Regulatory Use of Real World Evidence: Expectations, Opportunities, and Challenges

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Regulatory “objectives”: what key questions do we need clinical studies to answer?

• Does the drug work for the proposed indication?
  – Meeting the burden of substantial evidence of effectiveness

• Does the drug’s “benefit” (clinical relevance of efficacy in the indicated patients) outweigh the drug’s “risks” (expected or potential safety or tolerability concerns)?

• Can we properly describe the drug’s safety profile and risks? (Sections 5, 6: W&P, Adverse Reactions)

• Can we reasonably describe the supporting evidence from clinical trials (Section 14: Clinical Studies)?
RWE: Expectations in Law – 21st Century Cures Act

• FDA shall establish a program to evaluate the potential use of real world evidence (RWE) to support:
  o Approval of new indication for a drug approved under section 505(c)
  o Satisfy post-approval study requirements

• Program will be based on a framework that:
  o Categorizes sources of RWE and gaps in data collection activities
  o Identifies standards and methodologies for collection and analysis
  o Describes the priority areas, remaining challenges and potential pilot opportunities that the program will address

• Framework will be developed in consultation with stakeholders
Many **potential** uses of RWE beyond Regulatory

<table>
<thead>
<tr>
<th>Uses of RWE</th>
<th>Details</th>
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<tbody>
<tr>
<td><strong>Hypothesis generating</strong></td>
<td>Retrospective or prospective observational studies (effectiveness)</td>
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<tr>
<td><strong>Comparative effectiveness</strong> research</td>
<td>Effectiveness / safety of approved drugs in broader populations in different practice settings</td>
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<td><strong>Treatment strategy</strong> assessments</td>
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<tr>
<td>Measure <strong>quality of care</strong> in health care delivery</td>
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<tr>
<td>Assess <strong>alternative dosing regimens</strong> for established medications (e.g., ASA in the ADAPTABLE trial) in clinical practices</td>
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<tr>
<td>Large pragmatic <strong>outcome trials</strong> in practice settings</td>
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<td><strong>Landscape analyses</strong> (e.g., drug uptake and utilization information, patterns of real world drug use)</td>
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<tr>
<td>Post-approval <strong>drug safety assessment</strong>: signal detection, signal evaluation</td>
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<tr>
<td>Detection / evaluation of <strong>drug-drug interactions, medication errors</strong></td>
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<tr>
<td>Prospective observational studies, including registries, used to <strong>support registration</strong> or <strong>label expansion</strong> (e.g., in cancer, rare diseases)</td>
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<tr>
<td>Large simple, pragmatic <strong>outcome trials</strong> in practice settings (e.g., PMRs)</td>
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<tr>
<td><strong>Assess alternative dosing regimens</strong> for established medications</td>
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<tr>
<td>RCTs with RWE supporting <strong>label expansion</strong> – new indications, new populations, additional endpoints (e.g., large pragmatic outcome trials)</td>
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Clinically relevant for physicians and payors + have utility in regulatory decisions

**Potential uses in regulatory decision-making**
Usual Phase 3 studies: value and limitations

• RCTs can provide a precise assessment of efficacy and safety
  – Potential for valid causal inferences
    = does the drug work – strong internal validity
  – Patients with the disease / status (defined, specific entry criteria); well-characterized response (established endpoints); responsive to treatment (enhanced adherence, exclusion criteria)
    = accurate effect size estimate in trial
  – Traceable, reliable data set upon which to base regulatory decisions

• But have limitations:
  – Resource intensive, long time to complete
  – Selected population vs post-approval use – internal validity vs external validity/generalizability
    • Limitations: fewer who are older, with multiple co-morbidities, on many concomitant medications
Drawing causal inferences: RCT vs Observational analyses

- **Patients with target disease and disease status – in intended indicated population**
- **Meet enrollment criteria**
- **Enter trial**
- **Study drug**
- **Comparator**

- **Enrollment criteria restricts population**
- **Access to sites, interest, time, willingness to participate**

**All factors that may influence risk of outcome event balanced by randomization – supports robust causal inference**

- **Greater external validity**
- **Greater internal validity**
Drawing causal inferences: RCT vs Observational analyses

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Greater external validity

Greater internal validity
Why expand use of RWD/RWE?

• **Much broader and diverse patient experience** vs traditional Phase 3 clinical studies
  – Includes settings and patients who will use drug post-approval
  – Patients with broader age, racial/ethnic, co-morbid disease, disease severity, concomitant medication

• **Very large sample sizes** – potential for detection of infrequent events, drug-drug interactions

• **Wide range of additional information that can be important in regulatory decision-making**

• **Lower resource intensity**
  – *Observational database studies*: utilizing data from routine interactions of patients with their health care system
  – *Pragmatic clinical trials*: usually non-blinded (low cost of drug supply), data emerging from patient’s usual health care - data extracted from EHR/claims, more limited eCRFs
Wide spectrum of potential uses of RWD / RWE in clinical studies

<table>
<thead>
<tr>
<th>Traditional Randomized Trial Using RWD Elements</th>
<th>Trials in Clinical Practice Settings</th>
<th>Observational Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>RWE to assess enrollment criteria / trial feasibility</td>
<td>eCRF + selected outcomes identified using EHR/claims data</td>
<td>Pragmatic RCT using eCRF (+/- EHR data)</td>
</tr>
<tr>
<td>RWE to support site selection</td>
<td>Mobile technology used to capture supportive endpoints (e.g., to assess ambulation)</td>
<td>Pragmatic RCT using claims and EHR data</td>
</tr>
</tbody>
</table>

*Increasing reliance on RWD*

- **Traditional RCT**
- **RWE / pragmatic RCTs**
- **Observational cohort**
RCTs vs non-interventional database studies

Randomized Controlled Trials
- Random treatment assignment
- Controlled outcome measurement
- Clear and easy to understand implementation

Non-interventional Database Studies
- Study design choices balance patient characteristics
- Non-standardized observations
- Complex study design and analytic methods

Controlled study environment and self-evident methodology provides confidence in decision making

Transparent, structured reporting of complex methodology clarifies study validity for decision makers

Figure courtesy of S. Schneeweiss
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But….reasons **not** to expand use of RWD/RWE

- Risk of *falsely concluding effectiveness* from observational dataset analyses – unclear if strong basis for causal inferences
- RCTs are “gold standard”: robust determination of efficacy *and safety of primary importance* in regulatory decision-making
  - Broader understanding of effect estimate in indicated population highly desirable

- **Improvements** in analytic and design methodologies *may* overcome limitations of observational analyses
  - New user designs
  - New methods for matching to balance outcomes risks in drug and comparator groups
  - Improving database quality (and quantity)
  - “Hardening” of EHR, and increasing claims, EHR, and pharmacy database linkages
  - Experience with pragmatic clinical trials

*Can these solutions now allow us to draw robust causal inferences?*
Experience with RWE generation
# Historical controls (RWE) often used in rare diseases

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Status</th>
<th>Data source</th>
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<tbody>
<tr>
<td><strong>Voraxaze (glucarpidase)</strong></td>
<td>Treatment of MTX toxicity</td>
<td>Approved 2012</td>
<td>- Approval based on open-label, NIH compassionate Use Protocol</td>
</tr>
<tr>
<td><strong>Uridine Triacetate</strong></td>
<td>Treatment of 5 FU overdose</td>
<td>Approved 2015</td>
<td>- Two single-arm, open label expanded access trial of 135 patients compared to case history control</td>
</tr>
<tr>
<td><strong>Brincidofovir</strong></td>
<td>Treatment of Ebola</td>
<td>Phase II ongoing</td>
<td>- Non-random open label single arm trial with historical and contemporary controls with multi-stage trial design</td>
</tr>
<tr>
<td><strong>Carbaglu® (Nagamicin Oral Tablets)</strong></td>
<td>Treatment of NAGS deficiency</td>
<td>Approved 2010</td>
<td>- Retrospective, non-random, un-blinded case series of 23 patients compared to historical control group</td>
</tr>
<tr>
<td><strong>Myozyme® (Mucluclase FL)</strong></td>
<td>Treatment of Pompe disease</td>
<td>Approved 2004</td>
<td>- Open-label, non-randomized study of 18 patients compared to historical control group of 62 untreated patients</td>
</tr>
<tr>
<td><strong>Refludan®</strong></td>
<td>Anti-coagulation in heparin-induced thrombocytopenia</td>
<td>Approved 1998</td>
<td>- Two non-randomized, open-label multicenter trials using historical control comparator group from chart review</td>
</tr>
<tr>
<td><strong>ANTIZOL® (Thiometolease®)</strong></td>
<td>Treatment of methanol or ethylene glycol poisoning</td>
<td>Approved 1997</td>
<td>- 2 open-label, uncontrolled studies with historical control dating back to 1946 collected from chart reviews</td>
</tr>
<tr>
<td><strong>Ucephan</strong></td>
<td>Treatment of urea cycle disorder</td>
<td>Approved 1987</td>
<td>- Multi-center open-label, non-randomized study of 56 patients compared to survival rates of untreated historical controls</td>
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**Bold** = RWE
Considerations

• Whether the RWD are fit for use

• Whether the trial or study design used to generate RWE can provide adequate scientific evidence to answer or help answer the regulatory question

• Whether the study conduct meets FDA regulatory requirements
FDA is actively engaging stakeholders in efforts to increase use of RWE
Demonstration Project: Assessment of Non-Interventional Designs

• Attempted duplication of results of phase 3 & 4 RCTs over three years to provide empirical evidence base that could inform our level of confidence in high quality non-interventional designs

• FDA reviewers and researchers from the Brigham and Women’s Hospital/Harvard Medical School Division of Pharmacoepidemiology jointly
  – Selected trials in which claims data are sufficiently fit for purpose in a research environment
    • Oral hypoglycemic, novel oral anticoagulant, antiplatelet, antihypertensive, anti-osteoporosis, asthma, COPD, heart failure, anti-arrhythmic, and lipid lowering medications
  – Concurred with pre-specified measures of agreement
  – Reviewed an implementation process

• Goal: 30 trials completed by March 2020
### Issues to consider: non-interventional observational studies to support regulatory decisions

<table>
<thead>
<tr>
<th>The Research Question</th>
<th>Patient and Group Selection</th>
<th>The Endpoint</th>
<th>Database Quality and Traceability</th>
</tr>
</thead>
<tbody>
<tr>
<td>• What “type” of research question</td>
<td>• Is patient selection appropriate</td>
<td>• Can the endpoint be assessed in RWD</td>
<td>• Database quality: accuracy, completeness</td>
</tr>
<tr>
<td>• Can the question be answered using RWD: are there sufficient patients</td>
<td>• Are comparison groups balanced</td>
<td>• Are the outcomes accurately evaluated</td>
<td>• Is data traceable to source</td>
</tr>
<tr>
<td>• Is the endpoint assessable – available in RWD</td>
<td>• Is patient management comparable</td>
<td>• Is duration in RW database sufficient</td>
<td>• Is source data available for inspection</td>
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And study integrity: pre-specification, posting, no data “dredging”
The effectiveness requirement: the statutory standard for approval

- Requirement to demonstrate *substantial evidence*

- *As defined in Section 505(d), substantial evidence is:*
  - “evidence consisting of *adequate and well-controlled investigations*, including clinical investigations, by *experts qualified by scientific training and experience to evaluate the effectiveness* of the drug involved, on the basis of which it could *fairly and responsibly be concluded* by such experts that the drug will have the effect it purports or is represented to have *under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof*.”

- FDAMA (1997) added *flexibility*: one A&WC trial and *confirmatory evidence*, if considered appropriate

- **21 CFR 314**: defines characteristics of an adequate and well controlled study

  - The FDA *standard* requirement for *two* A&WC studies
  - Reduces risk of false positive findings, bias or confounding in a single trial
Application of the effectiveness requirement

• The statutory and regulatory framework for approval is *not* changing (FDCA 505, 21 CFR 314)
• But, application will be tailored to the characteristics of individual programs
• *One size does not fit all*
  – Common, chronic diseases vs small population programs
  – Serious and life-threatening illness with substantial unmet need vs drugs for less severe symptomatic disorders
  – Feasibility and ethics of study conduct
• The application of our frameworks will change as the types of programs change
• And, will change as the reliability of new sources of effectiveness data – e.g., RWE, mobile technology, decentralized trials – becomes clearer
But...reasons **not** to expand use of RWD/RWE

- Risk of *falsely concluding effectiveness* from observational dataset analyses – unclear if strong basis for causal inferences
- Double-blind RCTs “gold standard”: robust determination of efficacy (drug works or doesn’t) and safety of *primary importance* in regulatory decision-making
  - Broader understanding of treatment effect estimate in indicated population highly desirable – but not critical to regulatory decision

**However...** many improvements in analytic and design methodologies *may* overcome limitations of observational analyses

- New user designs and new methods for matching to balance outcomes risks in drug and comparator groups
- Improving database quality (and quantity)
- “Hardening” of EHR; claims, EHR, and pharmacy database linkages
- Experience with pragmatic clinical trials and observational database analyses

Can these solutions now allow us to draw robust causal inferences?
The effectiveness requirement: the statutory standard for approval

• Requirement to have substantial evidence

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  o “evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.”

• FDAMA (1997) added flexibility: one A&WC trial and confirmatory evidence, if considered appropriate

• And, the drug must be show to be “safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling” (21 CFR 314.125)

• The FDA standard requirement for two A&WC studies
• Reduces risk of false positive findings, bias or confounding in a single trial