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USE OF REAL WORLD DATA ("BIG DATA") FOR REGULATORY PURPOSES

ISCTM Meeting
Feb 22, 2017

Terms and Uses

There is some confusion over what we mean by

- Real world data, and
- Real world evidence

In a NEJM Sounding Board paper (Dec 8, 2016), Sherman, et al., we set forth our view of what it meant and how it could be best used.

“We believe it refers to information on health care that is derived from multiple sources outside typical clinical research settings including electronic health records (EHR‘s), claims and billing data gathered through personal devices and health applications.”

NB: It can sometimes be used as evidence (it is really epidemiologic data) but more important, at present, it can facilitate and enhance “traditional” randomized trials.

Real World Data
What is Meant?

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, the use in effectiveness assessments that the Souding Board paper was most optimistic about. I will start 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 enrich the population by identifying people with greater disease severity (prognostic enrichment) or predictors of response (biomarkers, history), i.e., predictive enrichment. Trials also include close monitoring for adherence and careful specification of effectiveness and safety endpoints, often with study-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 in-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.

Diabetes 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 to increase event rates 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.

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, such as AMI, stroke, CV surgery
  - Lab findings considered pertinent, such as renal function
  - 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, at least for many studies, and depending the endpoints 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, perhaps with additional lab (CRP, BNP, or functional EF, increase ability test)
- 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, unless they can be replaced by PRO's.

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 patients and endpoints? And would compliance be as good?

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 as a substitute.

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 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) which did not. 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, 2016 Duke Workshop, FDA participants (Dr. Woodcock and I) said that we were generally skeptical about the credibility of such trials for assessing effectiveness at this time, similar to the Sounding Board article, 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 non-randomized 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. This has to some degree been done for anti-coagulants, although the initial focus was safety (bleeding), and there are no controlled comparisons of the new anticoagulants.

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), frequent for rare genetic diseases.

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.


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