Publicly Funded Clinical Trials in the Era of Comparative Effectiveness Research

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Goals of Therapeutic Clinical Trials

Commercial Sponsor
Public Sponsor

Drug Registration
Optimize Treatment
Goals of Therapeutic Clinical Trials

- Commercial Sponsor
  - Drug Registration
  - Label Extension
  - Expand Market Share
  - Create Shareholder Value
  - Improve Public Health
- Public Sponsor
  - Optimize Treatment
  - Create New Knowledge
  - Improve Public Health

Expand Market Share
Create New Knowledge
Improve Public Health
Create Shareholder Value
Optimize Treatment
Create New Knowledge
Why Publicly Funded Trials are Important

- Compare the effectiveness of various treatment options
- Combine/compare drugs developed by different sponsors
- Develop therapies for rare diseases
- Address optimal dosing
- Test multi-modality therapies such as radiation therapy in combination with drugs

Why Publicly Funded Trials are Important

- Identify patient and tumor subsets most likely to benefit from interventions
- Study screening and prevention strategies
- Focus on survivorship and quality of life
- Publish negative results
- Assess cost and cost-effectiveness
- Provide “gold standard” databases for registry studies

Comparing Efficacy
SWOG Comparison of Lymphoma Treatments


ECOG Comparison of 4 Chemotherapy Regimens for NSCLC


Compare Treatments from Different Sponsors
A randomized phase 3 trial of weekly paclitaxel compared to weekly nanoparticle albumin bound (nab)-paclitaxel or ixabepilone combined with bevacizumab as first or second-line therapy for locally recurrent or metastatic breast cancer.

Bevacizumab mab + Cetuximab b

FOLFOX 6 or FOLFIRI

M.D. Choice

Bevacizumab mab + Cetuximab b

Roche

BMS

Re-stage q 3 cycles until PD

Pre-Rx

CTC sampling

CALGB 40502
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A randomized phase 3 trial of weekly paclitaxel compared to weekly nanoparticle albumin bound (nab)-paclitaxel or ixabepilone combined with bevacizumab as first or second-Line therapy for locally recurrent or metastatic breast cancer

ECOG 2805 ASSURE Trial
Renal Cell Carcinoma post nephrectomy
Stratify by risk group, histology, PS, type of surgery
Sunitinib
Sorafenib
Placebo
Primary endpoint, DFS. 1923 patients/ 842 events required for HR 0.80 of either treatment compared to placebo (4.9 to 6.5 y)

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Rare Disease Treatments

5-Azacitidine in MDS

Optimize Dosing
**GOG 172: IP vs IV Cisplatin plus Paclitaxel in Advanced Ovarian Cancer**


**CALGB 9741: Comparing Density and Sequence**

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**CALGB 9741: Disease-Free S**

By Density

Chi-square = 8.1244  p-value = 0.0044

Events = 270  Median = NA

Events = 328  Median = NA

N = 988  N = 984

2 wks  3 wks
Who Benefits from Adjuvant Paclitaxel?

Adjuvant paclitaxel primarily benefits women with ER negative and/or Her2 positive breast cancer.


Study Prevention Strategies

STAR Trial Breast Cancer

Cumulative Incidence of Invasive and Noninvasive Breast Cancer

Invasive Cancer

Non Invasive Cancer

Cumulative Incidence of Invasive Uterine Cancer and Thromboembolic Events

STAR Trial Adverse Events

Uterine Cancer

Thromboembolic Events

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2010 Update: Tamoxifen increases risk of invasive uterine cancer (RR 0.55, p=0.003) and of thrombotic events (RR 0.75, p=.007).

Cumulative Incidence of Invasive and Noninvasive Breast Cancer

STAR Trial Breast Cancer

Invasive Cancer

Non Invasive Cancer

Copyright restrictions may apply.


2010 Update: Tamoxifen superior to raloxifene in reducing risk of invasive breast cancer, RR 1.24, p=0.01.
Publish Negative Results

CALGB 9082 High Dose Chemotherapy for High Risk Breast Cancer

CALGB 9082 Outcomes
Assess Cost Effectiveness

BR.21: Erlotinib vs. Placebo in Advanced NSCLC-Overall Survival

HR=0.70 (0.58–0.85) stratified log rank p<0.001


BR.21 Cost Effectiveness

- Median overall survival benefit: 2 months
- Incremental cost effectiveness ratio: $94,638/year of life saved
- ICER for EGFR amplified subset: $33,353
- ICER for Never-smoker subset: $39,487

Bradbury et al. JNCI 102:1-9, 2010
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

Provide Gold Standard Databases

Practical Problem

• Most people who are diagnosed with cancer are elderly
• Most people who are on clinical trials of anti-cancer therapy are not elderly
• The risks and benefits of anti-cancer therapies in the elderly is uncertain
CALGB-Medicare Data (N=175)

- Unique ID#
- CALGB DATA
  - Drug
  - DFS
  - CTC Toxicities
- MEDICARE DATA
  - Part A
  - MEDPAR file
  - Part B
  - NCH file
  - OUTPT file

DFS According to Data Source

Advantages of Groups
- Access to large, diverse (unique) patient populations
- Research resources: administrative and data management centers; specimen repositories; reference laboratories; image archives
- Quality assurance procedures in place
- Staff and investigator training and mentoring
- Study results definitive
Disadvantages of Groups

- Cumbersome bureaucracy with review at many levels
- Years to launch and complete may limit relevance
- Results may not be reproducible in “real world” patients
- Uniform tissue handling and acquisition of complex data sets difficult
- Competing priorities with industry

Time to Activation of Cooperative Group Phase III Trials (2006 – 2008)

OEWG Target Timeline – 300 days

Timeline pauses if industry negotiations cause delay

Feedback on major challenges in 5 days

If registration trial, FDA review in 30 days

Concept revision/cycle

Protocol development

Protocol revision/review cycles

Forms development

Timeline excludes IRB, contracting, drug supply

Protocol terminated if not activated in two years

IOM Report on CER

"Comparative effectiveness research is the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat and monitor a clinical condition or to improve the delivery of care.

The purpose of CER is to assist consumers, clinicians, purchasers and policy makers to make informed decisions that will improve healthcare at both the individual and population levels."

Characteristics of CER

• CER has the objective of directly informing a specific clinical decision from a patient perspective or a health policy decision from the population perspective.
• CER compares at least two alternative interventions, each with the potential to be "best practice".
• CER describes results at the population and subgroup levels.
• CER is conducted in settings that are similar to those in which the intervention will be used in practice.
Cooperative Groups and CER

- Specialists from all oncology modalities and scientific disciplines
- Studies broadly accessible to patients through national networks
- Investigator-initiated trials that directly compare therapies
- Collect cancer outcomes and QoL data
- High quality biospecimens to identify/assess subsets

CER Strategies

- "Pragmatic" clinical trials
- Prospective observational studies
- Prospective or retrospective registries
- Meta analyses
- Literature review
- Technology assessments

Pragmatic Clinical Trials

- Brass, EP, Clin Pharm Ther 87:351, 2010
The Case of Laparoscopic Colectomy

COST Trial Recurrence


COST Trial Overall Survival

CLASSIC Trial 3 Year Overall Survival

Colon cancer

Rectal cancer

Laparoscopic Colectomy Can Work!

But Does It?
Dissemination of LapCol

- Survey of 1266 members of Royal College of Physicians and Surgeons of Canada
- 462 (67% of respondents) perform colorectal surgery, 54% perform laparoscopic colorectal surgery
- Uptake related to fewer years in practice, male sex, practice in Quebec, university hospital affiliation, MIS fellowship
- Barriers: lack of OR time and formal training

Mooloo, et al., Canadian J. Surg. 52:455, 2009

Outcomes for Laparoscopic-Assisted Colectomy Compared with Open Colectomy for Cancer

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Laparoscopic-Assisted Colectomy (n=100)</th>
<th>Open Colectomy (n=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Median: 65 (IQR 55-75)</td>
<td>Median: 65 (IQR 55-75)</td>
</tr>
<tr>
<td>Sex</td>
<td>Male: 50%</td>
<td>Male: 50%</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Median: 2 years (IQR 1-3)</td>
<td>Median: 2 years (IQR 1-3)</td>
</tr>
<tr>
<td>In-hospital stay</td>
<td>Median: 5 days (IQR 3-7)</td>
<td>Median: 7 days (IQR 5-10)</td>
</tr>
<tr>
<td>30-day mortality</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>90-day mortality</td>
<td>3%</td>
<td>4%</td>
</tr>
</tbody>
</table>


Survival Comparing Laparoscopic-assisted Colectomy with Open Colectomy

- Improved survival for Laparoscopic-assisted Colectomy (LAC) compared to Open Colectomy

Conclusion

• Laparoscopic colectomy can work
• Laparoscopic colectomy does work
• But not as well as it can!

Publicly Funded Trials in the Era of Comparative Effectiveness Research

• Publicly funded clinical trials are essential to:
  - directly compare drug treatments;
  - develop combined modality treatments;
  - study chemoprevention and rare diseases;
  - identify patient subsets;
  - study cost and cost-effectiveness
• Cooperative groups are well-positioned to conduct comparative effectiveness research