The State of the Oncology Clinical Trials Portfolio: Insights from ClinicalTrials.gov

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Background

ClinicalTrials.gov is one of the largest databases of clinical research, comprising over 120,000 trials in 175 countries. With over 50 million page views a month, it is also the most utilized source for clinical trial information worldwide.

While the database was initially created as a result of the US Food and Drug Administration (FDA) Modernization Act of 1997, the FDA made registration a requirement as of 2007 for all new clinical trials expected to contribute to an FDA submission. In addition, the International Committee of Medical Journal Editors mandates that all trials be included in a public registry as a requirement for publication of results in peer-reviewed medical journals.

Through a collaboration between the FDA and Duke University, as part of the Clinical Trials Transformation Initiative (CTTI), the goal of this project is to systematically summarize the relevant information in the ClinicalTrials.gov database to understand the full portfolio of clinical trials and the potential gaps therein. In this project we describe the portfolio of studies enrolling patients with cancer in ClinicalTrials.gov.

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Methods

- A dataset comprising 96,346 clinical trials was downloaded from ClinicalTrials.gov on September 27, 2010 in XML format and a database for the Aggregate Analysis of ClinicalTrials.gov (AACT) was created to facilitate analysis.
- A subset of trials was identified, corresponding to the FDA enactment of mandatory registration in 2007.
- A process was developed to annotate and validate disease conditions in order to create specialty datasets. A combination of National Library of Medicine (NLM) MeSH terms and additional non-MeSH (free-text) terms were used to do so as follows:
  - MeSH condition terms were identified using the 2010 MeSH thesaurus.
  - Non-MeSH condition terms (free-text) which appeared in five or more interventional studies registered after September 2007 were also identified.
  - MeSH and non-MeSH terms were reviewed by clinicians and faculty within each clinical discipline at the Duke University Medical Center in order to annotate them by disease.
  - Next, the disease annotations provided by the clinicians and faculty were combined with MeSH condition terms generated by the NLM algorithm to generate a summary algorithm that categorized trials by disease specialty, as outlined in Figure 1.
  - Trials identified as "oncology" were manually reviewed by clinicians to exclude false-positive studies and further classify the oncology trials by cancer subtype.

Results

- Of 40,970 interventional studies registered between October 2007 and September 2010, 8942 (22%) focused on oncology, the highest among all sub-specialties represented.
- In comparing oncology trials to those in other specialties, oncology trials were more likely to be single-arm (62% vs. 24%, p<0.001), open label (88% vs. 47%, p<0.001), and nonrandomized (64% vs. 23%, p<0.001).
- Oncology trials were also more likely to be early-phase (84% phase I or II in oncology vs. 53% in non-oncology).
- There was moderate but significant correlation between number of trials conducted by cancer subtype and associated U.S. incidence and mortality (incidence: correlation 0.56, P=0.037; mortality:correlation 0.77, P=0.001).
- Only 65% of trials in oncology have a North American study-site. Among the top ten cancer types by incidence, less then half have the majority of trials conducted only in North America.

Limitations

- There are limits to the registry's comprehensiveness as there is no obligation to register phase I trials that do not involve a device or drug or to register trials conducted solely outside US jurisdiction.
- Missing data, the medical sophistication of persons entering the data, ambiguous terminology, and free-text input options all further complicate analysis efforts.
- The lack of standard ontology is a significant concern.

Conclusions

- The ClinicalTrials.gov database provides a unique opportunity to understand the breadth of interventional trials in oncology.
- Oncology trials are more frequently single arm, open label, non-randomized, and early-phase than in other areas of medicine.
- These data identify strengths and weaknesses in trial design, patient populations, and evidence development that need to be carefully considered in an era of increasing focus on research design and comparative effectiveness research.
- Subsequent analyses by CTTI will focus on sub-segmenting these results by cancer type and impact of trial sponsor on the portfolio, to identify opportunities for improving the evidence development process in cancer.

Figure 1. Grouping Trials into Specialty Datasets (adapted with permission by A Tasneem, ACRT 2011)

Table 1. Attributes of Clinical Trials in the AACT Dataset: Oncology vs Other Specialties, 2007-2010.

Trial Attribute	Oncology (N=8942)	Non-oncology (N=32,028)
Masking		
Open	88%	47%
Single Blind	3%	13%
Double Blind	9%	39%
Allocation		
Randomized	36%	77%
Non-randomized	64%	23%
Arms		
1	62%	24%
2	29%	54%
≥ 3	8%	22%
Phase		
1	24%	20%
1/2	12%	5%
2	45%	23%
2/3	2%	4%
3	13%	23%
4	3%	24%

Figure 2. Comparison of Incidence to # of Trials for Top Ten Cancers by Incidence, 2007-2010.