Utility of Industry-Sponsored Oncology Registries For Clinical Trials – A Perspective

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Disclaimer

• I am a current employee of Celgene Corporation
• Prior to Celgene, I was an employee of Genentech, A Member of the Roche Group, for 7 years
• Prior to Genentech, I conducted prospective observational cohort study research at Kaiser Permanente’s Division of Research for 2 years
• All views shared today are my own and not those of my current or past employers
“Registry” Definition in This Talk

• Prospective observational cohort study conducted in U.S.
• Sponsored by a pharmaceutical/biotech company
• Treatment and disease registries
• Settings: advanced cancers, primarily solid tumor
• Not post-marketing commitments
• Primarily community settings; > 200 sites across U.S.
• N = 1,000 - 4,000 patients
Example Study Design: U.S. Oncology Disease Registry With 3-Month Enrollment Window From Time of Diagnosis

- Study protocol with broad study objectives and broad inclusion criteria. IRB approval and informed consent required.
- Patients treated and followed per standard of care (MD’s discretion).
- Data cleaned/queried throughout the course of study. Minimal SDV/monitoring.
- Analyses and publications generated throughout the course of the study and beyond.
- An external Scientific Steering Committee (SSC) provides guidance on study conduct, analyses and publications.

Consent
Demographics
History (medical, conmeds)
Cancer stage, histology, treatment
Performance status
Clinical eval, labs
Quality of life (QoL)

Treatment status (change, stop)
Disease status/ tumor response
Change in performance status
Δ non-cancer medical hx, conmeds
Adverse events
Clinical eval, labs
QoL
Study termination

Drug X

Cancer diagnosis
Enrollment

≤3m

TIME

3m

3m

3m

3m

3m

3m

PD

PD

Death

eCRFs
EDC

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eCRF = electronic case report forms; EDC = electronic data capture system; PD = disease progression
Considerations:

- Institution/site may not be trained, staffed or set up for conducting clinical trials
  - Community sites may be less experienced and fewer staff for clinical research
  - Increased paperwork and monitoring required for trials
  - Enrollment process would need to be expedited
  - IRB re-approval needed for each trial
  - Active patients would need re-consent for each trial
  - Follow-up visits, types of procedures, diagnostic tests would be protocol specified for trials
  - Clinicians would be required to follow formal/protocol-specified response criteria (e.g., RECIST) for trials
  - Trials require comprehensive safety collection with expedited reporting requirements

- Budget adjustments: site fees (for data entry) are generally lower for a registry than for a clinical trial

- *Most importantly, registry study design can allow certain biases to be inadvertently introduced in the patient population and the data collection*
Potential Types of Bias in Oncology Registries To Consider For Embedded Clinical Trials

- Selection Bias: biased sampling of study population
- Information Bias: missing or erroneous information
- Confounding Bias: out of scope here, reduced in trials via randomization and/or strict protocols
Selection Bias - Sampling Considerations

General Cancer X Population

- Age
- Race/ethnicity
- Sex
- Performance Status
- Comorbidities
- Histology
- Income
- Education
- Geo Location
- MD
- Site type
- Time to progression
- Adjuvant tx
- Insurance

Registry study inclusion criteria are generally broad to get heterogeneous patient population.
Ideal Scenario: “On target” sampling over time (several years, usually). General popn characteristics stay relatively constant during enrollment phase and study popn is representative of general popn.
General population characteristics stay constant during enrollment period, but sampling is off target from the start [e.g., low number of sites; limited geographic distribution; high % academic site patients].
Sampling starts on target, but as enrollment time lengthens, general cancer popn characteristics change during the enrollment period even though sampling methods and rates stay relatively consistent [e.g., median survival lengthens in certain subgroups (age, new treatments), new diagnostic criteria or new diagnostic tests emerge].
CONCERN: Patient-Level Selection Bias

It generally takes longer to enroll a patient into a non-interventional study. This window of time can introduce “survivorship” bias. Additionally, informed consent requirement can introduce a “participation” bias. Oncology registries involving very aggressive cancers are more prone to these types of selection bias.

EDC = data collection in electronic data capture system; Tx = treatment; PD = disease progression
Information Bias

- **Missing data**
  - Loss to follow-up (LTFU)
  - Variable time between clinic visits and reporting frequency
  - Underreporting/overreporting
    - E.g., - Not ALL adverse events are collected in registry studies

- **Erroneous data**
  - Recording errors/Reporting errors

- **Unresolved queries**

- **May result in differential exposure and outcome misclassification**
Industry-Sponsored Registries – High Costs For High Quality Data

Site personnel transfers data to separate registry electronic data capture system

CONCERN: High costs!
Site fees, CRO/operational costs and resources are high for industry and increasing over time

EDC = data collection in electronic data capture system; Tx = treatment; PD = disease progression

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## Current Situation: The Industry-Sponsored Oncology Registry Model Needs To Evolve

<table>
<thead>
<tr>
<th>Situation</th>
<th>Needs</th>
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<tbody>
<tr>
<td>Increasingly complex cancer disease and treatment landscapes</td>
<td>Large patient populations, possibly from multiple data sources</td>
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<td>Rapidly emerging new therapies</td>
<td>Real-time data to address current questions for approved and future products</td>
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<td>Questions rapidly changing</td>
<td>Study design flexibility to:</td>
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<tr>
<td></td>
<td>• START and STOP quickly</td>
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<tr>
<td></td>
<td>• Phase (sub)studies in and out over time</td>
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<td></td>
<td>• Gate on milestones and data availability</td>
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<td>High costs of large, sponsored registries are not sustainable for <em>every cancer type</em> or <em>every new treatment</em></td>
<td>More resource efficiencies; more external collaboration</td>
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What Changes Are Needed For This Evolution?

- Provide means to sites to increase resources/staff quickly.
- Provide mechanisms to enroll quickly.
- Continually accrue patients for long period of time.
- Implement a user-friendly process for submitting clinical trial proposals to a governance body, like a Steering Committee, for review, approval and prioritization.
- Prepare sites early in the registry for higher safety reporting and study monitoring requirements for trials.
- Consider RCTs, if feasible, as randomization can improve internal validity.
- Develop company SOPs/guidance documents specifically for registries designed for conducting trials.
- Engage stakeholders, customers (e.g., FDA) early in registry study planning and design.
- Consider industry-supported studies, rather than industry-sponsored.
  - External collaborations, multiple partners.
Thank You!