Regulatory Use of Real World Evidence

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Background: Problems with Current Evidence-generation Methods in Medical Product Development

- Very costly and time-consuming
- At the end of a development program, after expenditure of huge amounts of dollars and effort, many questions about product use remain unanswered
- Limits what can be asked premarket
- Postmarket many questions remain unanswered
- Most health care practices not evidence-based

FDA is Committed to Exploring Use of RWE in Regulatory Decisions

- Provisions of CURES Act require exploration
- PDUFA 6 commitments
- Demonstration project: IMPACT-Afib
- Recent September 13 workshop with Duke-Margolis on the topic
- CDRH/CBER just issued guidance for devices

Device Guidance 9/17

- “Use of Real World Evidence to Support Regulatory Decision-Making” CBER/CDRH
- Discusses challenges with current device evidence development
- Uses of RWE for device regulation
  - Historical control
  - Concurrent control
  - Expand label for approved device
  - Surveillance for safety
- Characteristics of evidence: relevance, reliability, data accrual, QC

Similar Considerations apply to Use of RWE in Drug Development

- Investigational product use (drug, biologic, device) requires informed consent, as would randomized trials of new uses that utilize medical records or claims data for outcomes
- RWE currently used extensively for evaluation of safety of marketed products
- Very little historical use of RW experience in drug regulatory decisions about effectiveness

Use of Real World Evidence (RWE)

- There are no hard and fast rules about how evidence is generated, with the exception of informed consent and patient privacy
- Settings can vary along a spectrum from the standard clinical trial setup to a pragmatic trial run in the healthcare system(s).
- There are trade-offs among data reliability, pragmatism, control of errors, safety, and other factors
- Clearly you don’t want to run a first-in-human trial in the real world setting, for example

FDA is Evaluating Use of RWE for Drugs

- We have approved drugs for rare diseases based on data from registry-like case series
- We have used registry data as external controls
- We are exploring how randomization would work in registry or healthcare settings
- We are collaborating with groups working to improve the validity of key data elements collected in the process of health care
- We have spoken to many groups that are assembling oncology care data in various ways and hope to provide valid platforms for investigations

Very Rare Diseases: Examples of FDA Approvals

- Lumizyme for Pompe Disease: survival data from an international registry of infantile-onset disease
- Carbaglu: Plasma level ammonia reductions in a case series
- Cholbam for bile acid synthesis disorders: data on growth, survival and reduction in abnormal cholestatic markers in a case series
- Glucarpidase for MTX toxicity: data on approx. 20 patients from NIH treatment protocol

New Science Drives Development Trends Requiring Change

- Many more rare and orphan diseases
- More narrowly (molecularly) targeted therapies with companion diagnostics or NGS, often with very small target populations
- Breakthrough therapies
- Cancer, neuroscience, immunology⇧
- Cardiovascular disease down
- Rise of biologic therapeutics
- Increase in drug-device combos

Drug Development Uses of RWE Similar to Devices

- Natural history information
  - Trial and endpoint planning
  - Use of external control, historical or concurrent
- Biomarker development
- Evaluate investigational drug in hybrid model using some RW data
- Add new indications to approved drug
- Postmarket safety evaluation (e.g., Sentinel)

RWE can contribute the Knowledge that Underpins a Development Program

- Understanding natural history—what will happen to people in the trial, and when?
- What do people with the disease want to have mitigated? (patient focused drug development)
- If you are using novel clinical endpoints, or standard endpoints in a new disease, how will they perform?
- What about PROs? Use in practice?
- Power calculations are not enough, you should model and simulate based on what you know, to see if design is feasible

Natural History of Disease: Critical to Planning a Development Program

- Burden of disease
  - What are the symptoms?
  - What would patients most like to have relieved?
  - Are there instruments to measure these?
  - Tradeoffs: how much risk is acceptable for benefits?
- Rate of progression of symptoms
  - Over what time period does measurable change occur?
  - What symptoms progress faster and is this true for everyone?
  - Don’t just rely on experts, they are usually wrong, due to sampling bias

Natural History

- Disease heterogeneity
  - Often, rare diseases are heterogeneous in their expression; rare subsets may or may not be
  - Introduces more variability, which is the bane of finding signal within noise
  - With highly variable disease, self controlled trials may be best
- Many natural history studies are done by academia through registries, etc. May lack documentation, may not be representative sample
- Disease treatment (and even expression) may vary across regions

Biomarker Issues

- Development program may be centered around a predictive (of patient response) or prognostic (for patient selection), or pharmacodynamic (for assessing activity) biomarker
- The crucial biomarkers may not be reproducible, precise, accurate, or informative. Their operating characteristics may not be known and how to designate a “positive” response (e.g. a threshold or cutoff) may be unexplored

Biomarker Issues

- Relying on the performance of such a biomarker as the basis for a clinical development program is folly, in my view
- However, some pragmatic compromises must be made
- Biomarkers critical to a development program should be explored, *in humans,* as thoroughly as possible, prior to initiating human studies
- RWE approaches can be essential to gathering the needed information

Adding a New Indication to an Approved Drug, or Extending an Indication via Off-label Use

- Extending indication—ivacaftor example
- We expect such extensions may occur for targeted drugs, e.g., in cancer or rare diseases with a lot of underlying heterogeneity of target status
- Significant effort going on right now in assembling experiences of cancer patients
- New indication—evidence may be compelling enough vs. natural history that randomized trial not needed

Studying Investigational Drugs or Adding New Indications via Trials Incorporating RWD

- Will likely require hybrid approach
- Bring clinical trial universe and health care universe as close together as possible
- Integrate trial into care process, collecting as much data as possible in the course of standard care
- NIH “Collaboratory” and others have used this approach successfully—requires respectful interaction with caregivers as partners

“Incentive” for Change: Master Protocols/Trial Platforms

- Continuous, ongoing trials rather than start and stop
- Goal: continuous improvement in disease outcomes
- Usually run by consortium with experienced trialists as PI’s
- Capacity to evaluate multiple interventions, biomarkers, patient subgroups over time
- Opportunity to incorporate RWD

Advantages of Master Protocols/Trial Platforms

- Save time overall
- Opportunity to include community practitioners—better recruitment, better research/practice integration
- Answer multiple questions instead of one
- Investigators seen as unbiased towards a given treatment
- Patient centric
- Can use adaptive designs creatively

Challenges of Master Protocols/Trial Platforms

- Novel
- Not comport with pharmaceutical development model
- Not comport with academic rewards model
- Harder to set up in the beginning
- Who supports? Not comport with standard grant structure

Opportunity

- As new Master Protocols or Trial Platforms are set up (and they are becoming more widespread), explicitly design to incorporate RWD as extensively as possible
- Will require additional work in standardization, data verification, training, and curation (as various groups are now doing with RWD), HOWEVER,
- Could pay off in terms of lower costs, greater efficiency, engagement of first-line practitioners, and ability to answer more questions

Conclusion

- I personally believe that the clinical trial system is broken and that master protocols, trial platforms and clinical trial networks need to be the future, utilizing health care data when at all possible
- IMI in Europe and groups here in the US are working towards a transformation that will utilize digital health data within a trial system, but there is a long way to go
- Our inability to generate the needed evidence, both for drug development and to guide clinical practice overall, efficiently and in a cost-effective manner, will continue to be a major barrier to innovation and to the quality of care, until we devise a solution
- Regulators are highly willing to make decisions based on RWE, provided this evidence has the characteristics need to rely on it