State of Diabetes-Related Trials in the ClinicalTrials.gov Dataset

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Disclosures

- Dr. Green receives institutional grant support for research from Merck and Amylin, and has received honoraria from Merck and Takeda for lectures.
- Dr. Lakey receives funding from Amarin and Janssen.
- Dr. Batch has participated in CME activities funded by Sanofi-Aventis.
- Dr. Bethel receives institutional research support from Merck, Amylin, Eli Lilly, and Bristol Myers Squibb. She receives individual research support from Novartis and Bayer.
- Drs. Barnard, Chiswell, and Tasneem have no activities to disclose.
Background

- The goal of this project is to characterize the diabetes-related clinical trials registered in the ClinicalTrials.gov dataset

- A collaboration between the US FDA and Duke University through the Clinical Trials Transformation Initiative (CTTI)
<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nov 21, 1997</td>
<td>Food and Drug Modernization Act of 1997 (FDAMA) section 113 enacted</td>
<td>Mandated the creation of the clinicaltrials.gov registry for efficacy trials in serious and life-threatening conditions and interventions regulated by the FDA</td>
</tr>
<tr>
<td>Feb 29, 2000</td>
<td></td>
<td>First version ClinicalTrials.gov publicly available</td>
</tr>
<tr>
<td>September 2004</td>
<td>International Committee of Medical Journal Editors’ (ICMJE) policy established</td>
<td>Required studies published in their journals be registered in Clinicaltrials.gov or other equivalent publicly available registries.</td>
</tr>
<tr>
<td>September 27, 2007</td>
<td>US Public Law 110-85 FDA Amendments Act (FDAAA) section 801 enacted</td>
<td>Created a legal requirement for the registration of trials of drugs, biologics, and devices</td>
</tr>
<tr>
<td>September 23, 2008</td>
<td></td>
<td>Results reporting launched</td>
</tr>
<tr>
<td>September 28, 2009</td>
<td></td>
<td>Adverse Event reporting launched</td>
</tr>
</tbody>
</table>
Methods

- A dataset of 96,346 studies was downloaded from ClinicalTrials.gov on September 27, 2010.
- A database for the Aggregate Analysis of ClinicalTrials.gov (AACT) was created to facilitate analysis.
- The subset of interventional trials corresponding to the FDA enactment of mandatory registration in 2007 was identified.
Creation of the Diabetes Trials Dataset

- **Condition terms identified from:**
  - *Selected disease nodes of the 2010 MeSH thesaurus*
  - *Non-MeSH (free-text) terms appearing in ≥ 5 studies*

- MeSH and non-MeSH terms were reviewed by specialists at Duke University and annotated for relevance to Endocrinology

- Terms further classified to identify those with relevance to diabetes or diabetes-related complications
Creation of the Diabetes Trials Dataset

MeSH terms
Insulin Resistance
Islets of Langerhans Transplantation
Diabetes Complications
Diabetes Mellitus
Diabetes Mellitus, Type 1
Diabetes Mellitus, Type 2
Diabetes, Gestational
Diabetic Foot
Diabetic Ketoacidosis
Diabetic Nephropathies
Diabetic Neuropathies
Diabetic Retinopathy
Foot Ulcer
Glucose Intolerance
Glucose Metabolism Disorders
Hyperglycemia
Hyperinsulinism
Prediabetic State
Pregnancy in Diabetics

Non-MeSH terms
Diabetes
Diabetes Mellitus Type 2
Diabetes Mellitus, Non-Insulin-Dependent
Diabetes Mellitus, Type 1
Diabetes Mellitus, Type II
Diabetes Prevention
Diabetes Type 2
Diabetes, Type I
Diabetic Foot Ulcer
Diabetic Foot Ulcers
Diabetic Gastroparesis
Diabetic Macular Edema
Diabetic Nephropathy
Diabetic Neuropathy
Diabetic Neuropathy, Painful
Diabetic Peripheral Neuropathy
Diabetic Polyneuropathy

Non-MeSH terms
Foot Ulcer, Diabetic
Gestational Diabetes
Gestational Diabetes Mellitus
Glucose Metabolism
Glycemic Control
Impaired Fasting Glucose
Impaired Glucose Tolerance
Insulin Sensitivity
Painful Diabetic Neuropathy
Pre-diabetes
Prediabetes
Proliferative Diabetic Retinopathy
Type 1 Diabetes
Type 1 Diabetes Mellitus
Type 2 Diabetes
Type 2 Diabetes Mellitus
Type 2 Diabetes Mellitus (T2DM)
Type II Diabetes
Type II Diabetes Mellitus

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Studies downloaded from ClinicalTrials.gov on 27 Sept 2010. 40,970 studies registered 1 Oct 2007 or later with "Interventional" study type. 1,220 unique non-MeSH terms that occur in 5 or more studies. 146 terms annotated Y for endocrinology. 8,302 studies with at least one term annotated Y for endocrinology. 2,484 studies with at least one term annotated Y for diabetes. 36 annotated Y for diabetes. 19 annotated Y for diabetes. 9,031 unique MeSH terms (subset of 2010 MeSH dictionary). 1,031 terms annotated Y for endocrinology. 1,353 unique MeSH terms in CONDITIONS or CONDITION_BROWSE for these studies. 96,346 studies downloaded from ClinicalTrials.gov on 27 Sept 2010.
RESULTS
Characteristics of Diabetes-Related Trials

Funding Source

- Industry: 50.9%
- NIH: 7.5%
- Other: 41.6%

Funding source derived from lead sponsor and collaborator data

n = 2,484
Primary Purpose of Diabetes-Related Trials

Number of Trials

- Treatment: 1800
- Prevention: 200
- Basic Science: 160
- Health Services Research: 140
- Supportive Care: 120
-Diagnostic: 100
-Screening: 80

Total n = 2327
Types of Interventions in Diabetes-Related Trials

Number of Trials

Drug: 1,800
Behavioral: 200
Other: 200
Device: 100
Dietary supplement: 50
Procedure: 50
Genetic: 50
Radiation: 50

Total n = 2484
Characteristics of Diabetes-Related Trials

Number of arms per trial

- None: 13.4%
- One: 19.1%
- Two: 54.7%
- Three: 5.2%
- Four: 7.5%
- Five or more: 5.2%

n = 2,351
### Characteristics of Diabetes-Related Trials

#### Number of Participants in Trials

<table>
<thead>
<tr>
<th>Percent of Trials</th>
<th>Planned enrollment</th>
</tr>
</thead>
<tbody>
<tr>
<td>91%</td>
<td>≤ 500 subjects</td>
</tr>
<tr>
<td>58.6%</td>
<td>≤ 100 subjects</td>
</tr>
<tr>
<td>38.4%</td>
<td>≤ 50 subjects</td>
</tr>
</tbody>
</table>

n=2,449
Characteristics of Diabetes-Related Trials

Duration of trials

Mean +/- SD 1.8 +/- 1.48 years
Median (25th, 75th) 1.4 (0.8, 2.3) years
Min, Max 0.0, 12.1 years

Duration defined as years from study start date to date when f/u for primary endpoint complete

n=2,295
### Characteristics of Diabetes-Related Trials

<table>
<thead>
<tr>
<th>Ages of Participants</th>
<th>Number of Trials (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum age ≤ 18 years</td>
<td>92 (3.7)</td>
</tr>
<tr>
<td>Minimum age ≥ 18 years</td>
<td>2225 (89.6)</td>
</tr>
<tr>
<td>Excludes ages &gt; 65 years</td>
<td>764 (30.8)</td>
</tr>
<tr>
<td>Excludes ages &gt; 75 years</td>
<td>1364 (54.9)</td>
</tr>
<tr>
<td>Minimum age ≥ 65 years</td>
<td>15 (0.6)</td>
</tr>
<tr>
<td>Minimum age ≥ 75 years</td>
<td>1 (0.0)</td>
</tr>
</tbody>
</table>

Total n = 2,484

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[Graph of age distribution and diabetes prevalence]

http://www.idf.org/diabetesatlas/5e/diabetes
Characteristics of Diabetes-Related Trials

Number of Trial Sites

<table>
<thead>
<tr>
<th>Type</th>
<th>Number of Trials</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single</td>
<td>1473</td>
<td>65.8%</td>
</tr>
<tr>
<td>Multiple</td>
<td>764</td>
<td>34.2%</td>
</tr>
</tbody>
</table>

$n = 2,237$

Number of Sites (Multiple Site Trials)

- Mean +/- SD: 34.6 +/- 60.25
- Median (25th, 75th): 11.0 (3.0, 44.0)
- Min, Max: 2, 741
### Characteristics of Diabetes-Related Trials

<table>
<thead>
<tr>
<th>Locations of Trial Facilities</th>
<th>Number of Trials (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>US only</td>
<td>907 (40.5)</td>
</tr>
<tr>
<td>Outside US only</td>
<td>1111 (49.7)</td>
</tr>
<tr>
<td>Both US and Outside US</td>
<td>219 (9.8)</td>
</tr>
</tbody>
</table>

Total n = 2,237
Distribution of diabetes studies by country

Number of studies with at least one facility:
- 0
- 26-50
- 51-100
- 101-250

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Trials distribution as compared to 2011 IDF estimates of disease prevalence
Characteristics of Diabetes-Related Trials

Primary Outcomes* (n = 2,500)

- Mortality or Major Adverse Cardiovascular Events: 35 studies
- Bone Metabolism or Disease: 7 studies
- Malignancy: 1 study

*Derived from manual review of free-text outcomes descriptions
No trials listed a primary outcome related to pancreatitis

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Conclusions

The majority of diabetes-related trials:

- Are funded by industry
- Have a therapeutic rather than preventive, supportive or diagnostic purpose
- Involve drug therapy rather than behavioral or non-drug interventions
- Compare few interventions
Conclusions

The majority of diabetes-related trials:

- Include relatively small numbers of patients
- Take place at a single site
- Exclude those at extremes of age
- Do not focus upon clinically significant cardiovascular complications

Trial distribution does not correlate with the prevalence of diabetes in many locations
Conclusions

Recently registered trials may not sufficiently address important diabetes care issues or involve affected populations.

Information available from this analysis may be meaningful in the allocation of future research activities and resources.
Limitations

ClinicalTrials.gov

- Does not include information for all studies worldwide
- Data collection
  - Has changed over time
  - Completeness and quality variable across trials
  - Some data may be entered as “other” or in free text
- Difficult to fully assess proportionality of trial activity within given areas
Limitations

Methods

- Annotation of terms and classification of trials not independently validated
- Data presented do not reflect changes in trial characteristics over time
Financial support for this work was provided by grant U19FD003800 from the U.S. Food and Drug Administration awarded to Duke University for the Clinical Trials Transformation Initiative