOTAL		$1,970.65	$652.00	$785.30	$1,104.00	$528.50	$792.00	$246.50	$280.00	$1,616.00	$280.00	$246.50	$1,542.50	$1,506.00	$150.00	$100.00	$950.00	$12,749.95	
Overhead for INDUSTRY studies	30%	$591.20	$196.50	$236.59	$331.20	#######	$237.60	$73.95	$84.00	$484.80	$84.00	$73.95	$462.75	$451.80	$45.00	$30.00	$285.00	$3,824.99	
Total Per Patient (incl. Overhead)		$2,561.85	$847.80	$1,020.88	$1,436.20	$887.05	$1,029.60	$320.45	$364.00	$2,100.80	$364.00	$320.45	$2,005.25	$1,957.80	$195.00	$130.00	$1,235.00	$16,574.94	
Sponsor will pay																		$26, 683.00	(If pt on study for 12 cycles & is flu for 24 mos)
Administrative Costs																			
	Industry	Sponsor will provide																	
Administrative start-up fees	$3,500.00	$3,905																	
Pharmacy start-up fees	$1,000.00																		
CRA eCRF training time (2 hrs) plus back-up (4 hrs)	$300.00																		
SAE management fee (For OCREB-Centre studies, this fee can be as intergroup)	$2,000.00																		
Storage Fees (see formula below to complete)	$210.00																		
Monitoring (200$ per visit; about 10 visits per year)	$2,000.00																		
TOTAL	**$8,010.00**																		
Overhead (30%)	$2,703.00																		
Total Administrative Costs (incl. Overhead)	*$11,713.00*																		
One time costs (no overhead)																			
Radiation Safety Review	$400.00																		
REB review fee (OCREB-C)	$0.00	$3,015																	
Cardiopulmonary Review Fee	$60.00																		
Diagnostic Review Fee	$78.00																		
Invoiceables																			
Amendment or Annual Renewal (each, with overhead)	$0.00																		

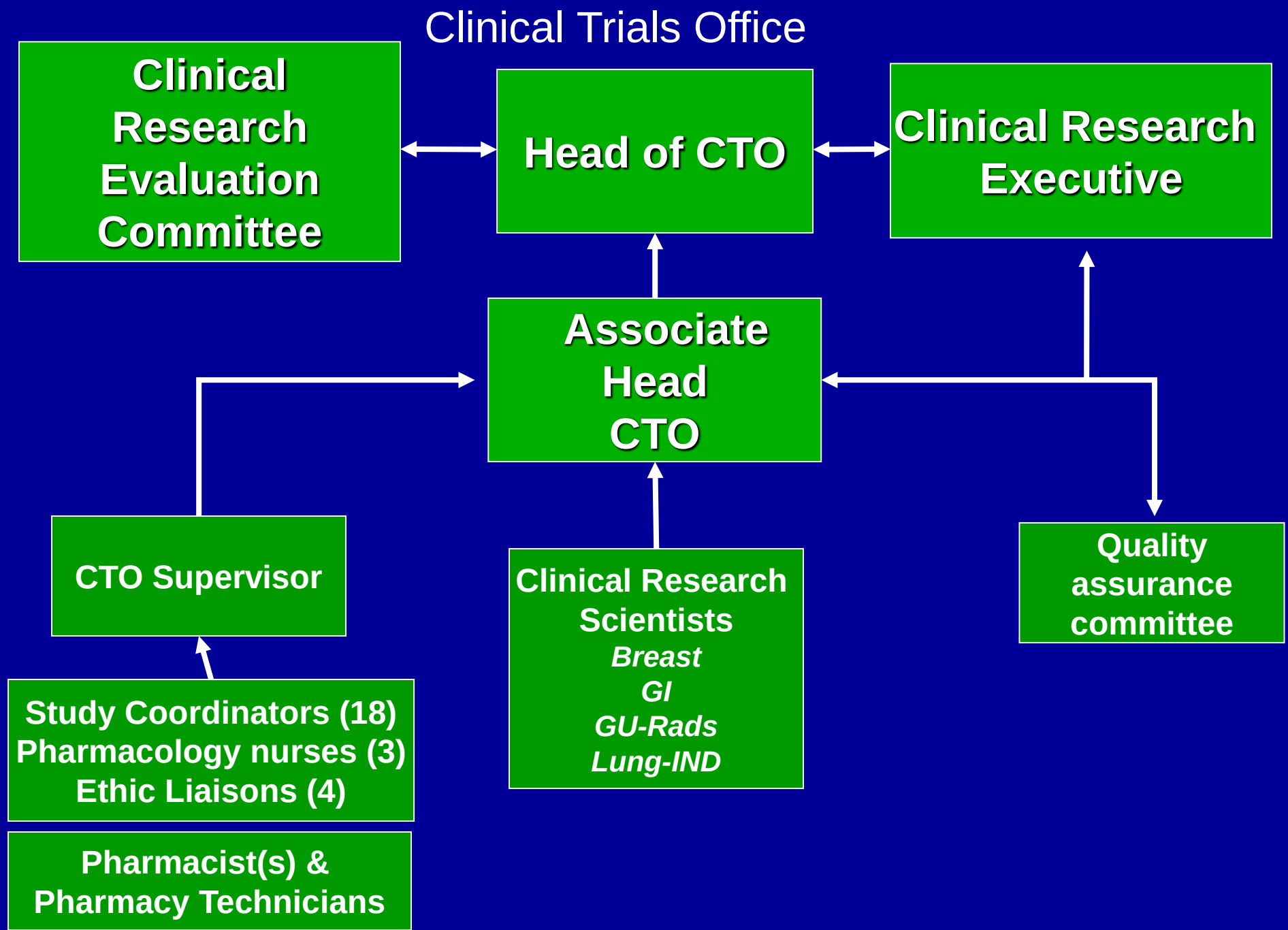
Procedure	*COST*
Signed Informed Consent	$150.00
Medical history	$100.00
Physical exam	$200.00
Imaging	$2,974.80
Pharmacology	$687.00
CRA: time (per hour)	$50.00
CRA: eCRF time (per hour)	$50.00
TOTAL	
Overhead for INDUSTRY studies	30%
Total Per Patient (incl. Overhead)	

Administrative Costs

	Industry
Administrative start-up fees	$3,500.00
Pharmacy start-up fees	$1,000.00
CRA eCRF training time (2 hrs) plus back-up (4 hrs)	$300.00
SAE management fee (For OCREB-Centre studies, this fee can be as Intergroup)	$2,000.00
Storage Fees *(see formula below to complete)*	$210.00
Monitoring (200$ per visit; about 10 visits per year)	$2,000.00
TOTAL	**$9,010.00**
Overhead (30%)	*$2,703.00*
Total Administrative Costs (incl. Overhead)	***$11,713.00***

Human Resources

- Currently no adequate tool to assess workload
- Traditionally based on number of new patients accrued in a year
- Significant workload not measured
  - Monitoring visits
  - Patients on follow-up
  - Amendments, annual renewals, SAE's


Clinical Trials Office
Clinical Research Evaluation Committee
Head of CTO
Clinical Research Executive
Associate Head CTO
CTO Supervisor
Clinical Research Scientists
Breast
GI
GU-Rads
Lung-IND
Quality assurance committee
Study Coordinators (18)
Pharmacology nurses (3)
Ethic Liaisons (4)
Pharmacist(s) & Pharmacy Technicians

Clinical Trials Support

www.3ctn.ca

- The **Canadian Cancer Clinical Trials Network (CCCTN)** is a pan-Canadian initiative to improve the efficiency and quality of clinical trials in Canada

- CCCTN will provide support and coordination for a network of teams at cancer treatment centres and hospitals. With regional participation, CCCTN will develop a business plan to enable sites to increase their capacity and capability to conduct academic trials. Canada

Research Ethics Support

Central Review of Cancer Clinical Trials

Ethical Review of Research at the British Columbia Cancer Agency

by the

University of British Columbia – British Columbia Cancer Agency

Research Ethics Board (UBC BCCA REB)

Summary

- Clinical Trials are complex
- Adequate Infrastructure support essential to conduct clinical trials
- Financial stability necessary to maintain successful clinical trials program
- Need to prioritize trials based on sound science, feasibility, resources and academic merit