Site Selection: Lessons from Cancer Clinical Trials

Presentation by
John Eckardt, MD
Chief Medical Officer
Phone: 214.451.4520
jeckardt@davaonc.com

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Site Selection: Lessons from Cancer Clinical Trials

- Cancer clinical research
- Challenges to site selection
- Understanding sites and investigators
- Identifying the right site
- Case studies in site selection
In 2010, 31% of all compounds in clinical testing were oncology drugs or immunomodulators.
Multiple site selection challenges

*Site Selection is a critical step in the timely completion of a clinical study*

<table>
<thead>
<tr>
<th>Poor Site Performance</th>
<th>Protocol Complexity</th>
<th>Investigator and Trial Demographics</th>
<th>Physician Perceptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>30% of sites enroll 70% of patients (Tufts CSDD/McKinsey)</td>
<td>Comparing 2000-2003 to 2004-2007 (PhRMA)</td>
<td>Finite pool of clinical investigators and sites</td>
<td>Physician knowledge of clinical trial data may be incomplete (Hoffman 2010)</td>
</tr>
<tr>
<td>50% of sites enroll 95% of patients (Tufts CSDD/McKinsey)</td>
<td>49% increase in total procedures</td>
<td>Over one third of oncology investigators are new (Clinical Trial Magnifier)</td>
<td>Primary physicians may discourage patients from clinical trial participation (Hoffman 2005)</td>
</tr>
<tr>
<td>Difficult patient recruitment accounts for 85-95% of days lost in clinical trial delays (McKieney/Lehman)</td>
<td>54% increase in execution burden</td>
<td>Competition among sponsors for high performance sites</td>
<td>Patient interest in clinical trial participation is driven by physician</td>
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<tr>
<td>Each day a clinical trial is delayed can result in $600,000 or more in lost sales (Cutting Edge)</td>
<td>58% increase in total eligibility criteria</td>
<td></td>
<td>40-80% of cancer patients are unaware that clinical trials may be an option for them (NCI, Lara)</td>
</tr>
<tr>
<td>Delays in approval of survival benefitting agents cause even higher losses for potential patients collectively as a group financially and socially (Philipson)</td>
<td>Average trial has 2.3 protocol amendments resulting in average delay of 4 months (Getz)</td>
<td>Pathology requirements are more prevalent, require inter-practice coordination, and can delay start of treatment</td>
<td></td>
</tr>
</tbody>
</table>

For full citation information see references 2-12
What is required of a site?

1. Dedication to clinical research
2. GCP, ICH, and regulatory compliance
3. History of high patient enrollment
4. Commitment to an accelerated opening timeline
5. Excited by the study rationale
6. Significant patient population

Although most oncology sites have very strong regulatory compliance and GCP, patient recruitment and data collection remain difficult.
Significance of investigators in cancer clinical research

- Cancer is a life-threatening illness
- Cancer diagnoses often result in fear, uncertainty, and has emotional impact
- Oncologists are important sources of psychological support for patients
- Unique relationship between oncologist and patient
- Shared decision-making
- Patients’ unmet need is information

- May not be life-threatening
- Less emotional impact on patients
- Specialty physicians may not be involved
- Patients may make decisions without consulting with their physician
- Individual decision-making
- Information easily accessible for patients in various media outlets
Oncology physician profiles

**Academic Oncologists**
- 46% of time devoted to Oncology patient care
- 14% of time devoted to Clinical research
- 10% of time devoted to Teaching
- 10% of time devoted to Admin
- 7% of time devoted to Non-onc pt care
- 12% of time devoted to Lab
- 1% of time devoted to Other

**Private Practice Oncologists**
- 76% of time devoted to Oncology patient care
- 3% of time devoted to Clinical research
- 2% of time devoted to Teaching
- 4% of time devoted to Admin
- 14% of time devoted to Non-onc pt care
- 0% of time devoted to Lab
- 1% of time devoted to Other

- 60% of time devoted to patient care or clinical research
- High prevalence of KOLs
- Principal investigator may travel frequently
- Sub-investigator, fellow, and research staff participation ideal

## Cancer trial site segmentation

<table>
<thead>
<tr>
<th>Academic Centers</th>
<th>Large Private Practice</th>
<th>Small Private Practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>• High patient volume</td>
<td>• High patient volume</td>
<td>• Patient volume varies</td>
</tr>
<tr>
<td>• Physicians frequently specialize by tumor type</td>
<td>• Physicians occasionally specialize by tumor type</td>
<td>• Most oncologists are generalists</td>
</tr>
<tr>
<td>• Fellows also discuss treatment with patients</td>
<td>• Private hospital or multi-clinic networks are common</td>
<td>• Participation in clinical trial by non-investigator partners varies</td>
</tr>
<tr>
<td>• Most recent technology</td>
<td>• Participation in trials by satellite sites varies</td>
<td>• Need for equipment, study staff, or other resources may be higher than average</td>
</tr>
<tr>
<td>• New patients frequently return home for treatment</td>
<td>• Patient population may be segmented by satellite locations</td>
<td></td>
</tr>
</tbody>
</table>

**Average site initiation**

- **Academic Centers**: 120 days (Farfel)
- **Large Private Practice**: 30 days (Farfel)
- **Small Private Practice**: N/A

**32% of US oncologists (Goldstein)**

**58% of US oncologists (Goldstein)**

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**Significant numbers of eligible patients are lost prior to enrollment**

St. Michael’s Hospital, Toronto, ON  
Breast Cancer Clinical Trials  
1984 – 1989 (prospective study, Kotwall)

- 592 Patients evaluated for clinical trial
  - 273 (46.1%) Protocol ineligibilities
  - 319 Protocol eligible
    - 213 (36.0%) Protocol eligible but not entered
      - 106 (17.9%) Randomized to clinical trial

Two-thirds of eligible patients did not participate

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Non-participation by patients can be due either to patient preference or investigator commitment

University College London Hospitals NHS Trust 1996-97
St Bartholomew’s and The London NHS Trust 1995-98
Big Lung Trial (BLT): SOC +/- cisplatin based chemo
(Spiro, prospective study)

688 Patients with non-small cell lung cancer

161 (23.4%) Logistic reasons for ineligibility BLT

527 (76.6%) Potential participants

274 (39.8%) Patients clinically ineligible for BLT

253 (36.8%) Patients approached for consent

186 (27.0%) Patient refused

67 (9.7%) Randomized to clinical trial

Can investigators influence this loss of patients?

Non-participation by patients can be due either to patient preference or investigator commitment

Centre hospitalier affilié universitaire de Québec 2002-2008
17 hematology protocols (Lemieux, Retrospective study)

1394 Hematology protocol-patients

1199 (86%) Ineligible per main criteria

195 (100%) Potential protocol-patients

62 (31.8%) Protocol ineligible

133 (68.2%) Eligible protocol-patients

47 (24.1%) Protocol not offered

34 (25.6%) Patient refused

13 (9.8%) Other

45 (23.1%) Randomized to clinical trial

35% of eligible protocol-patients were not offered clinical trial as treatment option

26% of eligible protocol-patients refused participation

Can investigators influence this loss of patients?

**Case 1: Academic Practice NSCLC Trial**

### Trial Design

- **Age ≥ 18 years**
- **Inoperable metastatic NSCLC**
- **1 prior platinum based regimen in the met. setting**

### Arm A: docetaxel + NEW Drug

### Arm B: docetaxel + placebo

### Site Profile: Academic Center

- 900 NSCLC – new or existing patient, staging, and progression rates provided

### General Information

- 18,000 patients/yr., 25 medical oncologists
- 900 New NSCLC patients/yr.
- 2 institutional 2nd line metastatic NSCLC trials

### Data Coordinator

- 900 NSCLC – treatment team membership
- Distribution of patients between PI, Sub-I, and non-study medical oncologists

### Principal Investigator

- KOL for Lung cancer
- NSCLC standard of care pem/carbo or gem/carbo 1st line, erlotinib or docetaxel 2nd line
- Investigator segmentation of patient population based on patient’s presentation and clinical goals

### Study Coordinator

- NSCLC treatment team membership
- Distribution of patients between PI, Sub-I, and non-study medical oncologists

### Sub Investigators

- Awareness of study and relationship with study coordinator and principal investigator

### Patient Consent

- 900 new NSCLC pts
  - 300 - 2nd opinions only
  - 150 – Stage I-IIla
  - 75 - 2+ prior lines of therapy
  - 60 – single agent 1st line
  - 105 – not candidates for 2nd line

- 600 – Treatment at institution
  - 450 – Stage IIIb-IV
  - 375 – 0-1 prior lines of therapy
  - 315 – platinum doublet 1st line
  - 210 – candidates for 2nd line therapy

- 18 patient went on institutional trial
- 6 patient went on trial

- 41 patients presented trial
- 7 patients presented trial

- 48 patient presented trial information
- 24 patient refused any trial

- 3 investigators see 65% of NSCLC pts and put 30% on clinical trials
- 15 investigators see 35% of NSCLC and put 10% on clinical trial

- 41 patients presented trial
- 7 patients presented trial
### Case 1: Academic Practice NSCLC Trial

**Demographics**
- **Trial Design**
  - Age ≥ 18 years
  - Inoperable metastatic NSCLC
  - 1 prior platinum based regimen in the met. setting

**General Information**
- 18,000 patients/yr., 25 medical oncologists
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**Site Profile: Academic Center**
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**Data Coordinator**
- NSCLC treatment team membership
- Distribution of patients between PI, Sub-I, and non-study medical oncologists

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- KOL for Lung cancer
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- Investigator segmentation of patient population based on patient’s presentation and clinical goals

**Study Coordinator**
- NSCLC treatment team membership

**Sub Investigators**
- Awareness of study and relationship with study coordinator and principal investigator

**Arm A: docetaxel + NEW Drug**
- 1:1

**Arm B: docetaxel + placebo**

**The investigator is the key to enrollment**
- Site potential is not the same as site performance
- If the investigators are motivated to enroll, this could significantly impact enrollment

**Note the effect of increased physician engagement**

**Investigators**
- 3 investigators see 65% of NSCLC pts and put 30% on clinical trials
- 41 patients presented trial

- 15 investigators see 35% of NSCLC and put 10% on clinical trial
- 7 patients presented trial

**Patient Consent**
- 900 new NSCLC pts
- 300 - 2nd opinions only
- 600 - Treatment at institution
- 150 - Stage I - IIIa
- 450 - Stage IIIb - IV
- 60 - single agent 1st line
- 315 - platinum doublet 1st line
- 105 - not candidates for 2nd line
- 215 candidates for 2nd line therapy

**Investigator statistics**
- 48 patient presented trial information
- 24 patient refused any trial
- 18 patient went on institutional trial
- 6 patient went on trial

**Notes**
- Site potential is not the same as site performance
- If the investigators are motivated to enroll, this could significantly impact enrollment

- Note the effect of increased physician engagement
Case 1: Academic Practice NSCLC Trial

**Trial Design**
- Age ≥ 18 years
- Inoperable metastatic NSCLC
- 1 prior platinum based regimen in the met. setting

**Arm A:** docetaxel + NEW Drug

**Arm B:** docetaxel + placebo

**1:1**

**The motivation for investigators**
- Publication
- Patient benefit
- Access to new therapies
- Patient referral

**Standard of Care**
- Arm A: docetaxel + NEW Drug
  - Age ≥ 18 years
  - Inoperable metastatic NSCLC
  - 1 prior platinum based regimen in the met. setting

**Site Profile:** Academic Center

**General Information**
- 18,000 patients/yr, 25 medical oncologists
- 900 New NSCLC patients/yr
- 2 institutional 2nd line metastatic NSCLC trials

**Data Coordinator**
- 900 NSCLC – new or existing patient, staging, and progression rates provided

**Principal Investigator**
- KOL for Lung cancer
- NSCLC standard of care pem/c or carbo/ or gem/carbo
- 1st line, erlotinib or docetaxel
- 2nd line
- Investigator segmentation of patient population based on patient’s presentation and clinical goals

**Study Coordinator**
- NSCLC treatment team membership
- Distribution of patients between PI, Sub-I, and non-study medical oncologists

**Sub Investigators**
- Awareness of study and relationship with study coordinator and principal investigator

**Demographics**

| 900 NSCLC | 300 2nd opinions only |
| 150 – Stage I-IIa | 315 – platinum doublet 1st line |
| 75 – 2+ prior lines of therapy | 215 – candidates for 2nd line therapy |
| 60 – single agent 1st line | 105 – not candidates for 2nd line |

**Investigators**
- 3 investigators see 65% of NSCLC pts and put 50% on clinical trials
- 15 investigators see 35% of NSCLC and put 20% on clinical trial

**Patient Consent**
- 48 patient presented trial information
- 24 patient refused any trial
- 18 patient went on institutional trial
- 6 patient went on trial

**Increasing investigators’ interest from 30 to 50% of patients approached and from 10 to 20% for other physicians increases patient participation 4-fold**
**Case 2: Large Private Practice NSCLC Trial**

**Trial Design**
- **General Information**
  - 5,000 patients/yr., 25 medical oncologists
  - 200 New NSCLC patients/yr.
  - No 2nd line metastatic NSCLC trials

**Demographics**
- **Site Profile:** Large Private Practice
- **Data Coordinator**
  - 200 NSCLC – new or existing patient, staging, and progression rates provided

**Principal Investigator**
- In charge of the research program
- NSCLC standard of care pem/carbo +/- bev or gem/carbo 1st line, erlotinib or docetaxel 2nd line
- Switch maintenance in 20% of patients

**Study Coordinator**
- Reviews all new patients to practice
- Distribution of patients between PI and Sub-I’s is even

**Sub Investigators**
- Awareness of study and relationship with study coordinator and principal investigator

**Arm A: docetaxel + NEW Drug**
- Age ≥ 18 years
- Inoperable metastatic NSCLC
- 1 prior platinum based regimen in the met. setting
- 200 new NSCLC pts
- 50 – Stage I-IIla
- 150 – Stage IIIb-IV
- 10 - 2+ prior lines of therapy
- 160 – 0-1 prior lines of therapy
- 30 – single agent 1st line
- 130 – platinum doublet 1st line
- 40 – not candidates for 2nd line
- 90 – candidates for 2nd line therapy

**Arm B: docetaxel + placebo**
- R 1:1

**In community practices the engagement of sub investigators can have significant impact on trial accrual**

5 investigators see 20% of NSCLC pts and put 30% on clinical trials

20 investigators see 80% of NSCLC and put 5% on clinical trial

10 patient presented trial information

6 patients presented trial

5 patient refused any trial

5 patient went on trial
**Case 3: Small Private Practice NSCLC Trial**

**Trial Design**
- **General Information**
  - 2,500 patients/yr, 10 medical oncologists
  - 100 New NSCLC patients/yr.
  - No 2nd line metastatic NSCLC trials

**Site Profile:** Small Private Practice

**Data Coordinator**
- 100 NSCLC – new or existing patient, staging, and progression rates provided

**Principal Investigator**
- In charge of the research program
- NSCLC standard of care pem/carbo +/- bev or gem/carbo 1st line, erlotinib or docetaxel 2nd line
- Switch maintenance in 20% of patients

**Study Coordinator**
- Reviews all new patients to practice
- Distribution of patients between PI and Sub-I’s is even

**Sub Investigators**
- Awareness of study and relationship with study coordinator and principal investigator

**Patient Consent**
- 100 new NSCLC pts
  - 25 – Stage I-IIla
  - 75 – Stage IIIb-IV
  - 5 - 2+ prior lines of therapy
  - 70 – 0-1 prior lines of therapy
  - 15 – single agent 1st line
  - 55 – platinum doublet 1st line
  - 20 – not candidates for 2nd line
  - 35 – candidates for 2nd line therapy

**Standard of Care**
- 1st line: erlotinib or docetaxel
- 2nd line: Switch maintenance in 20% of patients

**Demographics**
- Age ≥ 18 years
- Inoperable metastatic NSCLC
- 1 prior platinum based regimen in the met. setting

**Arm A: docetaxel + NEW Drug**
- 100 new NSCLC pts
  - 25 – Stage I-IIla
  - 75 – Stage IIIb-IV
  - 5 - 2+ prior lines of therapy
  - 70 – 0-1 prior lines of therapy
  - 15 – single agent 1st line
  - 55 – platinum doublet 1st line
  - 20 – not candidates for 2nd line
  - 35 – candidates for 2nd line therapy

**Arm B: docetaxel + placebo**

** Investigators**
- 4 investigators see 40% of NSCLC pts and put 35% on clinical trials
- 6 investigators see 60% of NSCLC and put 5% on clinical trial
- 6 patient presented trial information
- 3 patient refused any trial
- 3 patient went on trial

**Similarly in small practices, if most physicians are engaged the accrual can be as good as that of larger sites**
Choosing the Right Sites & Investigators

Identification
Use DAVA physician database to generate comprehensive potential site list based upon study criteria, our experience with the sites and DAVA MD relationships.

Analysis
DAVA MDs analyze sites and evaluate their qualifications, capabilities and potential enrollment through site specific questions. DAVA MD contacts site MDs to discuss study rationale and any potential hurdles to the protocol.

Recommendation
DAVA MDs obtain site interest. Once interest is expressed, Clinical Trial Specialists contact sites to complete site documents. DAVA gains commitment from qualified sites and discusses recommended sites with the sponsor.
Case study: 70% increase in site commitment

- Sponsor requested DAVA to re-engage sites regarding participation in clinical trial
- DAVA recommended 47 uncommitted sites out of 67 total sites previously contacted by sponsor.
- Personal medical oncology calls and visits with PI’s and research staff were the most effective means of enlisting support for the trial

### Recruited Sites

<table>
<thead>
<tr>
<th>Type</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previously unresponsive to sponsor</td>
<td>22</td>
<td>46.8%</td>
</tr>
<tr>
<td>Previously declined to sponsor</td>
<td>22</td>
<td>46.8%</td>
</tr>
<tr>
<td>Were not contacted by sponsor</td>
<td>3</td>
<td>6.4%</td>
</tr>
</tbody>
</table>

DAVA Site Recommendations

Utilizing a direct physician-to-physician approach to engage potential investigators is effective in generating interest and commitment at the site level. This model reflects a finding by Coomis et al (J Onc Prac. 2009; 5: p50) that 73% of overall clinical trial awareness was generated by physicians’ interest in the scientific rationale of the study. 

*White Paper 2011*
Lessons in Cancer Site Selection

- Protocol designed to work within standard of care
- Significant patient population
- History of high accrual
- Investigator understands study rationale and challenges from discussion with study affiliated medical oncologist or other clinical expert
- Investigator is excited by study
- Site meets all GCP/ICH and FDA guidelines
- Site has appropriate facilities, staff, equipment and technology to complete study
Thank you for your participation!

Join us for our next presentation!
Recruiting Patients for Cancer Trials:
Focus on the Physicians!

February 8, 2012
4:05 pm - 4:20 pm
Symphony Ballroom II

If you have any questions, please contact me!
John Eckardt, MD
Chief Medical Officer
214.451.4520
jeckardt@davaonc.com

www.davaonc.com