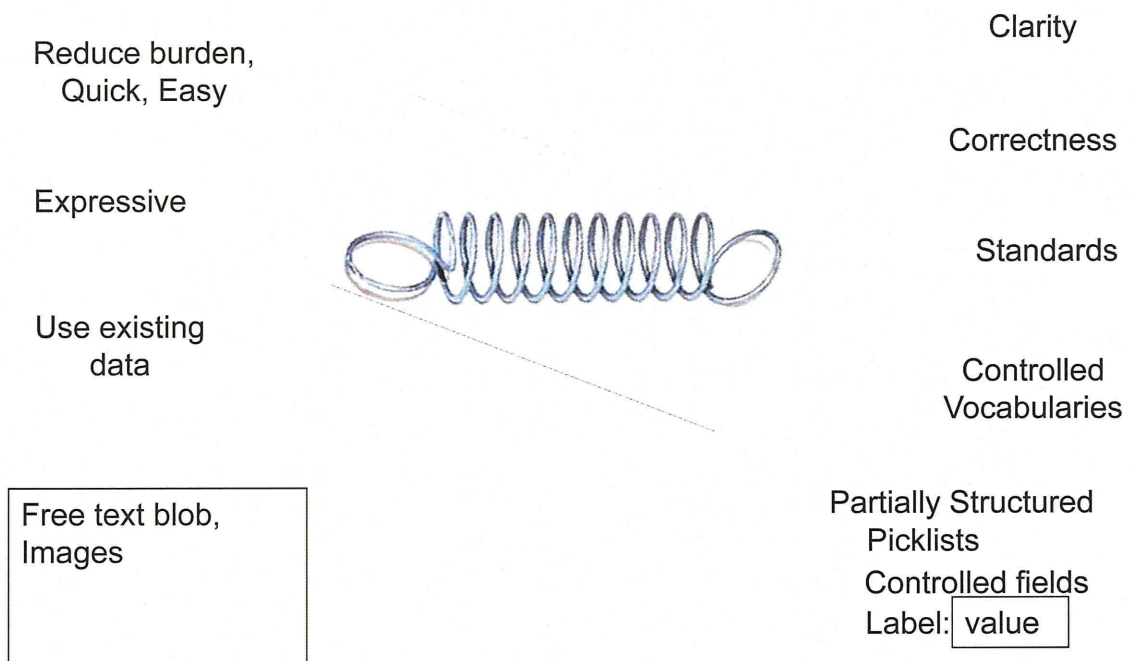


Challenge

- Goal
 - Accurate and computable information
- Challenges
 - We don't know ground truth
 - Information comes from others
 - Data providers have diverse incentives
 - Structured data is hard work for data providers
 - We don't have that much enforcement clout
 - Hard to get the right people to be attentive
 - The world changes

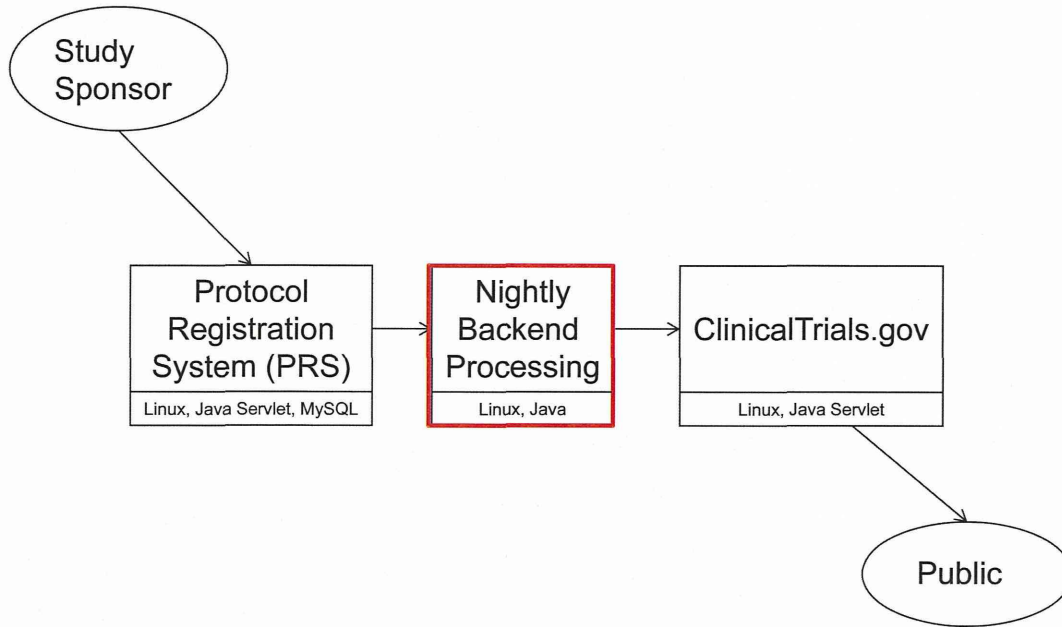
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Collecting Information



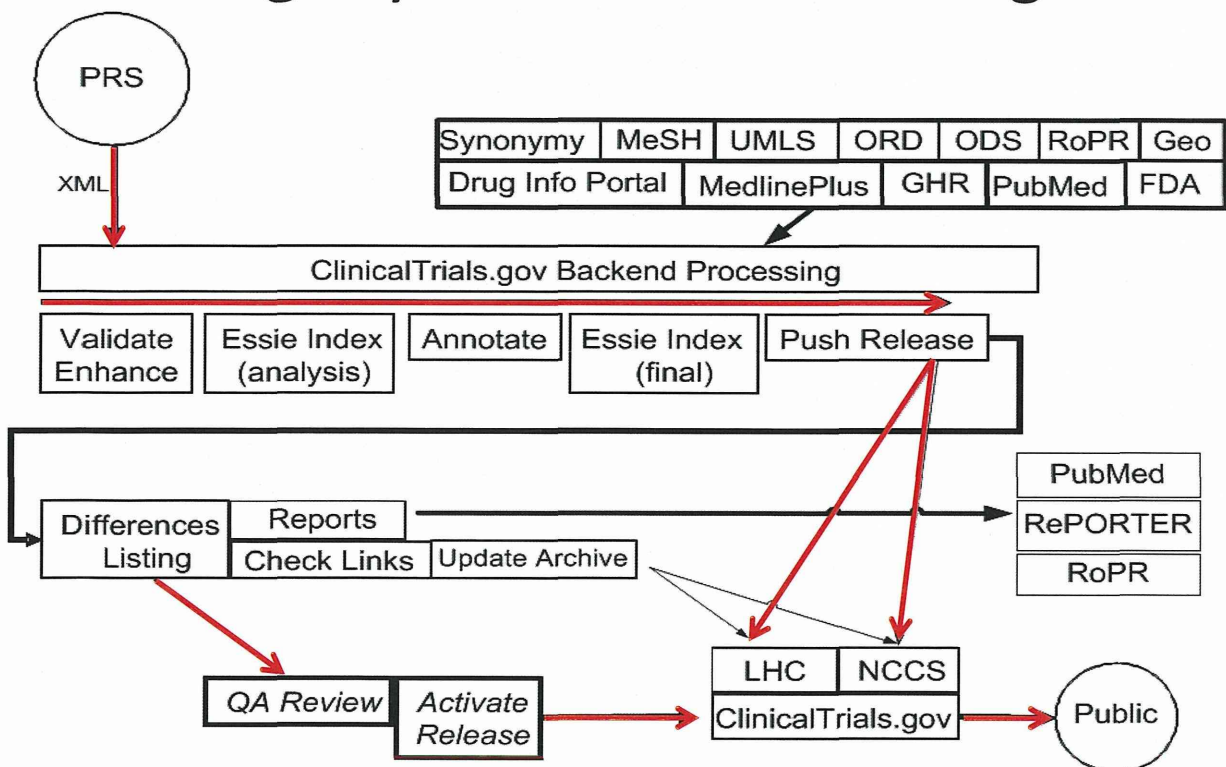
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Highest Level Overview



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Nightly Backend Processing



Annotations for Display

- MeSH Terms and Ancestors
 - Search “crohn disease”, “Granulomatous colitis”, etc...
 - Add “Inflammatory Bowel Disease”, “Gastrointestinal Diseases”, ...
- Add links to other resources
 - PubMed citations
 - MedlinePlus Health Topics
 - Genetics Home Reference
 - Drug Information Portal
- Attempt to normalize collaborator names
 - “Gates Foundation” → “Bill and Melinda Gates Foundation”

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The image shows a screenshot of a PubMed abstract page with several annotations and overlays. On the left, a sidebar contains the following information:

- Safety and Efficacy Study of Inhaled Aztreonam Lysine for Chronic Airway Pseudomonas (AIR-CF2)**
- This study has been completed.**
- Sponsor:** Gilead Sciences
- Information provided by:** Gilead Sciences
- Buttons for **Full Text View** and **Tabular View**
- Purpose:** The purpose of this study was to evaluate the safety and efficacy of inhaled aztreonam lysine for chronic airway Pseudomonas aeruginosa infection due to Pseudomonas aeruginosa in patients with cystic fibrosis.
- Condition:** Cystic Fibrosis
- More Information:** No publications provided by Gilead Sciences. Additional publications automatically included.
- Authors: McCoy KS, Quittner AL, Oermann CM, et al.

The main abstract content includes:

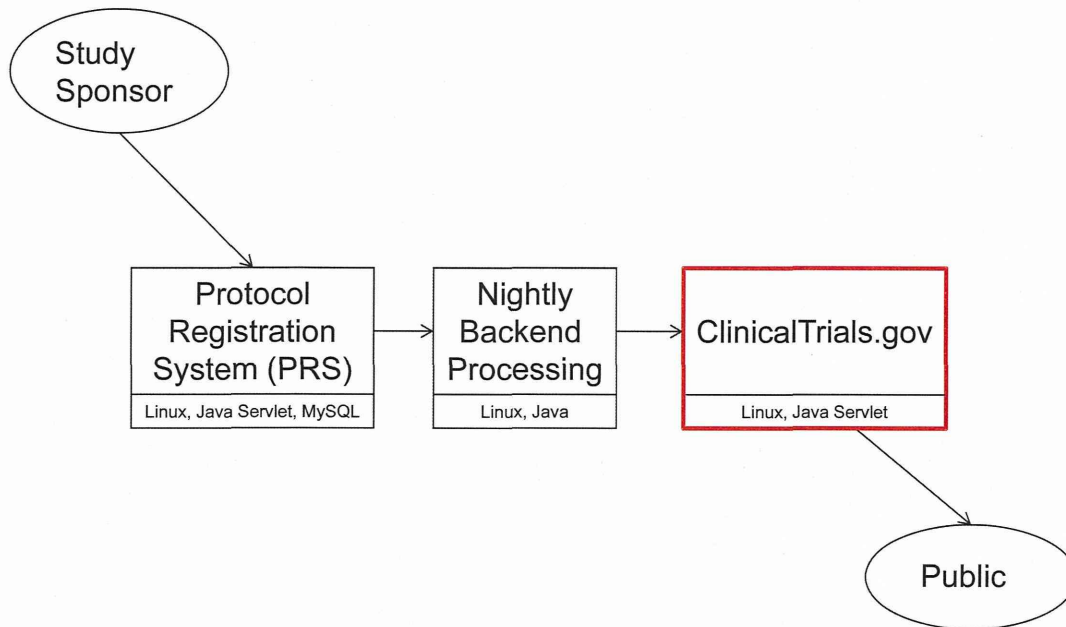
- Title:** Inhaled Aztreonam Lysine for Chronic Airway Pseudomonas aeruginosa in Cystic Fibrosis
- Authors:** Karen S. McCoy¹, Alexandra L. Quittner², Christopher M. Oermann³, Ronald L. Gibson⁴, George Z. Retsch-Bogart⁵, and A. Bruce Montgomery⁶
- Footnote:** ¹Ohio State University, Columbus, Ohio; ²University of Miami, Coral Gables, Florida; ³Baylor College of Medicine, Houston, Texas; ⁴Children's Hospital and Regional Medical Center, Seattle, Washington; ⁵University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; and ⁶Gilead Sciences, Inc., Seattle, Washington
- Rationale:** The effectiveness and safety of aztreonam lysine for inhalation (AZLI) in patients with cystic fibrosis (CF) on maintenance treatment for Pseudomonas aeruginosa (PA) airway infection was evaluated in this randomized, double-blind, placebo-controlled study.
- Objectives:** To evaluate the safety and efficacy of inhaled aztreonam lysine in controlling PA infection in patients with CF.
- Methods:** After randomization and a 28-day course of tobramycin inhalation solution (TIS), patients (n = 211; ≥ 6 yr; ≥ 3 TIS courses within previous year; FEV₁ ≥ 25% and < 75% predicted values) were treated with 75 mg AZLI or placebo, twice or three times daily for 28 days, then monitored for 56 days. The primary efficacy endpoint was time to need for additional inhaled or intravenous antipseudomonal antibiotics. Secondary endpoints included changes in respiratory symptoms (CF Questionnaire-Revised [CFQR] Respiratory Scale), pulmonary function (FEV₁), and sputum PA density. Adverse events and minimum inhibitory concentrations of aztreonam for PA were monitored.
- Measurements and Main Results:** AZLI treatment increased median time to need for additional antipseudomonal antibiotics for symptoms of pulmonary exacerbation by 21 days, compared with placebo (AZLI, 92 d; placebo, 71 d; P = 0.007). AZLI improved mean CFQR respiratory scores (5.01 points, P = 0.02), FEV₁ (6.3%, P = 0.001) and sputum PA density (-0.66 log₁₀ cfu/g, P = 0.006) compared with placebo; no AZLI dose-response was observed. Adverse events reported for AZLI and placebo were comparable and consistent with CF lung disease. Susceptibility of PA to aztreonam at baseline and end of therapy were similar.
- Conclusion:** AZLI was effective in patients with CF using frequent TIS therapy. AZLI delayed time to need for inhaled or intravenous antipseudomonal antibiotics, improved respiratory symptoms and pulmonary function, and was well tolerated. Clinical trial registered with www.clinicaltrials.gov (NCT 00104520).

Annotations include:

- A red circle around the clinical trial registration number: www.clinicaltrials.gov (NCT 00104520).
- A box titled "AT A GLANCE COMMENTARY" with sub-sections:
 - Scientific Knowledge on the Subject:** Cystic fibrosis is a chronic disease often involving endobronchial infection with Pseudomonas aeruginosa, which is difficult to treat.
 - What This Study Adds to the Field:** Safety and efficacy data on inhaled aztreonam show that this new formulation may be an alternative treatment option for patients with cystic fibrosis and chronic P. aeruginosa infection.
- A box containing text about older patients and management of patients with CF, including a reference to a study (10, 11).
- A box containing text about the formulation of the monobactam antibiotic aztreonam and lysine (9).

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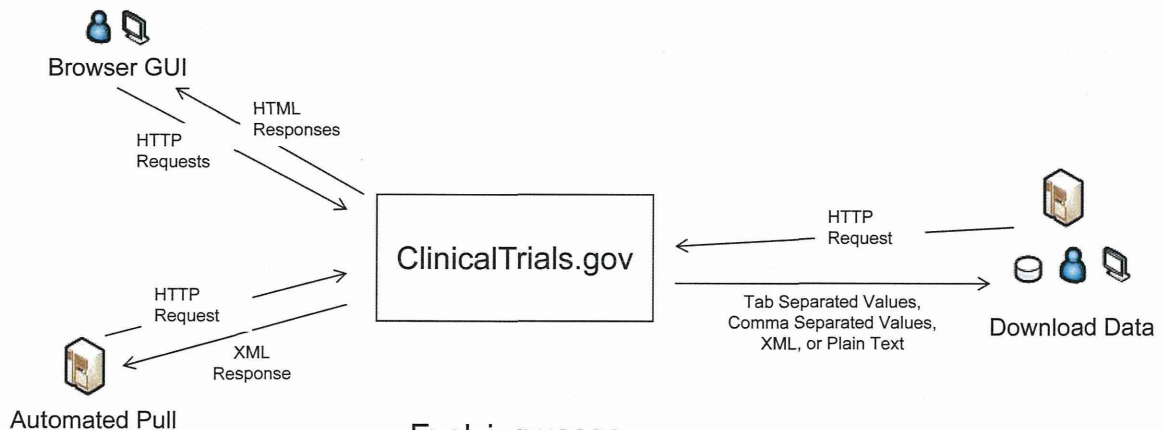
Highest Level Overview



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ClinicalTrials.gov

Public Site



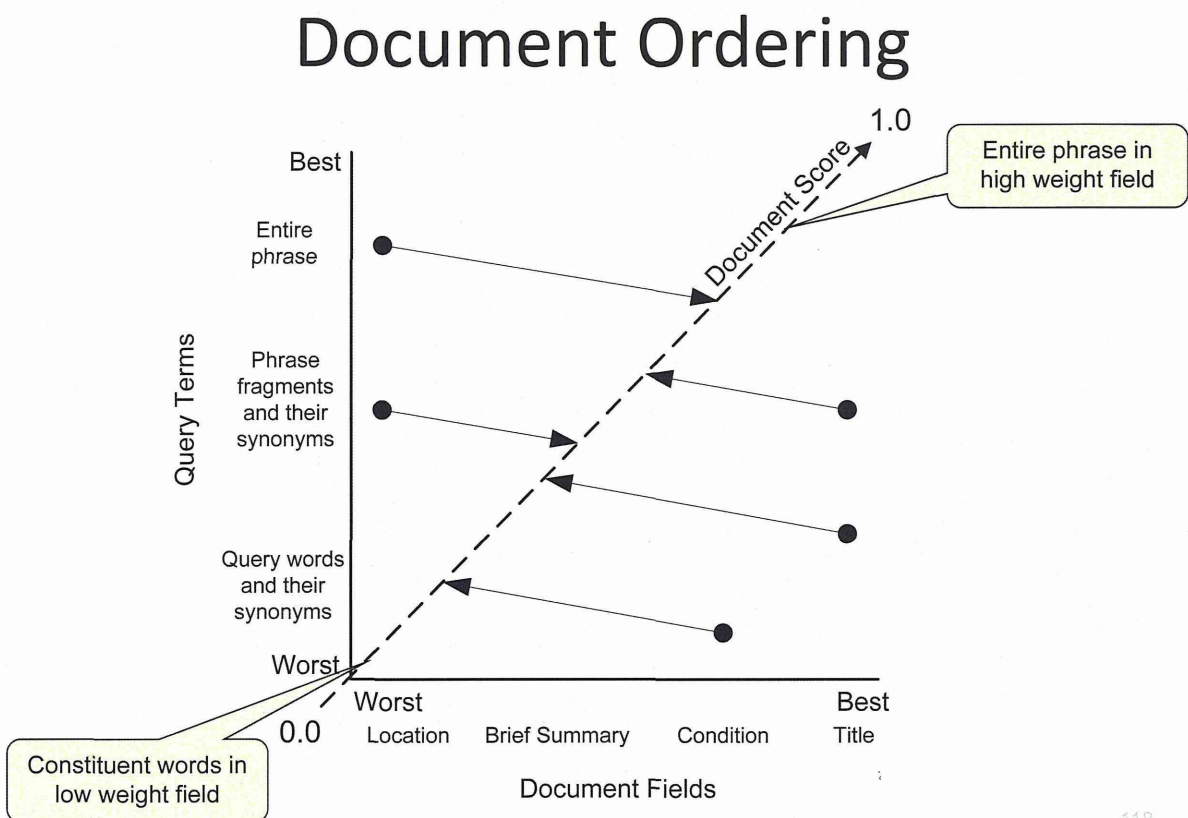
Evolving usage:

- Initially for “public” to find trials
- Increasingly used as research database serving the clinical research community.

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Search Overview: Essie

- Finding documents
 - Uses synonymy derived from UMLS
 - Lexical variants from UMLS
 - Fine grained tokenization **JAK-2**, **d-ala(2)**
- Ordering documents
 - Leverages knowledge of document structure
 - Query relaxation (prefer phrases over words)



Example of Ranking

266 studies found for: aspirin for heart attack

Rank	Status	Study
1	Completed	<p><u>Warfarin After Anterior ST-Elevation Myocardial Infarction</u></p> <p>Condition: Myocardial Infarction</p> <p>Interventions: Drug: aspirin + clopidogrel; Drug: aspirin + clopidogrel + warfarin</p>
2	Terminated Has Results	<p><u>Aspirin in Patients With Myocardial Infarction and Thrombocytopenia</u></p> <p>Conditions: Thrombocytopenia; Myocardial Infarction</p> <p>Intervention: Drug: Aspirin</p>
• • •		
Rank	Status	Study
221	Recruiting	<p><u>Renal Acute MI Study</u></p> <p>Conditions: Myocardial Infarction; Kidney Function</p> <p>Intervention:</p>
222	Active, not recruiting	<p><u>Assessment of Revascularization Versus Conservative Treatment in Heart Transplant Patients for a Clinical Event Reduction</u></p> <p>Condition: Heart-lung Transplant Rejection</p> <p>Interventions: Device: Stent; Drug: optimal medical therapy</p>

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Archival Data: Tracking Changes in the Record

- Each record is expected to be corrected or updated throughout the trial's life cycle, and all changes are tracked on a public archive site that is accessible from each record (through a "History of Changes" link).
- Tabular View
 - Current Outcome Measures
 - Original (First Registered) Outcome Measures

“World Chaos”

Policies That Help Avoid World Chaos

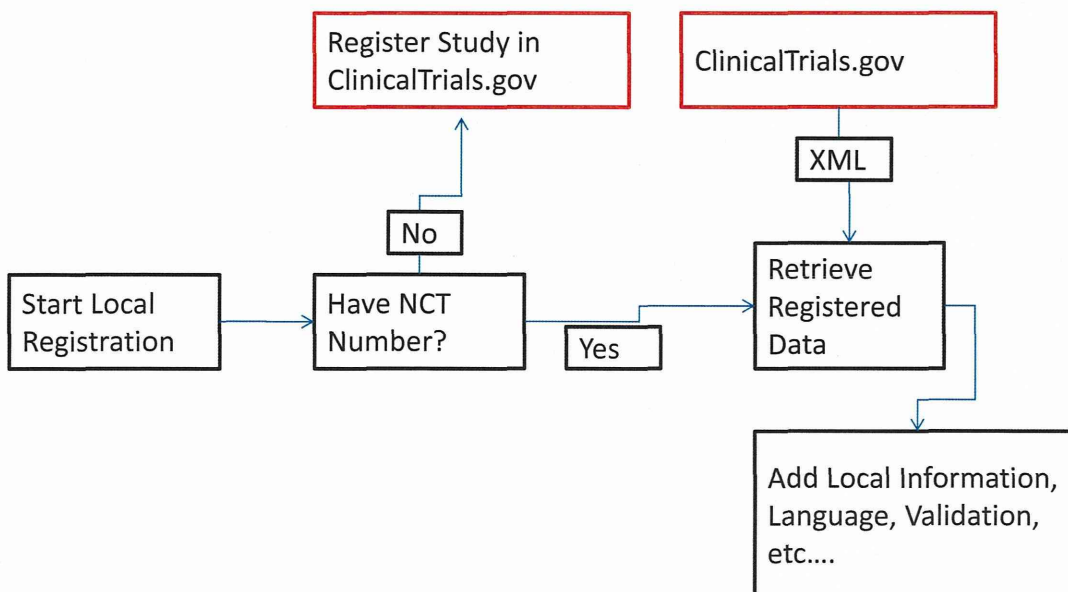
- **Ministry of Health, Israel:** “...controlled prospective clinical trials must be registered at the NIH website, <http://www.clinicaltrials.gov>.”
- **Health Canada:** “...registration of clinical trials ... within 21 days of the trial’s onset ... in ClinicalTrials.gov or ISRCTN [UK registry]”

Collaborative Models: Data Collection

Collaboration is essential and complicated

- Register in ClinicalTrials.gov first *then* collect additional information in local system if necessary.
 - Record ClinicalTrials.gov identifier (NCT Number) in the country registry.
- What data items are desired that are not already collected in ClinicalTrials.gov?
 - ClinicalTrials.gov could add data elements which a country could require.

Collaborative Data Collection



Components of Global System

	<u>ClinicalTrials.gov</u>	
Incentives	U.S. FDAMA, ICMJE, Other laws,	
Communication	Some Need Help !	←
Database	Done	
Validation	Some Need Help !	←
Dissemination	Done English Only!	←

Options on Language Issues

- Parallel Registration
 - Register in English site, capture identifier, then register in language specific registry with cross links between the registries
 - Data provider does the translation
- Capture multiple languages in one database
- Translated Site
 - Using software and human translators, translate some or all of the English data to the target language
- Data Entry Assistance for non-English
 - Is this something the countries could help with ?

Partner Models

- Content Validation Partner
 - Assist ClinicalTrials.gov with validation of organizations based in other countries
 - Assist ClinicalTrials.gov with validation activities for studies conducted outside of the United States
- Content Dissemination Partner
 - Take data from ClinicalTrials.gov,
 - translate portions of the data,
 - make information available in other language

Content Validation

