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FDA

REAL WORLD DATA
USE IN OBTAINING VALID & RELIABLE
DATA ON CV SAFETY

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Real World Data

What Is it and What Can We Use it For?

The focus described in the program is CV safety and the title refers to phase three development. Well, we need to work on what we mean by real world data. You obviously cannot have a phase 3 study of an unapproved drug evaluated with data collected from a health care system (the drug can not be used in the system prior to approval). But we could perhaps do a controlled study within the Healthcare System.

What I will try to do is consider a full range of "real-world data" and its potential uses in phase 3 development (effectiveness), large safety studies pre- or post-marketing, focusing on use of these data in randomized trials and in externally (i.e. non-randomized) controlled studies.

Real World Data
What is Meant?

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The term needs to be carefully defined and it is critical to separate the data collected (drug use, specific outcomes, concomitant illness, history, patient characteristics) from the specific uses of the data (observational studies, randomized trials). There are important concerns about the accuracy and consistency of data collected in healthcare settings (EHR, billing data, registries, possibly personal devices), and how it can be optimized when it is collected outside of a formal trial, as well as how it compares with data from formal trials. With respect to the quality of a non-randomized study using those data, there are the usual concerns about how various designs will assure comparable populations, minimize bias, etc. always an issue for any non-randomized trials.

I will start by considering use of real world data in a randomized trial setting, starting with consideration of "pragmatic trials."

Real World Data

I.   Controlled Trials

   A.   Pragmatic Trials

   The settings for most clinical trials differ in many ways from clinical care: different physicians, different visit frequency, selection criteria intended to control patient variability (e.g., limiting or requiring concomitant therapy, limiting concomitant illness) or to identify people with greater disease severity or predictors of response (biomarkers, history), close monitoring for adherence, careful specification of effectiveness and safety endpoints, often with specific definitions.

   All these requirements can allow a trial to validly demonstrate the effect of a treatment under specified and sometimes narrow conditions of use, i.e., the treatment "works," and such approaches are the norm in drug development.

Real World Data – What Is It? (cont)

A. Pragmatic Trials (cont)

But there is long-standing concern that these maneuvers limit "generalizability" and the applicability of results to the broad population, e.g., by excluding people on other treatments or with concomitant illness or who fall short of very detailed entry criteria. This has led to proposals (first in 1984, Yusuf, Collins, Peto) and by many others in later years for "large, simple trials," studies of great rigor, but simpler and with broader, less restricted, populations, i.e., "real world patients." The GISSI study of streptokinase an early example of an LST, randomized a large fraction of patients who went to a majority of the coronary care units in Italy with a recent MI to streptokinase or placebo and assessed a primary outcome of hospital mortality. The study called for no change in standard care. It showed a significant reduction in mortality.

Controlled Trials

A. Pragmatic Trial (cont)

But even though a broad population is attractive, care must be taken not to abandon crucial enrichment maneuvers and assurance of well-defined endpoints, as diabetic safety CVOTs illustrate.

Diabetic drugs, under current guidance, must conduct randomized studies (post approval or pre plus post) to rule out an increased CV risk (usually MACE: major adverse cardiovascular events – CV death, AMI, or stroke) of > 1.8 pre-marketing and > 1.3 post-marketing. To have enough events to attain these results, the studies are prognostically enriched (age, duration of diabetes, history of MI, angina, stroke, CV procedure). That is obviously a narrower population than all diabetics, but enrichment is critical to a meaningful study. A lower risk population could not rule out the 1.3 HR.

Similar maneuvers are used in trials of lipid-lowering drugs, heart failure drugs, drugs to reduce heart attacks and stroke, and anticoagulant drugs to decrease stroke rates in AF. Even if the population is broadened, these selection criteria are needed to succeed with a reasonable sample size.

Control Trials (cont)

A. Pragmatic Trials (cont)

Enrichment designs, although they clearly help demonstrate an effect in a higher risk or responder population, always leave open the question of whether the drug will work in a

lower-risk population (and whether benefits will still outweigh risks) or in a broader population, often difficult to answer. Historically, for heart failure drugs and statins, much larger trials in lower risk populations have been carried out.

Controlled Trials

B. Real World Data in Controlled Trials

Turning now to use of data collected in the healthcare environment, there are several potentially important uses of real world data in randomized trials.

1. Finding Patients

Within a well-monitored health care system (VA comes to mind, but other HMO settings could do this) it would be possible to search available records for people who meet entry criteria for a study (elevated BP, history of CAD event, AF, diabetes) and who do not meet exclusion criteria, and ask them about interest in participating in a trial.

Controlled Trials (cont)

It should be possible to screen for

- Presence of most chronic diseases
- Current RX
- Enrichment characteristics
  - Severity
  - Prior events
  - Lab findings
  - Disease duration

One can certainly imagine use of online consent procedures, which in fact we have seen. This could perhaps be supported by providing more general information to patients in the system about ongoing trials and why trials are good.

Controlled Trials (cont)

At some point, presumably, the patients' treating physician would need to be informed (possibly after consent). There are many critical details that need to be considered.

- Need for initial evaluation by an investigator
- Need for periodic monitoring beyond ordinary care
- Endpoints other than outcomes likely to be reliably collected (MI, stroke, or hospitalization), such as increased angina, worsened heart failure, suicidality, HAM-D score. Those would seem to require an involved investigator.

Controlled Trials

Good Candidates – studies of needed duration of treatment with endpoints that WOULD be recorded. These may need little to no special follow up. Candidates are people already on the Rx. Some illustrative possibilities

- How long to give bisphosphonates to prevent fractures
- How long to give adjuvant chemotherapy
- PEGASUS study

    21,000 on ticagrelor with MI 1-3 years before age > 50, and with at least one other risk factor (> 65, DM, another MI, multivessel CAD, or chronic renal disease) randomized to ticagrelor 60 or 90 mg, or plbo, all added to ASA

    Endpoint, CV death, MI, stroke
    HR 0.84 (0.74-0.95), p < 0.004

Done with distinct investigators but could it have used EHR to find these endpoints?

Controlled Trials

B. Real World Data in Controlled Trials (cont)

2. Doing the Trial – How much simpler could it be?
- Still need consent – as noted, could be online (we have seen an example).
- Must there be interaction with the investigator? Could that too be done online? Perhaps only one contact at initiation or at specified times with usual caregiver. This seems possible for the bisphosphonate study or the adjuvant study.
- Certainly, PRO's can be online, perhaps with triggers for investigator contact; in fact, we have seen such a study.
- Depending on the drug, may need to be investigator assessment, so they need to sign up and agree.

Controlled Trials

B. Real World Data in Controlled Trials (cont)

2. Doing the Trial

In almost all clinical trials, study outcomes are measured by the investigator (clinical scales), by patient reported outcomes (PROs), or by events that occur outside the trial but are reported (heart attack, stroke, death). There is a growing possibility that healthcare systems will have recorded many of these study endpoints, a major potential for study efficiency. As noted, PEGASUS may be a good example to consider.

It must be appreciated, however, that there is a reason so much effort is devoted in clinical trials to defining study endpoints precisely, as imprecision (even if not biased) can create "noise" that undermines a finding. It is common, therefore, to have a blinded endpoint evaluation committee to avoid this imprecision. Although it is conceivable that medical records could be examined to validate recorded endpoints, there is little experience I am aware of in doing this.

Controlled Trials

2. Doing the Trial (cont)

Endpoint choices may be critical

- CHF – short-term, now use standardized exercise test; could you instead use agreed upon scales (Minnesota, K.C.)?
- CHF chronic – death and hospitalization for CHF. Would EHR be accurate re cause of hospitalization or could you just count ALL hospitalizations, most of which would probably be for CHF in a sick population
- AMI – certainly noted in medical records but accuracy can be critical in these trials. It would be of interest in some large CV outcome studies to compare investigator and EHR designations.
- Most psychiatry and neurology trials collect physician developed data (HAM-D, ADAS Cog). Conceivably, PRO's could be developed.

Controlled Trials

2. Doing the Trial (cont)

It is hard to imagine an NI trial in the healthcare setting using EHR as there is no prior similar experience on which to base the NI margin. It seems possible that if there was a very large effect and a very standardized endpoint it might be possible (anticoagulants for AF).

Illustrations:

- The Mini-Sentinel Data Partners have been thinking actively about such studies, one of which is ongoing (IMPACT-AF) an evaluation in a cluster-randomized trial of how to increase appropriate use of anticoagulants in AF

Controlled Trials

- TASTE: Thrombus Aspiration during ST-Segment Elevation Myocardial Infarction.

  The study tested whether intracoronary thrombus aspiration before percutaneous coronary intervention (PCI) in patients with STEMI is beneficial. It used the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) to identify all patients with STEMI with planned PCI seen within 24 hours of chest pain. Patients were then randomized to thrombus aspiration followed by PCI or to PCI alone. Endpoints were evaluated using the national population registry (30 day mortality) and other registries (SWEDEHEART) for recurrent MI, stent thrombosis etc.

Controlled Trials

2. Doing the trial (cont)

Obviously, the multiple registries in Sweden made the study possible, but as noted, healthcare systems like the VA or some Sentinel members may have similar endpoint access.

There were other helpful factors
- The intervention did not require long-term treatment, so that there was no need to assure that patients used the drug or to monitor treatment side effects.
- The critical endpoint (death) was easily measured. Other endpoints (rehospitalization secondary to MI, stent thrombosis, target vessel revascularization) could be more subjective. These showed favorable trends in contrast to mortality (the primary endpoint. Could this represent bias in this open-label study?

Real World Data

II. Non-Randomized Trials – Especially Safety Trials

The discussion on effectiveness studies has so far focused on randomized trials conducted within the healthcare setting and there are clearly many possibilities.

Whether real world data could be used in a non-randomized setting, for retrospective (really externally controlled effectiveness) trials is being discussed with, needless to say, many viewpoints expressed. At a March 3-4 Duke Workshop, FDA participants (Janet and I) said that we were generally skeptical about the credibility of such trials for assessing effectiveness at this time, but Janet suggested that a "retrospective/prospective" experiment could be of value, i.e., take the results of a randomized trial and see how they match real world data on the same two treatments. I should note an obvious place to do this would be for comparisons of anti-platelet drugs (clopidogrel, ticagrelor, prasugrel) or anti-coagulants (as Mary Ross Southworth will show you, this has to some degree been done for anti-coagulants, although the initial focus was safety).

Real World Data

II. Non-Randomized Trials – Safety

So why are safety evaluations, where non-randomized data are REGULARLY used, different? There are several reasons.

1. You don't have time for a new RCT. There is a concern that arose based on existing data and a large RCT will take years. The first thing to do is one (or more) epi studies.

2. With some exceptions, the effects you are worried about are large. And epidemiologic studies are credible in assessing large effects HR ≥ 2.0 or maybe > 1.5. Drug effectiveness of that magnitude is unusual, but when it exists, it is not uncommon for us to accept historical controls (frequently baseline controlled trials).

But despite this there are a number of cases where randomized safety trials WERE called for.

Real World Data

III. Safety Studies

Consider Diabetes CVOT

Given availability of multiple drugs, wide use, and a vulnerable population, even a small increased risk (30%) would not be   acceptable for these drugs and the required controlled trials post-marketing are required to rule out such an increase (after ruling out an 80% increase pre-approval). To meet the requirement, trials are markedly enriched for patients with increased rates of CV outcomes (duration of DM, prior events, etc.) and are of long duration to have enough events.

But suppose a drug is not directed at a high risk population, that multi-year treatment is unlikely and that it is a symptomatic condition (making a high rate of drop-outs more likely). Much as you might like one, a randomized CVOT may not be feasible, and an epidemiologic study to rule out, say, an HR of 2 might be the best you can do.

Real World Data

III. Safety Studies

Recent Experience – Mary Ross Southworth will give some detailed cases, but I will mention a few

- **Varenicline**

    Epidemiologic data, while benign, were not reassuring enough. A large RCT, recently reported, showed that suicidality and other psychotic problems were not notably increased.

- **NSAIDS**

    The vast amount of epidemiologic data did not produce clear data on CV effects (nor did many RCTs). The trial of about 20,000 patients comparing ibuprofen, naproxen, and celecoxib (PRECISION) is now announced as complete.

Real World Data

III. Safety Studies

- NOACs

    There are no randomized direct comparisons of the new anti-coagulants with each other (all tested vs coumadin) but many epidemiologic studies have looked at this. So far I would say the small differences seen have not been convincing.

    BUT, after dabigatran was marketed a cascade (hundreds) of FAERS reports of major bleeding were submitted, far more than seen with warfarin, even though the RCTs had shown less breeding with dabigatran. A study conducted quickly, using Sentinel database, gave very rapid recurring results, ruling out any large increase (say 2-fold or more).

Real World Data

III. Safety Studies

NOACs

A second larger study using Medicare data, also to be presented by Mary Ross, was very interesting. Results generally were consistent with previous controlled trials for overall bleeding, GI bleeding, etc. showing no striking increase, but also showed a very notable 65% lower rate of intracranial bleeding, very similar to the 75% lower rate in the controlled RELY study.

It seems at least possible that doing the kinds of analyses Janet suggested and with modern approaches to balancing populations, these kinds of epidemiologic approaches could become more credible for large, effectiveness effects, as they now are for safety assessments.