Prospective Cohort Studies for Safety & Effectiveness
Designing Practical Studies that are Fit for Purpose

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24 October, 2014
ICPE, Taipei
Disclosures

• Some work referred to in this course was funded, in part, by these sources
  • US Agency for HealthCare Research and Quality funded the registries handbook, book on protocols for CER and development of the Registry of Patient Registries
  • European Commission’s Innovative Medicines Initiative provided partial funding for the PROTECT study of new tools for pharmacovigilance
• These personal or financial relationships existed during the past 12 months
  • Senior executive and full-time employee of Quintiles, where we conduct research for pharmaceutical and medical device companies and the US National Football League
  • I serve on the board of DIA
• I accept no personal consulting fees
• No confidential or proprietary data are included in these slides
Overview

• Introduction
• Rationale & Terminology
• Operational Considerations
• When Prospective Studies are Not Appropriate
• Closing thoughts
  —Expanding use of observational studies
  —Choosing a study that is fit for purpose
E.g., Cardiology

The Example of Cardiovascular Drugs: Percentages of All Patients in a Given Age Group Treated with Cardiovascular Drugs (Italy) versus Percentages in Each Age Group Included in Cardiovascular Drug Trials (Globally).

Data on all patients treated are for 2011 and come from the Italian census and the Italian ministry of health; data on patients in clinical trials are for drugs approved between 2009 and 2012 and come from the drug-registration dossiers submitted to the EMA during that period.

... Roughly 53 percent of new cancer diagnoses, for example, are in people 65 or older, but this age group accounts for just 33 percent of participants in cancer drug trials.
Registries & Prospective Cohort Studies
Rationale & Terminology
Evidence Generation

Different Stakeholders, Different Needs, Different Purposes

- Meet commitments
- Add to the safety profile
- Evaluate efficacy to improve patient outcomes
- Prove value
- Secure reimbursement
- Enhance understanding of unmet patient needs
- Explore new indications
- Generate publications

- Detect safety signals
- Ensure long-term effectiveness

- Determine value and coverage
- Monitor usage within criteria
- Cost-effectiveness

- Obtain evidence
- Advance science
- Improve care
- Ensure continued reimbursement
- Generate publications

- My own health—what choices do I have?
- What are the risks/benefits?
- Which treatment will improve my quality of life?
- Which treatment is safer, more convenient and affordable?
Non-Interventional Study
a.k.a. “real-world” & “Observational” Studies
EU Definition

the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation.

The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and:

the prescription of the medicine is clearly separated from the decision to include the patient in the study.

no additional diagnostic or monitoring procedures shall be applied to the patients and;

epidemiological methods shall be used for the analysis of collected data.

EU Directive 2001/20/EC (Clinical Trial Directive), Article 2, Definition.
A Patient Registry

- Is an organized system that uses observational study methods to collect uniform data (clinical and other)

- Evaluates specified outcomes for a population defined by a particular disease, condition, or exposure

- Serves a predetermined scientific, clinical, or policy purpose

Focus on registries with some element of prospective data collection
Prospective Studies

If the outcome occurs after the research begins, it is prospective...

From EudraLex Vol 9A“1.7A 1.2.2
Prospective Studies

Data collection may be supplemented with information from existing sources, like medical records
A Guide to Terminology
Patient Registries: Typical Goals

- Evaluate effectiveness: clinical or comparative
- Measure/monitor safety and tolerability including comparative risk-benefit
- Measure and/or improve quality of care
- Describe natural history
  - Incidence, prevalence, trends
  - Identification of high risk groups
  - Resource utilization
  - Paths to diagnosis and treatment, etc.

*Goals are not mutually exclusive; may adapt over time*
Prospective Observational Example
Asian Sudden Cardiac Death in Heart Failure (ASIAN-HF) registry

<table>
<thead>
<tr>
<th>Project Details</th>
<th>Assumptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Type</td>
<td>Prospective Disease Registry</td>
</tr>
<tr>
<td>Indication</td>
<td>Heart Failure</td>
</tr>
<tr>
<td>Study Sites</td>
<td>46</td>
</tr>
<tr>
<td>Patients</td>
<td>8,000</td>
</tr>
<tr>
<td>Countries</td>
<td>China; Hong Kong; India; Indonesia; Japan; Korea; Malaysia; Philippines; Singapore; Taiwan; Thailand</td>
</tr>
<tr>
<td>Study period</td>
<td>Study Start- End: 2012 – 2018</td>
</tr>
<tr>
<td></td>
<td>Enrollment: 3 years</td>
</tr>
<tr>
<td></td>
<td>Follow-up: 3 years</td>
</tr>
<tr>
<td>Study objectives</td>
<td>Understand the burden and predictors of death and hospitalization among these HF patients.</td>
</tr>
</tbody>
</table>

"Most people are just realising now, you cannot just extrapolate the Western data to us ... we respond differently and have different disease patterns." — Carolyn Lam, a consultant at the National University Heart Centre who is leading the study, said the finding is "frightening." She added that it will have important implications for risk factors, control, and treatment for the prevention of heart failure.

"Asians get the short end of the stick despite being slimmer and having a lower Body Mass Index," said Associate Professor Lam. The findings were derived from the first 2,000 patients enrolled in a first-of-its-kind multinational study that included a total of 8,000 patients in 11 Asian territories, including Singapore, Malaysia and Hong Kong.

Singapore topped an unwanted..."
Target: 55,000 patients with newly diagnosed AF followed for 2 years

33 countries including Australia, China, India, Japan, Korea, Singapore, Thailand
Global Anticoagulation in the Field (Garfield) Atrial Fibrillation Registry

GOALS

• Describe the real-life treatment patterns in newly diagnosed AF patients with $\geq 1$ risk factor for stroke

• Assess rates of stroke and systemic embolization

• Assess outcomes, with specific reference to bleeding complications + therapy persistence (including discontinuation, interruption and changes)

• For patients on Vitamin K Antagonist, fluctuations of INR over time
Designing studies that are fit for purpose

1) Who is audience? How much certainty is needed?

2) If an RCT is not required, are existing data sufficient, accessible & sufficient or could they be supplemented by direct data collection?

3) How much follow-up is needed?
   > What is expected induction time for risks and benefits?
   > What are stakeholders expectations for follow-up period?

4) Are comparators needed?
   > Are historical data sufficient?
     » Reasonable overlap of patient characteristics between treatments?
     » Treatment complexity? Single, multiple, etc.?

5) Time and budget?

See GRACE Checklist. J Managed Care Pharmacy 2014;20(3):301-8
Operational Considerations for Prospective Observational Studies
Operational Considerations

• Regulatory and logistical challenges, especially for multi-country studies
  – e.g., can a non-interventional study collect blood, tissue and/or genetic material?
• Data Protection
• Ethics
• Informed consent in the electronic age
• Recruitment and retention
• Management of safety data
• Plan for Missing data
Regional Execution

**US**
- Single large market
- One culture and language
- Common regulatory framework
- Single health care system
- Evolving gov’t cost containment
- Market pricing
- Rapid market access
- Single price

**EU & Asia**
- Many smaller markets
- Multiple cultures and languages
- Complex regulatory map
- Varied health care systems
- Patchwork of cost control policies
- Pricing / reimbursement controls
- Slow and varied market access
- Price differentials
More Detailed Guidance for NIS

**European Union**

1. Is this a study of one or more medicinal products which have a marketing authorisation in the European Member State concerned? ✓
2. Are the products prescribed in the usual manner in accordance with the terms of that authorisation? ✓
3. Does the assignment of any patient involved in the study to a particular therapeutic strategy fall within current practice and is not decided in advance by a clinical trial protocol? ✓
4. Is the decision to prescribe a particular medicinal product clearly separated from the decision to include the patient in the study? ✓
5. Will no diagnostic or monitoring procedures be applied to the patients included in the study, other than those which are applied in the course of current practice?* ✓
6. Will epidemiological methods be used for the analysis of the data arising from the study? ✓

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- *The Rules Governing medicinal Products in the European Union Volume 10 – Guidance documents Applying to Clinical Trials Q&A (1.1 Q4), Version 4.0, July 2009*
- *MHRA Algorithm-Is it a Clinical Trial of a Medicinal Product?*
- *EudraLex Vol.9A provides clarification that interviews, questionnaires and blood samples may be considered as normal clinical practice (Section 1 Chapter I.7) in a PASS*
Regulatory Guidance for Non-Interventional Studies

United States

Observational Study
The investigator “observes and evaluates results of ongoing medical care without 'controlling' the therapy beyond normal medical practice.”
These are not “clinical investigations;” no permission required from the FDA;

Quality Assurance standards
Declaration of Helsinki, ICH GCP, GPP, ISO-14155

Legal frame
Data Protection - HIPAA

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Regulatory Challenges: US

- FDA regulations address routine pharmacovigilance, i.e., compliance with applicable post-market reporting requirements under FDA regulations

- FDA Guidance Documents
  - Guidance for Industry E2E Pharmacovigilance Planning
  - Guidance for Industry Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment

- To the extent data would be obtained from particular institutions (e.g., hospitals), it is recommended to consult institutional policies regarding observational studies

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2 Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment U.S. Department of Health and Human Services J:\GUIDANCE\6359OCC.doc
Non-Interventional Studies

Regulatory governance of NIS not harmonized in EU

- Austria: no legislation
- Spain: detailed legislation exists
- France: legislation exists – unique process
- Greece: follow clinical trial legislation

Or Asia
Informed Consent in the Electronic Age: Example

Innovative Medicines Initiative: PROTECT WP 4: New tools for data collection from consumers

An exploratory study of self-reported medication use in pregnant women

New methods of data collection in pharmacovigilance including methods for collecting data in the natural language and research on how to simplify data collection from reporters whoever they are.
Women learn about study in 1 of 4 countries

They enroll for web or phone (IVRS) data collection. Choose response frequency (2 or 4 weeks) & reminder methods

Web

n = 1200 per country
Completes surveys online.

IVRS

n = 200 per country
Complete baseline survey

Final outcome + satisfaction surveys completed at end of pregnancy.

n = 1200 per country
Completes surveys online.

PROTECT WP4 Study Overview
Informed Consent in PROTECT WP4 Study
Web vs. Interactive Voice Response System

UK and the Netherlands
   Enroll on-line for EDC and by phone for IVRS

Denmark
   Must enroll on-line for both EDC & IVRS

Poland
   Enroll on-line for EDC and by phone for IVRS
   and
   Must provide written consent which is mailed but not reconciled with study files
Minimizing Bias
(Systematic Error)

To maximize study quality, give great thought to site and patient selection and retention

• Choose sites to be broadly representative of key markets for which you want to draw conclusions, e.g., government and private hospitals, urban and rural settings, etc.

• Sites should document efforts to enroll all eligible patients sequentially, and not choose optimal patients

• Invest in retention efforts to minimize loss-to-follow-up

• Verify small amount of source data (10%-25%), if any
To Minimize Confounding
*(Mixing of Effects)*

• Consider characteristics of typical product users, recognizing that
  — Where patients are treated may be a proxy for other factors that influence prognosis, e.g., public vs. private hospitals
  — 1st in class medications are often used in patients with more severe disease

• Collect clinically relevant product use data, e.g., dose, method of administration, frequency of use, etc.

• Use objective outcome assessments
Focus on “must-have” data to address main study objective

1. Focus on data that will address your main objectives
2. Resist the urge to look for all the data that might be of interest
3. A Case Report Form should be able to be completed in ~15 minutes
Other Planning Considerations

1) Who are using the treatment and how could you find them?
   - Can be challenging for pediatric and off-label treatment

1) Make meaningful comparisons
   - Untreated patients
   - Historical data, or comparators from other regions
   - Treatment sequencing (and time windows for risks/benefits)

2) Think about the potential for differential follow-up
   - May be due to health systems or safety/tolerance, e.g., patients with worsening disease may be lost to follow-up
Physician Recruitment

- Physicians participating in observational studies should receive incentives commensurate with fair market value for the work performed.
- Payments should not represent inducement to prescribe.

Recruitment & Retention – Physicians and Patients

- Understand what motivates doctors & patients
- Appreciate that you may be working with research-naïve sites
- Deliver value to sites and/or patients
- Keeping it simple and focused makes it more likely that patients will complete the study.
Is the study company-sponsored?

Follow good public health practices for new or serious AEs in individual populations (recommended practice; not mandated)

Notify company and/or FDA

Company Contact  FDA MedWatch

Establish rules, roles, responsibilities for oversight and reporting in conformance with registry design and applicable regulations.

Does the study have data collection with individual patient information and contact?

Registry trains study site(s) on identification, reporting, and 'expectedness' of AEs and SAEs associated with product.*

Are serious AEs recognized in association with registry drug by a knowledgeable person who has patient contact?

Is SAE "unexpected" (based on drug labeling) in terms of type or severity?

Does reporter believe that drug SAE is related causally, or causality cannot be ruled out?

Reasonable possibility of causality AND unexpected

Company and/or registry notified ASAP

Company reports SAE for own drugs to FDA within 15 days or original report as Expedited report; device reports for serious injuries and malfunctions are due within 15-30 days.

*For devices, no attribution of expectedness is required; "association" is interpreted in the context of an event that is considered as being likely to cause or contribute to death or serious injury if the malfunction were to recur.
Adverse Event Reporting

Practical challenges to collecting and interpreting Serious Adverse Events

— Stimulated v passive reporting
— Reporting by patients and physicians
— Many registries do not collect comparators
Missing Data is More Common in Observational Studies than RCT

When choosing a study design, consider
- Stakeholder needs and expectations
- Potential risks & harm of making a wrong decision
When is a registry not appropriate?

Registries are not appropriate OR very difficult when:

Intervention
- No one in the population of interest is using the product
- Intervention is illegal or users/prescribers do not want to identify themselves
- When treatment is ubiquitous, it is hard to evaluate findings (e.g., autologous BMT for breast cancer)

Outcomes
- Outcome of interest do not come to medical attention
- Patients are likely to be lost to follow-up (e.g., mental illness)
- Physicians who treat patients are not those who follow-up the patients (possibly, but can be challenging)

Physicians & Patients
- Issues of interest are inconsequential or of little interest to physicians
- Patients may not report truthfully or are highly mobile, unmotivated and unconnected

*Data collection is expensive. People will not waste their time… for long… with things that don’t matter to them*
Growing recognition and reliance on contributions of good quality observational studies
Oncology: Extending an existing indication

Metastatic Colorectal Cancer in Combination with Fluoropyrimidine-based Chemotherapy

On January 23, 2013, the Food and Drug Administration (FDA) approved bevacizumab (Avastin®, made by Genentech U.S., Inc.) for use in combination with fluoropyrimidine–irinotecan- or fluoropyrimidine–oxaliplatin–based chemotherapy for the treatment of patients with metastatic colorectal cancer (mCRC) whose disease has progressed (i.e., the cancer continues to grow or spread) while on first-line treatment with a bevacizumab-containing regimen. Bevacizumab is a recombinant humanized monoclonal antibody that binds to human vascular endothelial growth factor (VEGF), thereby preventing the interaction of VEGF with its receptors on the surface of endothelial cells.

This approval is based on the results of a randomized, open-label, multinational clinical trial conducted in patients with mCRC that had progressed during, or within 3 months of, discontinuation of first-line bevacizumab-based combination chemotherapy with fluoropyrimidine–oxaliplatin or fluoropyrimidine–irinotecan.

In the clinical trial, 820 patients were randomly assigned to receive chemotherapy alone (N=411) or chemotherapy in combination with bevacizumab (N=409). Patients received chemotherapy with either fluoropyrimidine–irinotecan-based therapy or fluoropyrimidine–oxaliplatin-based therapy, depending on their prior treatment (i.e., patients who received prior treatment with oxaliplatin received irinotecan-based therapy and patients who received prior treatment with irinotecan received oxaliplatin-based therapy). The treatment cycles for both groups were repeated every 2 or 3 weeks, depending on the chemotherapy regimen used, and bevacizumab was administered at a dose of 5 mg/kg by intravenous infusion every two weeks or 7.5 mg/kg by intravenous infusion every three weeks. Bevacizumab was continued until disease progression or unacceptable toxicity.

A line indication extended on the basis of
• One randomized controlled trial
• 2 registry-based studies
Broader Indication for Intraocular Lenses

Analysis of data from FDA databases, the AAO NEON database, post mortem eyeballs and explanted IOLs from the Center for Research on Ocular Therapeutics and Biodevices, and the published literature, allowed FDA personnel to conclude that there was substantial scientific evidence to support the use of IOLs in adults younger than 60 years. Their conclusions were presented in the publication, ‘Retrospective evaluation of intraocular lenses in adults younger than 60 years’ [12]. References to this publication, with its extensive review of epidemiological data, has allowed manufacturers to request that FDA change the indication for their IOLs from ‘use in adults 60 years and older’ to ‘use in all adults’.

In summary, utilization of epidemiological data has played a major role in the evaluation of IOLs by FDA. It has allowed FDA to develop policies that helped to facilitate the 25 year improvement in the quality of cataract patients’ treatment unparalleled in medicine today [8].

Questions

Patient registries can ONLY be used to study:

a) Effectiveness
b) Safety
c) Burden of illness
d) Disease management
e) All of the above
Questions

Which of the following is true:

a) Patient registries are an informal type of study approach and don’t have many rules for good practice
b) Patient registries are becoming a well-respected scientific approach for prospective observational research.
c) Patient registries require that patients are randomized to treatment
d) Patient in registry studies must accept whatever treatment the investigator chooses for them
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