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 started 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!
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
Fighting cancer is hard enough—your government should not make it worse.
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

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Steps to activate a CALGB clinical trial

Dilts, et al JCO 2006
Copyright 2005 by Randy Glasbergen.
www.glasbergen.com

“Here are the minutes from our last meeting:
Marty wasted 12 minutes, Janice wasted 7 minutes,
Carl wasted 27 minutes, Eileen wasted 9 minutes...”
Lessons Learned

Wile E. Coyote's Gravity Lessons
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

- NCIC
- Industry
- Cooperative Group
- In House

Protocol

CTO/Physician

REB

Letters of Concern

CREC

Trial approval

Financial Agreement

Start-up Meeting

Trial approval

Trial locally activated

(Industry)
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)

- NCIC
- Industry
- Cooperative Group
- In House
- REB
- CTO
- CREC
- Disease Site Committee
- Impact Analysis
- Study Coordinator

1. Protocol
2. Trial Approval
3. Start-up Meeting
4. Trial locally activated
5. Education
6. Feedback
   - hospital staff
   - ORCC
   - patients
7. Concerns directed to DSC
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 disease site

<table>
<thead>
<tr>
<th>Site</th>
<th>Target # of active/pending trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>18</td>
</tr>
<tr>
<td>GI</td>
<td>18</td>
</tr>
<tr>
<td>Lung</td>
<td>18</td>
</tr>
<tr>
<td>GU</td>
<td>12</td>
</tr>
<tr>
<td>H&amp;Neck/CNS</td>
<td>7</td>
</tr>
<tr>
<td>Melanoma/sarcoma</td>
<td>5</td>
</tr>
<tr>
<td>Phase I/IND</td>
<td>12</td>
</tr>
<tr>
<td>Gyne</td>
<td>6</td>
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<tr>
<td>Radiation without site</td>
<td>4</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>Total 100</strong></td>
</tr>
<tr>
<td>Investigator initiated study</td>
<td>Points</td>
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<tr>
<td>--------------------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>Being a TOHRCC investigator initiated trial</td>
<td>1</td>
</tr>
<tr>
<td>Funded by peer-reviewed grant (CIHR/NCIC/OCRNCBCF etc...)</td>
<td>3</td>
</tr>
<tr>
<td>Funded by other grants</td>
<td>2</td>
</tr>
<tr>
<td>Significant publication contribution</td>
<td>2</td>
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<tr>
<td>Accrual &gt; 10; 5-10; &lt;5</td>
<td>3; 2; 1</td>
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<table>
<thead>
<tr>
<th>Peer-reviewed cooperative large phase II/III trials (NCIC RTOG NSABP)</th>
<th>Points</th>
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<tbody>
<tr>
<td>Led by TOHRCC PI</td>
<td>3</td>
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<tr>
<td>Expected significant publication contribution</td>
<td>2</td>
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<tr>
<td>Accrual &gt; 10; 5-10; &lt;5</td>
<td>3; 2; 1</td>
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<thead>
<tr>
<th>Phase I / small phase II trials</th>
<th>Points</th>
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<tr>
<td>Being a phase I/small II trial</td>
<td>1</td>
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<tr>
<td>Led by TOHRCC PI</td>
<td>3</td>
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<tr>
<td>Significant publication contribution</td>
<td>2</td>
</tr>
<tr>
<td>Accrual &gt; 10; 5-10; &lt;5</td>
<td>3; 2; 1</td>
</tr>
<tr>
<td>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</td>
<td>2</td>
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<tr>
<td>Generous budget (if Industry sponsored)</td>
<td>1-2</td>
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</table>

Point system to determine priority of trials
Process of prioritizing clinical trials

- **DSG**

  - **CREC**
    - **DSG** below target
      - **CREC** review and approval if feasible
    - **DSG** at or <3 above target
      - **Study >3 points**
        - **CREC** review and letter to DSG chair RE number of trials
      - **Study ≤3 points**
    - **DSG>3 above target**
      - **CRE** Review, with input from DSG
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

![Graph showing net added costs for THNMO 2007-08, Ottawa 2003, and current US regulations. The graph indicates the cost per patient in dollars. The net added costs for current US regulations are significantly higher than for THNMO 2007-08 and Ottawa 2003.]
Budget

• On average $9,800 to enroll a patient in a clinical trial in 2013
## Sample Budget

### Per Patient Costs

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Cycle 1</th>
<th>Cycle 2</th>
<th>Cycle 3</th>
<th>Cycle 4</th>
<th>Cycle 5</th>
<th>Cycle 6</th>
<th>Cycle 7</th>
<th>End of study</th>
<th>Follow-up after 1 year</th>
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<tbody>
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<td>COST</td>
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### Additional Costs

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<th>Cycle 5</th>
<th>Cycle 6</th>
<th>Cycle 7</th>
<th>End of study</th>
<th>Follow-up after 1 year</th>
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<td>Biopsy</td>
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### Sponsorship

- **Sponsor will provide $3,500**
- **Sponsor will pay $28,883, if at any study for 2 cycles & at a fee for 24 mos**

### One-time costs (no overhead)

- **Radiation Safety Review Fee**: $200.00
- **Radiation Review Fee**: $200.00
- **Cardiovascular Review Fee**: $200.00
- **Diagnostic Review Fee**: $100.00

### Indirect costs

- **Administrative Costs**: $1,000.00
- **Pharmacy Start-up fees**: $2,000.00
- **Pharmacy Start-up fees**: $3,000.00
- **Assessment and Annual Renewal (each, with overhead)**: $2,000.00

### Total Administrative Costs

- **$7,500.00**
<table>
<thead>
<tr>
<th>Procedure</th>
<th>Cost</th>
</tr>
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<tbody>
<tr>
<td>Signed Informed Consent</td>
<td>$150.00</td>
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<tr>
<td>Medical history</td>
<td>$100.00</td>
</tr>
<tr>
<td>Physical exam</td>
<td>$200.00</td>
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<tr>
<td>Imaging</td>
<td>$2,974.80</td>
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<tr>
<td>Pharmacology</td>
<td>$687.00</td>
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<tr>
<td><strong>CRA:</strong> time (per hour)</td>
<td>$50.00</td>
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<tr>
<td><strong>CRA:</strong> eCRF time (per hour)</td>
<td>$50.00</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
</tr>
<tr>
<td>Overhead for INDUSTRY studies</td>
<td>30%</td>
</tr>
</tbody>
</table>

**Total Per Patient (incl. Overhead)**

**Administrative Costs**

| Administrative start-ups fees     | $3,500.00 |
| Pharmacy start-ups 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 Support

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

[www.3ctn.ca](http://www.3ctn.ca)
Research Ethics Support

Central Review of Cancer Clinical Trials

Ontario Cancer Research Ethics Board (OCREB)

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