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)
## ClinicalTrials.gov History Overview

<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>
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 I
- 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

Duke Clinical Research Institute
Creation of the Diabetes Trials Dataset

96,346 studies downloaded from ClinicalTrials.gov on 27Sept2010

40,970 studies registered 1Oct2007 or later with “Interventional” study type

1,220 unique non-MeSH terms that occur in 5 or more studies

Submitted CONDITIONS

NLM-generated MeSH terms (CONDITION_BROWSE)

146 terms annotated Y for endocrinology

9,031 unique MeSH terms (subset of 2010 MeSH dictionary)

1,031 terms annotated Y for endocrinology

8,302 studies with at least one term annotated Y for endocrinology

1,353 unique MeSH terms in CONDITIONS or CONDITION_BROWSE for these studies

Submitted CONDITIONS

NLM-generated MeSH terms (CONDITION_BROWSE)

36 annotated Y for diabetes

19 annotated Y for diabetes

2,484 studies with at least one term annotated Y for diabetes
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

- **Treatment**: 1800 trials
- **Prevention**: 200 trials
- **Basic Science**: 200 trials
- **Health Services Research**: 100 trials
- **Supportive Care**: 35 trials
- **Diagnostic**: 30 trials
- **Screening**: 20 trials

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

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Number of Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>1600</td>
</tr>
<tr>
<td>Behavioral</td>
<td>200</td>
</tr>
<tr>
<td>Other</td>
<td>100</td>
</tr>
<tr>
<td>Device</td>
<td>50</td>
</tr>
<tr>
<td>Dietary supplement</td>
<td>30</td>
</tr>
<tr>
<td>Procedure</td>
<td>20</td>
</tr>
<tr>
<td>Genetic</td>
<td>10</td>
</tr>
<tr>
<td>Radiation</td>
<td>5</td>
</tr>
</tbody>
</table>

Total n = 2484
Characteristics of Diabetes-Related Trials

Number of arms per trial

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

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

### Ages of Participants

<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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[Diagram showing estimated percentage of people aged 20 years or older with diagnosed and undiagnosed diabetes, by age group, United States, 2005–2008.](http://www.idf.org/diabetesatlas/5e/diabetes)
### Characteristics of Diabetes-Related Trials

#### Number of Trial Sites

- **65.8%** are single-site trials (1473 trials)
- **34.2%** are multiple-site trials (764 trials)

#### 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

*n = 2,237*
# Characteristics of Diabetes-Related Trials

## Locations of Trial Facilities

<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 $n = 2,237$
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.*
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