Improving the impact of clinical research: A systematic analysis of kidney cancer trials

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Background
ClinicalTrials.gov is one of the largest databases of clinical research in the world, comprising over 120,000 trials in 175 countries. With over 30 million page views a month, it is also the most utilized source for clinical trial information worldwide. As of 2007, registration was mandated for clinical trials expected to contribute to an FDA submission. In addition, the International Committee of Medical Journal Editors mandated inclusion of trials in a public registry at the time of enrollment initiation in order to later consider the work for publication in peer-reviewed journals.

This project analyzes the portfolio of trials available on ClinicalTrials.gov through a collaboration between the FDA and Duke University, as part of the Clinical Trials Transformation Initiative (CTTI). In particular, we analyzed the renal cell carcinoma (RCC) trial portfolio. RCC is an area of great change and opportunity, given the ClinicalTrials.gov database provides a source for clinical trial information worldwide. As of 2010, it is also the most utilized source for clinical research in the world, comprising over 120,000 trials in 175 countries. With over 30 million page views a month, it is also the most utilized source for clinical trial information worldwide. As of 2007, registration was mandated for clinical trials expected to contribute to an FDA submission. In addition, the International Committee of Medical Journal Editors mandated inclusion of trials in a public registry at the time of enrollment initiation in order to later consider the work for publication in peer-reviewed journals.

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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 (AAC) was created to facilitate analyses.
- A subset of trials was identified, corresponding to the FDA enactment of mandatory registration in 2007.
- A process was developed to analyze and validate data conditions in order to create datasets. A combination of National Library of Medicine (NLM) MeSH terms and additional non-MeSH (free-text) terms were annotated by disease, resulting in a summary algorithm used to classify trials as depicted in Figure 1.
- Trials identified as “oncology” were then manually reviewed by clinicians to exclude false-positive studies and further classify the oncology trials by cancer type.

Results
- Of 40,970 interventional studies registered between October 2007 and September 2010, 8942 (22%) focused on oncology, the highest amongst all specialties registered. 108 RCC trials studied treatment agent(s) which were registered and initiated in the defined timeframe.
- 45% assessed agents included in the NCCN RCC Guidelines at the time of study initiation and 18% studied FDA-approved treatments that were not included in the guidelines. 36% of trials included a novel agent.

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 reviewers entering the data, ambiguous terminology, and free-text input options all further complicate analysis efforts.

Conclusions
- The ClinicalTrials.gov database provides a unique opportunity to understand the breadth of interventional trials in oncology.
- Optimizing clinical research includes increasing studies of novel therapeutics and improving the comparative effectiveness research portfolio by increasing utilization of pragmatic designs, registries and late-phase trials.
- The findings 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 real-world and comparative effectiveness research.
- The majority of new studies and accrual in RCC assess questions of treatment sequence and setting for established therapies, many of which lack rigorous design. These insights need to be incorporated into funding decisions and similar analyses are needed for other cancer types.

Table 1: Attributes of clinical trials in renal cell cancer by approval status of study agent(s), 2007-2010

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All trials (n=108)</th>
<th>Phase I/II trials (n=60)</th>
<th>Phase III/IV trials (n=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor and/or collaborator</td>
<td>Industry 50%</td>
<td>58%</td>
<td>76%</td>
</tr>
<tr>
<td>Government</td>
<td>15%</td>
<td>32%</td>
<td>14%</td>
</tr>
<tr>
<td>Other</td>
<td>35%</td>
<td>58%</td>
<td>35%</td>
</tr>
</tbody>
</table>

Overall survival endpoint
- Primary 2% | 0% | 0%
- Secondary 56% | 47% | 24%
- Not included 42% | 53% | 68%

Figure 2. Stage of development of study agent across total renal cell trials, 2007-2010

Figure 3. Grouping Trials into Specialty Datasets (adapted with permission by Tasneem, ACRT 2011)