Task 3: Develop recommendations for the use of patient registry data as a complement to randomized clinical trial data.

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Workshop Overview

- Establish patient registry in the hierarchy of medical evidence
- Definition of terms
- Strengths and weaknesses of RCTs and Registry
- Hierarchy of evidence – where registry fits
- Preliminary survey to explore usefulness of registry and observational data for healthcare decision making
- Development of recommendations

What is a Registry?

- A patient registry is an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves a predetermined scientific, clinical, or policy purpose(s).
- The registry database is the file (or files) derived from the registry.

Registry Studies

- Individuals are enrolled on the basis of either disease or exposure status
- Physician (investigator) decides how a patient gets treated, not the protocol
- Results of ongoing disease process and medical care are observed
- Can be accomplished by direct data collection from physicians and/or patients
- May be conducted using existing data, collecting new data specific for a study, or some combination

Alternative Definitions

- Cohort study: Prospective, observational follow-up study of a particular disease, condition or intervention designed to evaluate safety and effectiveness
- Administrative claims databases: Electronic records to obtain reimbursement for medical services or medications that can be linked to other medical records
- Electronic health records and medical charts: Computerized medical records
- Others?
Randomized Controlled Clinical Trials

GOLD STANDARD FOR CLINICAL EVIDENCE

Strong Internal Validity*
- Designed to test focused clinical efficacy, effectiveness and/or safety hypotheses
- Treatment is assigned by randomization
- Behavior is largely driven by protocol
- Inferences are limited by inclusion/exclusion criteria

*how well the data collected reflects the truth about the pop'n under study

Randomized Controlled Trials - Strengths

- Randomization to avoid selection bias
- Prospective design using controlled conditions
- Blinding
- Defined sample
- Detailed covariate information
- Strong internal validity
- High integrity of data
- High acceptance by decision makers

Randomized Controlled Trials - Weaknesses

- Short follow-up (often 6-12 months)
- Generally small sample size
- Protocol driven care
- Center and patient selection narrowly defined
- Surrogate endpoints often necessary
- Difficult to implement in certain situations
- Do not always reflect real-world situations
- Analyze by intent-to-treat, not how drugs are actually used
- Do not give insights into why clinicians may use drugs off-label or in risky situations
- High cost

Why do we need more/different evidence?

Reality
- Data from RCTs do not always reflect real-world practice and outcomes

Generalizability
- Data from RCTs cannot necessarily be assumed to apply to subpopulations not studied in those RCTs

Applicability
- Data from RCTs do not answer questions of physician practice behavior and the resulting outcomes of that behavior

Availability
- There are a limited number of RCTs relative to the number of decisions that must be made

Registries

Strong external validity*
- Limited inclusion/exclusion criteria mean patients are more representative of usual practice
- Observed practice not dictated by protocol
- Comparative information from actual practice
- Estimates of impact of treatment are more realistic

*generalizability

Why not simply rely on clinical trials?

Data from RCTs do not always reflect real-world practice and outcomes
Generalizability
- Data from RCTs cannot necessarily be assumed to apply to subpopulations not studied in those RCTs

Applicability
- Data from RCTs do not answer questions of physician practice behavior and the resulting outcomes of that behavior

Availability
- There are a limited number of RCTs relative to the number of decisions that must be made
**Registry studies - Strengths**

- High external validity since data is collected in the setting of standard clinical practice
- Large sample size enables better estimation of event rates
- Long term follow-up
- Hard endpoints and outcomes
- More practical than RCT in certain situations

**Registry studies - Weaknesses**

- Difficult to identify and control all sources of bias
- More challenging to analyze than RCT
  - Variable time intervals between visits
  - More variability in treatment, populations, settings, etc.
  - Change in practice over time
  - Lower acceptance by decision makers?

**Where Does Registry Data Fit in Hierarchy of Medical Evidence?**

Do medical decision makers and policy advisors consider registry data in evidence reviews? Where does it fit?

**Review of Published Guidance**

CMS

- As a general matter, observational studies may be most helpful for describing the "natural history" of patient outcomes in a treated population, including development of better evidence on whether particular types of patients are likely to have important side effects.
- In contrast, studies involving some form of randomization may be required to provide definitive evidence on effectiveness or comparative effectiveness in particular types of patients.
- May include a broader range of studies than RCT including observational research ...

**Grading of Clinical Evidence:**

WP believes, other than being equal, that high quality randomized controlled trials and high quality meta-analyses have the greatest evidentiary claim. Trials which lack external validity through protocol inclusion criteria, which focus on a surrogate (disease oriented) endpoint, and which lack an active comparator will have a lower evidentiary weight in formulary decisions. Claims based upon a combination of the results of randomized, active control trials assessing patient oriented endpoints and pragmatic trials of similar design are those that WP would consider of good quality and providing a good basis for monitoring and validating claims for product performance.

*WellPoint HTA Guidelines 2005*
Evidence for relative treatment effects:

Hierarchies typically grade studies as follows: from level 1 (RCTs), through level 2 (controlled observational studies, for example, cohort studies, case-control studies), and level 3 (observational studies without control groups, for example, case series), to level 4 (expert opinion based on pathophysiology, bench research or consensus views).

It is important to recognize that RCT data are often limited to selected populations, short time spans and selected comparator treatments. Therefore, good-quality observational studies will often be needed to supplement the RCT data. In addition, the value of evidence from anywhere in the hierarchy will depend on its quality and relevance.

NICE Guide to the Methods of TA 2004

IQWIG:

- With its emphasis on the internal validity of studies of effectiveness, RCT are regarded as the gold standard for assessing interventions
- Only in exceptional cases will the Institute use non-randomized intervention studies or epidemiological studies in the assessment of effectiveness

Recent & New Initiatives to Advance Quality

GRACE Initiative

- Develop principles to address good practice for the design, conduct, analysis, and reporting of observational studies of comparative effectiveness
- Create an evidence hierarchy for observational CR research
- Ultimate goal of the principles: enhance quality and facilitate the use of this research to support decision-making by patients, physicians, and payers

www.graceprinciples.org

Survey to Assess the Usefulness of Observational and Registry Data for Health Care Decision-Making

- As of April 29, 2008, 28 survey responses (convenience sample)
- 11 questions
- Likert scale
  - Strongly disagree to strongly agree
Respondents

- Organization type
  - Provider/insurer (11), Industry (5), Research (12)
- Position
  - Manager (7), Other (21)
- Involvement in reimbursement decision
  - Decision maker (4), Support (19), None (5)

Q4: Observational or registry studies are required for access and reimbursement decisions

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Q5: Observational or registry data is given equal or greater weight compared to clinical trial results for coverage decisions

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Q6: Observational or registry data is useful for determining the epidemiology of disease states

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Q7: Observational or registry data is useful for determining burden of illness

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Q8: Observational or registry data is useful for determining cost of illness
Q9: Observational or registry data is useful for determining treatment patterns of illness

Q10: Observational or registry data is useful for determining safety of medical interventions

Q11: Observational or registry data is useful for determining effectiveness in the treated population

Q12: Observational or registry data is useful for determining treatment effects on healthcare resource use

Q13: Observational studies or registries need to be available in your specific geography

Q14: I have concerns for using data from observational studies or registries for coverage decisions
**Cumulative score (Likert reversed for q14)**

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**This Committee Recommends**

Registry could and should be used to complement and supplement RCTs for assessing real world outcome:
- Safety
- Effectiveness
- Treatment pattern (dose, population, and off-label use)
- Cost
- Patient-reported outcome
- Compliance

**Characteristics of a quality registry**
- Design with objective in mind (not every question can be answered by registry)
- Careful data collection and analysis
- Report data with strengths and limitations stated

**Your reactions?**