Why is FDA interested in the Collaboratory and PCORNET?

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FDA/Center for Drug Evaluation and Research: Mission

- Promote health by making safe and effective drugs available to the American public
- Protect health by making sure unsafe, ineffective drugs not on market
- Ensure that drug labels are truthful and informative
- FDA/CDER regulates entire pharmaceutical industry in US—prescription and OTC drugs, innovative and generic drugs
- Set standards for drug development and approval, in particular the amount and type of evidence needed

Developing Evidence About Drug Effects

- Clinical drug development programs, while very expensive, leave a large amount of residual uncertainty about drug effects
- Many questions remain about marketed drugs:
  - What is the correct dose/duration of rx/best drug combo?
  - Effects in varied populations/specific concomitant conditions
  - In which patients is this drug optimal vs other drugs for same condition?
  - The above questions evolve over time as new therapies become available; data about evolving risk/benefit over time usually lacking
  - Safety: increase in frequency of event over common background event (cardiovascular) OR rare safety problem OR greater severity than observed in clinical development

These are the questions that have to be answered to support evidence-based practice

Dealing with Uncertainty about Drug Effects

- Not feasible to withhold approval until all questions answered (that would be forever)
- FDA has the authority to require drug firms to conduct postmarket safety studies (and efficacy studies for drugs approved under accelerated approval); otherwise cannot usually require additional efficacy studies
- FDA (CDER) also operates the adverse event reporting system (AERS), collecting about 1M reports per year, and the mini-Sentinel network
- FDA may also require efficacy or safety studies about special groups (i.e., children) after drug approved

How Do FDA Issues Relate to CE?

- Drug safety outcomes and “comparative effectiveness” often two sides of same coin
- Most common diseases have more than one therapy—studies of marketed drugs usually comparative, what are the outcomes from resulting from using A vs using B?
- Similarly, since all drugs have safety issues, determining the optimum dose and regimen of a given drug usually involve comparative outcomes after exposure to various doses/regimens/durations of therapy.
- Basically, FDA’s approval decisions are a benefit/risk assessment, and except in extreme cases neither benefit nor risk is viewed in isolation

AERS System: Postmarket Safety Data

- Pharmaceutical sponsors collect and analyze reports from healthcare and submit to FDA
- FDA also receives reports directly from the public, primarily from pharmacists and physicians
- CDER studies show that these reports are still a major source of information about drug safety, leading to many label changes
- Signals from AERS frequently require additional study, leading to required postmarket safety evaluations by sponsors

Mini-Sentinel Network

- Operates under an FDA contract
- Distributed network so individual patient data retained by original data holders
- Activities not considered research but are defined as public health surveillance
- Currently can analyze against about 150M lives
- Establishment required under FDA Amendments Act of 2007

Mini-Sentinel Network

- Developed a common data model
- Primarily claims data although some data holders have e-HR data
- Fully operational: running projects ranging from rapid analyses to pharmacoepidemiologic studies
- Over 60 peer reviewed publications including comparative safety studies
- Addressing current drug safety issues: providing additional evidence but not definitive
- Evaluating capacity for randomized investigations

Mini-Sentinel Network: Types of studies

- Psychiatric events with Chantix™ vs other smoking cessation interventions
- Intussusception rates with rotavirus vaccine in infants
- Bleeding events with dabigitran vs warfarin
- Cardiovascular events with anti-diabetic drugs
- Prospective surveillance of new molecular entities for particular signals

FDA Amendments Act of 2007

- Gave FDA ability to stipulate postmarket safety studies
- Guidance: "Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Food, Drug and Cosmetic Act"
- Under certain circumstances, FDA can require postmarket safety studies at time of approval, or when new safety information surfaces after approval

Structure of FDAAA

- For purposes of this part of the Act, “studies” and “clinical trials” are different: a clinical trial is a prospective interventional clinical study, and everything else is a “study”
- When considering the need for a postmarket safety evaluation, FDA first has to consider whether Sentinel could provide the answer
- If not, then observational “studies” can be required
- If the above would not suffice, then a “clinical trial” can be stipulated

Can Required Postmarket Evidence Generation be Built into Emerging Electronic Health Record Networks?

- The NIH HCS Research Collaboratory: using integrated health system and electronic health records for pragmatic trials and other clinical research
- PCORNET: Using electronic records and registries for comparative effectiveness evidence generation
- Sentinel: Using electronic records for drug safety information

The NIH HCS Collaboratory

- Has integrated health system and electronic health records
- Plans to conduct pragmatic trials assessing various healthcare interventions; evaluate randomization within healthcare settings
- Serves as place to develop new methods with demonstration projects
- Providing insights for many NIH institutes into pragmatic health system based trials
- Relatively small in scope

PCORNET

- Strength includes wide range of representations of various populations
- Startup—so capacity to conduct analysis across various databases not yet demonstrated
- 18 month goal for completion of an initial analysis
- Need for a model for sustainability

Sentinel

- Currently FDA contract being re-competed
- FDA portion limited to medical product safety evaluations
- Congressionally-mandated
- Utilizing common data model
- FDA is open to evaluating linkage with other networks

Can Evidence Generation be Built into Healthcare?

- Can we plan towards common data platform that can fulfill different stakeholder requirements?
- Sustainability: can such a platform support required post-marketing studies for medical products? Such a platform could develop this evidence in a cost-effective manner, and be supported on an ongoing basis by all stakeholders
- Could such a platform also support CE studies, quality evaluations, and identification of patient populations for more intensive research?
- Can randomization be built into this concept?

Why is a Platform Needed?

- We don't have answers to most healthcare questions
  - Many recommendations in practice guidelines are based on expert opinion
  - New interventions coming onto market do not have ongoing evaluation
  - We cannot establish standards for quality if we don't know what best practices are
- There are not enough resources to do separate traditional randomized trials for every question that needs evidence
- We need to learn from healthcare itself, and set up a system that allows us to evaluate interventions in the course of care
- We owe this to the patients who entrust their lives to our healthcare system
- A system to generate evidence will enlist the participation and allegiance of the practitioners whom it enrolls and informs

Needed Steps

- Can we establish clear goals and objectives?
- Can we develop a work plan to move in deliberate steps towards a common goal?
- FDA is both willing and eager to participate in discussions around common interests
- Are pilots among the networks a feasible next step?

Summary

- FDA has established a Congressionally-mandated drug safety surveillance system using electronic health data
- Other networks using electronic data have been set up or are in process
- There are multiple opportunities to use such data to answer currently unresolved questions about the outcomes of interventions in health care
- Can we work together to build this capacity?