NCIC CTG Overview and
Opportunities

Ralph Meyer
Director, NCIC CTG
NCIC Clinical Trials Group

A research organization

A cooperative clinical trials group

Previously funded by NCIC

Now funded by CCSRI
National Cancer Institute of Canada: 1947-2009

- Non-governmental body supported by funds donated to:
  
  Canadian Cancer Society

  Terry Fox Foundation

- Supports a full spectrum of extramural (no intramural) cancer research

- Has supported national programs in epidemiology, clinical trials and behavioral research
Canadian Cancer Society Research Institute

• In 2008, CCS determined that its research initiatives should be brought “in house” rather than being directed by a separate organization

• As a result, the CCSRI was formed

• The NCIC was absorbed into the CCSRI, and no longer exists as a separate research organization

• The CCSRI is funded by donations to CCS
Funding

CCSRI

• Funds: operating grants
  program project grants
  personnel support awards
  other

• Funds two national networks / programs
  PROPEL
  ARCC
  NCIC CTG
2006 CANCER RESEARCH INVESTMENT BY FUNDING MECHANISM FOR EACH FUNDER SECTOR ($390.2M) [1]

[1] Refers to the sector of the organization that administered the funding program.
FIGURE 3.1.1
2006 CANCER RESEARCH INVESTMENT BY FUNDING MECHANISM FOR EACH FUNDER SECTOR ($390.2M) [1]

CCRA, 2008: see http://www.ccra-acrc.ca/default_en.htm
FIGURE 3.1.1
2006 CANCER RESEARCH INVESTMENT BY FUNDING MECHANISM FOR EACH FUNDER SECTOR ($390.2M) [1]

[1] Refers to the sector of the organization that administered the funding program.

CCRA, 2008: see http://www.ccra-acrc.ca/default_en.htm
FIGURE 3.1.1

2006 CANCER RESEARCH INVESTMENT BY FUNDING MECHANISM FOR EACH FUNDER SECTOR ($390.2M) [1]

- CCS ~ 60%
- 19%

CCRA, 2008: see http://www.ccra-acrc.ca/default_en.htm
The mission of the NCIC Clinical Trials Group (CTG) is to develop and conduct clinical trials aimed at improving the treatment and prevention of cancer with the ultimate goal of reducing morbidity and mortality from this disease.
NCIC Clinical Trials Group

- A research organization
- A clinical trials cooperative group
- Mandate is national
- Scope is international
- To include: all cancer disease sites, all treatment modalities
NCIC CTG: An Overview

- 1979: NCIC decides to have formal group
- 1980: CTG established in Kingston under Joe Pater
- 1982: IND Program established
- 1988: NIH funding received; formalized in 1997
- 1997: Directions reviewed by NCIC Task Force on Clinical Studies
- 2006: Recruitment of new Director
- 2010: Pediatric IND Program established
Funding

Canadian Cancer Society

Canadian Cancer Society Research Institute

NCIC CTG

National Cancer Institute (U.S.)
Funding

CCSRI Funding of NCIC CTG:

- Program grant issued every 5 years
- Contingent on successful site review
- Comprehensive grant submission
- Site visit by external reviewers
- Includes: scientific agenda, methodology and data centre
Funding

NCI (US):

• Program grant issued every 5 years

• Contingent on same criteria as NCIC / CCS, and:
  
  Leading initiatives with US groups

  Contributing to initiatives of US groups

  Includes correlative biology
Funding

Other Granting Agencies:

• e.g., CIHR
  OICR

Disease specific agencies

• Format varies: special opportunities
  companion questions

• In general, is project-specific
Industry:

- Funding is project – specific
- Partner is pharmaceutical / biotech
- Often includes correlative biology
- Relationships include additional complexities
DISTRIBUTION OF 2006 CANCER RESEARCH INVESTMENT BY FUNDING MECHANISM FOR EACH FUNDER SECTOR [1]

CCRA, 2008: see http://www.ccra-acrc.ca/default_en.htm
DISTRIBUTION OF 2006 CANCER RESEARCH INVESTMENT BY CSO CATEGORY ($390.2M)

- Biology: 45.2%
- Etiology (Causes of Cancer): 10.2%
- Prevention (Intervention): 1.9%
- Early Detection, Diagnosis & Prognosis: 9.8%
- Treatment: 23.3%
- Cancer Control, Survivorship & Outcomes: 8.6%
- Scientific Model Systems: 1.0%

CCRA, 2008: see http://www.ccra-acrc.ca/default_en.htm
DISTRIBUTION OF 2006 CANCER RESEARCH INVESTMENT BY CSO CATEGORY ($390.2M)

- Biology: 45.2%
- Etiology (Causes of Cancer): 10.2%
- Prevention (Intervention): 19%
- Early Detection, Diagnosis & Prognosis: 9.8%
- Treatment: 23.3%
- Cancer Control, Survivorship & Outcomes: 8.6%
- Scientific Model Systems: 1.0%

CCRA, 2008: see http://www.ccra-acrc.ca/default_en.htm
DISTRIBUTION OF 2006 SITE-SPECIFIC CANCER RESEARCH INVESTMENT ($183.5M) BY NEW CANCER CASES IN 2004 AND CANCER DEATHS IN 2004

CCRA, 2008: see http://www.ccra-acrc.ca/default_en.htm
Structure
Structure

NCIC CTG

Can be considered in two major categories:

External

- Network of nearly 100 investigative sites
- Committee structures involving nearly 1000 investigators and other research personnel

Internal

- Head office in Kingston - 150+ staff, 12 faculty
External Organization
External Structure

Refers to network of investigators

- **Canada:** approximately 70 sites
  - provincial cancer centers
  - university affiliations
  - special clinics

- **International:** major cooperative groups
  - single sites in many countries
External Organization

Clinical Trials Committee

- Advisory to the Director
- Considers / advises on policy, roles
- Evaluates all Phase III proposals
- Will assist in evaluating strategic directions
- Has internal + external representation
External Organization

Data Safety Monitoring Committee

- Advisory to the Director
- Responsible for: safety, data integrity, feasibility / relevancy
- Has no internal representation
- Has external + non-CTG representation
External Organization

Centre Representatives

• Deal with local operations of trial conduct
• Receive correspondence concerning their site
  Agenda, Minutes, Surveys, Drafts
• Communicate information within centre
• Advisory role relationship with central office
External Organization

Disease Site Committees

- Responsible for scientific leadership
- Each committee has executive and chair
- External and internal representation
- Chair is external, may have international role
- Selection of executive is based on:
  - Scientific leadership
  - Participation
  - Geographic / modality balance
External Organization

Disease Site Committee Membership

• Each centre has Site Committee members
• Multiple members per centre based disease / therapeutic modalities
• Some Sites have Working Groups
• Members are to *communicate* within their centre, with their executive
External Organization

Outcome – Based Committees

Correlative Sciences and Tumour Biology

Quality of Life

Working Group on Economic Analysis

- Scientific content to Sites / Trial Committees
- Methodologic research: measurement analysis
External Organization

Other Standing Committees

Radiation Quality Assurance
Audit and Monitoring Committee
Clinical Research Associates
Pharmacy Network

• Role in trial conduct
• Methodologic research
NCIC Clinical Trials Group

- Two programmatic components

Investigational New Drugs

Phase III
External Structure

Phase III Program

Agenda:

• Led by the Disease Site Committees
• Supported by the Working Groups
• Evaluated / prioritized by the CTC
• Conduct monitored by the DSMC
• Implementation assisted by: CRAs, Pharmacists
Investigational New Drug Program*

Scope:
- Phase I-II testing of new agents
- Range from ‘1st in man’ to novel combinations
- Prioritized to evaluating targeted mechanisms

Agenda:
- Led by IND executive
- Implemented by IND Committee

* Elizabeth Eisenhauer and Lesley Seymour
Internal Organization
Internal Structure

Refers to operations at Queen’s Centre for:

- Methodology and data management
- Trial coordination
- Quality management: assurance, monitoring, safety, regulatory / ethics
- Includes 14 faculty and 120 staff
Roles of Central Office Staff

**Director**
- Administer program; formulate, implement policy

**Physician Coordinators (Senior Investigators)**
- Provide medical and group input into specific trials, serve as central office medical contacts for each site
Roles of Central Office Staff

Senior Biostatisticians

• provide methodologic, statistical input into trials and analyses
• Each is responsible for a slate of sites
• Analyses conducted by biostatisticians, i.e., individuals with BSc or MSc training in statistics plus SAS / Oracle programming skills
NCIC CTG Director

Finance + Operations

Group Statistician

Trial Management

Information Technology

Ethics and Regulatory

Compliance Group

Director, Audit and Monitoring

External + Internal Audit and Monitoring

NCIC CTG Central Office Organization Chart, 2011
Activity Level
Phase III Program

Scope:

• Randomized controlled trials

• Selected phase II studies (enablers)
Broad Accomplishments

1980 – July 2011:

• 437 trials
• 65,000 patients

In 2004-2010 grant cycle:

• 200 trials were in some form of conduct
• 23,000 new patients were accrued
<table>
<thead>
<tr>
<th>Year</th>
<th>Month</th>
<th>Randomizations</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>AUG</td>
<td>41</td>
</tr>
<tr>
<td>2011</td>
<td>JUL</td>
<td>89</td>
</tr>
<tr>
<td>2011</td>
<td>JUN</td>
<td>64</td>
</tr>
<tr>
<td>2011</td>
<td>MAY</td>
<td>60</td>
</tr>
<tr>
<td>2011</td>
<td>APR</td>
<td>53</td>
</tr>
<tr>
<td>2011</td>
<td>MAR</td>
<td>51</td>
</tr>
<tr>
<td>2011</td>
<td>FEB</td>
<td>50</td>
</tr>
<tr>
<td>2011</td>
<td>JAN</td>
<td>49</td>
</tr>
<tr>
<td>2010</td>
<td>DEC</td>
<td>33</td>
</tr>
<tr>
<td>2010</td>
<td>NOV</td>
<td>25</td>
</tr>
<tr>
<td>2010</td>
<td>OCT</td>
<td>27</td>
</tr>
<tr>
<td>2010</td>
<td>SEP</td>
<td>9</td>
</tr>
<tr>
<td>2010</td>
<td>AUG</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>553</td>
</tr>
</tbody>
</table>
Selected Deliverables 2004-2010

Publications:
- > 500 trial-related manuscripts and abstracts
- > 110 Central Office faculty research reports
- 18 meta-analyses

"Building Capacity”
- 20 Fellows / PhD / Postdoctoral trainees
- 18 Masters / PhD Theses
- 2 New Investigator Workshops (total N = 70)
Changes to Canadian Health Care Practices

- Aromatase inhibitors for breast cancer (MA.17)
- Adjuvant therapy for lung cancer (BR.10)
- Erlotinib for lung cancer (BR.21)
- Temozolomide for glioblastoma (CE.3)
- Cetuximab for colon cancer (CO.17)
- Chemotherapy for Hodgkin lymphoma (HD.6)
- Limited role of RT in endometrial cancer (EN.5)
- Important role of RT in prostate cancer (PR.3)
Changes to Canadian Health Care Practices

ASCO 2011:

Three Best of ASCO Presentations:

- Aromatase inhibitors prevent breast cancer (MAP.3)
- Regional RT for breast cancer (MA.20)
- Intermittent hormone Rx for prostate cancer (BR.21)
Overall Survival

P < 0.001 by stratified log-rank test
Hazard ratio, 0.70 (95% CI, 0.58–0.85)

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>107</th>
<th>50</th>
<th>9</th>
<th>0</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erlotinib</td>
<td>488</td>
<td>255</td>
<td>145</td>
<td>23</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>
B Overall Survival, All Patients

![Graph showing overall survival for different treatments.](image)

- **Vinorelbine plus cisplatin**
- **Observation**

**Probability (%)**

- 100%
- 80%
- 60%
- 40%
- 20%
- 0%

**Years**

- 0
- 2
- 4
- 6
- 8
- 10

**P=0.009**

**No. at Risk**

<table>
<thead>
<tr>
<th></th>
<th>Observation</th>
<th>Vinorelbine plus cisplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>240</td>
<td>242</td>
</tr>
<tr>
<td>2</td>
<td>182</td>
<td>193</td>
</tr>
<tr>
<td>4</td>
<td>94</td>
<td>121</td>
</tr>
<tr>
<td>6</td>
<td>47</td>
<td>51</td>
</tr>
<tr>
<td>8</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Lung Cancer**

Winton, NEJM 2005
Glioblastoma

Stupp, NEJM 2005
Colonic Cancer

Jonker, NEJM 2007
Figure 1. Cumulative Incidence of Invasive Breast Cancer.
CI denotes confidence interval.
NCIC CTG: Productivity

IND Program

• More than 190 trials
• Enrolment of ~ 4,400 patients
• Testing of more than 70 new agents
• Multiple examples of:
  ‘to phase III’ results
  successful correlative observations
IND Program: Goals

• Acquire new agents for study in Canada
• Generate results leading to phase III trials
• Advance Phase I-II trial methodology
• Include laboratory / imaging correlative studies
• Train new specialists in drug development
Acquire Novel Agents for Study

High priority agents

- Novel / target - specific cytostatics / cytotoxics
- Antimetastatic agents or angiogenesis inhibitors
- Cytoprotectors or modulating agents
- Hormones / biologicals with immune basis
2008 – 2009 Strategic Planning Process
2008-09 Strategic Planning Process

Background:

- Completion of US NCI/CTEP review
- Entering a CCSRI grant cycle
- Important environment changes:
  Opportunities
  Threats
Framing the Issue

How do we develop a high-quality strategic agenda, and how do we operationalize this through our Central Office and at our member centres?
Process

1. Central Office Background

2. 2008 Fall Meeting Retreat

Scientific Strategy  Operational Issues

Systematic subsequent steps
Some Specific Recommendations
Group-Wide Strategic Agenda

Within the Phase III Program:

a) priority should be given to trials that directly change health care delivery practices and/or that address a paradigm-changing treatment principle;

b) priority should be given to trials that include endpoints that address multiple outcome domains including effectiveness, quality of life, economic implications, and correlative / translational research that includes biomarker development; and,

c) in meeting the priorities stated in a) and b) above, the need to conduct trials with international partners should be expected.

Recommendation #3
Progression of Trials

- Pre-clinical
- Phase 1
- Phase 2
- Phase 3
Progression of Trials

- Pre-clinical
- Phase 1
- Phase 2
- Phase 3

- Single Arm
- Randomized
Progression of Trials

Pre-clinical  Phase 1  Phase 2  Phase 3

Explanatory  Pragmatic
Progression of Trials

- Preclinical
- Phase 1
- Phase 2
- Phase 3

- Randomized
- Explanatory
Progression of Trials: Phase 3

EARLY
- Patients: Metastatic
- Design Principles: Explanatory
- Regulatory Approval: Primary
- Data Collection: Detailed

LATE
- Patients: Adjuvant
- Design Principles: Pragmatic
- Regulatory Approval: Secondary
- Data Collection: Less Detailed (?)
Progression of Trials: Phase 3

**EARLY**
- Emphasis of biologic POP
- Lesser direct relevance to health care delivery
- Correlative biology may emphasize tumour factors

**LATE**
Progression of Trials: Phase 3

**EARLY**
- Emphasis of biologic POP
- Lesser direct relevance to health care delivery
- Correlative biology may emphasize tumour factors

**LATE**
- Emphasis of effectiveness
- Direct relevance to health care delivery is essential
- Correlative biology may emphasize patient factors
Some NCIC CTG Trials: Explanatory vs. Pragmatic (1)

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>SS</th>
<th>HR</th>
<th>P</th>
<th>Absolute Difference*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PA.3</td>
<td>569</td>
<td>.82</td>
<td>.038</td>
<td>11 days (6.24 vs. 5.9 mos)</td>
</tr>
<tr>
<td>BR.21</td>
<td>731</td>
<td>.73</td>
<td>.001</td>
<td>60 days (6.7 vs. 4.7 mos)</td>
</tr>
<tr>
<td>CO.17</td>
<td>572</td>
<td>.68</td>
<td>&lt;.001</td>
<td>45 days (6.1 vs. 4.6 mos)</td>
</tr>
</tbody>
</table>

* Median overall survival
## Some NCIC CTG Trials: Explanatory vs. Pragmatic (2)

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>SS</th>
<th>HR</th>
<th>P</th>
<th>Absolute Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>PA.3</td>
<td>569</td>
<td>.82</td>
<td>.038</td>
<td>11 days (6.24 vs. 5.9 mos)</td>
</tr>
<tr>
<td>BR.21</td>
<td>731</td>
<td>.73</td>
<td>.001</td>
<td>60 days (6.7 vs. 4.7 mos)</td>
</tr>
<tr>
<td>CO.17</td>
<td>572</td>
<td>.68</td>
<td>&lt;.001</td>
<td>45 days (6.1 vs. 4.6 mos)</td>
</tr>
</tbody>
</table>

- Two trials were published in NEJM
- The 3\textsuperscript{rd} was an ASCO plenary paper
- All 3 had important correlative studies
  - Two of these were NEJM publications
Progression of Trials: Phase 3

**EARLY**

- Emphasis of biologic POP
- Lesser direct relevance to health care delivery
- Correlative biology may emphasize tumour factors
Progression of Trials: Phase 3

- **EARLY**
  - Emphasis of biologic POP
  - Lesser direct relevance to health care delivery
  - Correlative biology may emphasize tumour factors

Nature of the paradigm change
Quality of the CSTB
Progression of Trials: Phase 3

LATE

Emphasis of effectiveness

Direct relevance to health care delivery is essential

Correlative biology may emphasize patient factors
Progression of Trials: Phase 3

Magnitude of impact to health care delivery

LATE

Emphasis of effectiveness
Direct relevance to health care delivery is essential
Correlative biology may emphasize patient factors
The NCIC CTG should prioritize phase III trials that involve international collaborations. Among these collaborations, those associated with formal structures and processes (e.g., the NCI/CTEP Steering Committee / Task Force initiative) should be given the greatest priority. There is a need to more clearly enunciate the principles to be used to prioritize development of potential collaborations with other international partners.
Correlative / Translational Research

The NCIC CTG should prioritize phase III trials that include high-quality translational research. Given the unique role of phase III trials in the process of biomarker development, trials that include biomarkers as integral components of trial design should be particularly prioritized.

Recommendation #11
With best supportive care: K-ras is not prognostic
Overall Survival: By K-ras Mutational Status

A Mutated K-ras

No. at Risk
Cetuximab plus best supportive care 75 67 45 26 15 10 7 4
Best supportive care alone 76 64 39 26 19 12 10 7

B Wild-type K-ras

No. at Risk
Cetuximab plus best supportive care 110 101 88 75 48 31 19 8
Best supportive care alone 105 88 65 34 23 17 12 5

Test for interaction P < 0.001
K-ras is a predictive marker

Karapetis, NEJM 2008
Economic Evaluation: Implications of K-ras Determination

**All Patients:**

- **CEA ratio:** $199,742 / LYG
- **CUA ratio:** $299,613 / QALY

**K-ras Wild-type Patients:**

- **CEA ratio:** $120,061 / LYG
- **CUA ratio:** $186,761 / QALY

Mittmann JNCI, 2009
Specific Categories


2. To conduct *pragmatic phase III trials*. The NCIC CTG recognizes the unique positioning of an academic cooperative group in being able to conduct these trials that compare or test interventions for the purpose of direct application to health care delivery policies. This role is particularly important in informing delivery of health care that is relevant to Canadians.
3. To evaluate *biological endpoints* within clinical trials; in particular, identifying biomarkers that facilitate individualization of therapies may be crucial to improving the outcomes of cancer patients.

4. To evaluate *interventions that will prevent cancer*. Cancer prevention can be considered as primary (interventions in patients who do not have cancer), secondary (screening) or tertiary (prevention of cancer recurrence in patients who have had cancer). The NCIC CTG has and will continue to focus on testing interventions for primary (in high-risk individuals) and tertiary prevention.
Specific Categories

5. To develop and evaluate *new methodologies of clinical trial design, conduct and analysis*. Improving our abilities to obtain high-quality information is required to accurately and efficiently determine whether new interventions bring value.

6. To provide and facilitate *investigator education and training*. In particular, it is a priority for the NCIC CTG to contribute to assuring that there is a next generation of Canadians who will be international leaders in clinical cancer research.
New Projects and Funding
Projects by Funding Type

• Industry Contract
• Grant
  – CCSRI
  – Other
• NCI/CTEP (CTSU)
Progression of Trials: Phase 3

Primary Indication (‘NDA’):

- Usually led by company
- NCIC CTG somewhat unique
- Always for regulatory
- Complex
- Expensive
Progression of Trials: Phase 3

Primary Indication (‘NDA’):

Secondary Indication:

- Often ‘investigator’ initiated
- Thus, in remit of coop group
- Can be for regulatory
- Complex, but less so (?
- Expensive
Progression of Trials: Phase 3

Primary Indication (‘NDA’):
- Investigator initiated
- In remit of coop group
- Less likely for regulatory
- Can be ‘large / simple’
- Expense depends on scope

Secondary Indication:

‘Better / New’ Application:
- Investigator initiated
- In remit of coop group
- Less likely for regulatory
- Can be ‘large / simple’
- Expense depends on scope
Progression of Trials: Phase 3

Primary Indication (‘NDA’)  Secondary Indication

Better / New Application

Contract  Grant
Progression of Trials: Phase 3

- Traditional funding has been CCSRI + overhead
- These sources are now limited
- New sources, and thus new processes, are needed

Primary Indication (‘NDA’)
Secondary Indication
Better / New Application

Grant
How to “Get In”
How to “Get In”

• Come to meetings
• Be active in your centre
• Accrue to trials
• Bring your ideas forward
• Get on a committee

Disease Site Committee

Let any special backgrounds be known
Consider an operations committee
(eg Audit / Monitoring)
How to “Get In”

• Communicate your interest
  – Within centre-to-centre and site reps
  – To us
  – To site chair

• Respond to surveys, questions about studies

• Accrue to active trials

• If medical / heme onc, consider IND trials