A Textbook of Pharmacoepidemiology and Pharmacovigilance for Pharmacy Students

Lesson 8:

Measuring outcomes: PROMs & PREMs

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8.1. What is an outcome?

A clear way to understand outcomes is through **Donabedian's Structure–Process–Outcome (SPO) paradigm**. In this model, **structure** refers to the fixed characteristics of the healthcare setting, like resources, infrastructure, and workforce; **process** covers the activities and interactions involved in delivering care, such as prescribing practices or patient counseling; and **outcome** is the measurable end result for healthcare, including clinical changes (e.g., symptom relief, disease progression), patient-reported benefits (quality of life, satisfaction), and safety indicators (adverse drug events).

The **ECHO model**, introduced by Kozma and colleagues[1] in 1993, is a widely used framework in pharmacoeconomics and health outcomes research designed to capture the full impact of healthcare interventions, including medicines, by assessing three distinct but interrelated dimensions: **Economic, Clinical, and Humanistic Outcomes**.

Economic outcomes refer to the costs and resource use associated with medical treatments. These can include direct costs (e.g., drugs, hospitalizations, laboratory tests, and medical staff time), indirect costs (e.g., lost productivity due to illness or time off work), and intangible costs, which cover less easily measured effects (such as pain or anxiety resulting from treatments). In the ECHO model, economic analysis typically involves comparing these costs against the consequences or benefits of different treatment alternatives, helping assess value for money in medication use and guiding decision-makers in optimizing healthcare resource allocation.

Clinical outcomes are the observable, measurable effects of interventions on patient health. They include medical events resulting from disease or treatment, such as symptom improvement, cure rates, side effects, disease progression, or mortality outcomes. These can be further classified as **surrogate endpoints** (or intermediary), like lab test results or biomarker changes, and **final endpoints**, such as survival or relapse. Clinical outcomes often remain the primary measure in studies evaluating drug efficacy, but the ECHO model encourages simultaneous consideration of other dimensions.

[1] Kozma CM, Reeder CE, Schulz RM. Economic, clinical, and humanistic outcomes: a planning model for pharmacoeconomic research. Clin Ther. 1993;15(6):1121-1120.

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Humanistic outcomes focus on the patient's perspective, especially on aspects like quality of life, functional status, and satisfaction with care. These are usually measured using instruments that quantify health-related quality of life (HR-QoL), patient preferences, utilities, or direct patient-reported outcomes measures (PROMs). By including humanistic measures, the ECHO model acknowledges that the value of pharmacotherapy extends beyond biological effects, namely how a patient feels or their ability to function in daily life are critical endpoints for society and healthcare practice.

Understanding the difference between signs and symptoms

One of the key distinctions in clinical practice and health assessment is between signs and symptoms. Though these terms are sometimes used interchangeably in everyday conversation, they have clear, separate meanings.

Signs are objective indications of disease. They are phenomena that can be observed, measured, or detected by others, especially healthcare providers, during exams or tests. Examples include a visible skin rash, irregular heart rhythm detected via stethoscope, elevated blood pressure, or abnormal findings on laboratory tests or medical imaging. Signs are not dependent on the patient's perception; even when the patient is unaware of the underlying problem, a sign can alert clinicians to disease.

Symptoms, on the other hand, are subjective experiences. They are what the patient feels, notices, or reports, but are not directly observable by others. Symptoms can encompass pain, fatigue, nausea, or dizziness. Two people with the same illness may report different symptoms: one may feel short of breath, the other may just feel tired. The subjective nature of symptoms means they can only be known if the patient communicates them; they cannot be measured or detected by a third party without input from the affected individual.

8.1.1. Surrogate vs. final outcomes

Surrogate outcomes, also known as **surrogate endpoints**, are defined as laboratory measurements, biomarkers, or physical signs or symptoms used as substitutes for clinically meaningful endpoints that directly measure how patients feel, function, or survive. Examples of surrogate outcomes include hemoglobin A1c levels for diabetes, blood pressure measurements for cardiovascular risk, and tumor size for cancer trials. These proxies are attractive in clinical research because they often occur earlier, can be measured with fewer patients, and typically require shorter, less costly, and less invasive studies compared to research that evaluates ultimate health events such as mortality or major morbidity. The use of surrogate endpoints can expedite research and regulatory approval, providing earlier signals of efficacy, which is particularly useful for chronic conditions where clinical endpoints may take years to emerge. When validated by robust epidemiological and therapeutic evidence, surrogate outcomes can reliably predict final patient-relevant endpoints, streamlining drug development and access.

Final outcomes, in contrast, are endpoints of primary relevance that directly reflect the benefits or harms experienced by patients, such as survival, reduction of major morbidity, or improvement in quality of life. These are the 'true' measures of therapeutic value in clinical practice and are essential for health technology assessments and regulatory decisions.

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Despite their practical benefits, surrogate outcomes are associated with significant risks and limitations. **A favorable effect on a surrogate marker does not always translate into a genuine benefit for the patient**. For example, interventions that reduce blood pressure may not always lead to reduced cardiovascular morbidity or mortality, as seen in specific antihypertensive drug trials. Furthermore, trials using surrogate outcomes have been observed to report larger treatment effects than those measuring final patient-relevant outcomes, raising concerns about overestimating true efficacy and underappreciating possible harms. The reliability of a surrogate endpoint thus depends on the strength of the mechanistic and epidemiological links to final outcomes; misjudgment may result in inappropriate or harmful therapeutic policies.

Various frameworks for surrogate endpoint validation have been developed and discussed in expert consensus guidelines and regulatory literature. Ciani et al., emphasized that surrogate endpoints must be supported by clinical, pathophysiological, or epidemiological rationale, but stressed the importance of validation and context specificity[2].

The BELLINI Trial: Discordance between surrogate and final endpoints

The BELLINI trial offers an example of how apparent successes measured by surrogate endpoints can mask real harm when final outcomes are considered. Conducted as a randomized, double-blind, multicenter phase 3 study, BELLINI enrolled patients with relapsed or refractory multiple myeloma and tested the addition of venetoclax to bortezomib and dexamethasone vs. placebo. The trial's primary endpoint was progression-free survival (PFS), defined as the time patients live without disease worsening. PFS can be measured relatively quickly and is often presumed to predict longer overall survival (OS), the patient-relevant outcome.

At the interim analysis, the addition of venetoclax to the standard regimen significantly improved PFS: the median PFS was 23.4 months for the venetoclax vs. 11.4 months for placebo (HR 0.58, p=0.00026). However, subsequent analyses revealed a troubling finding: overall survival favored placebo, not venetoclax. Upon final assessment, the hazard ratio for OS was 1.19 (95%CI 0.80–1.77, p=0.39), indicating no improvement and even a trend towards increased mortality in the venetoclax group. Notably, more deaths were related to treatment in the venetoclax cohort, predominantly due to infections and organ dysfunction, a recognized risk for myeloma treatments that may cause immunosuppression.

This outcome creates a striking discordance: a drug regimen that doubled PFS, the surrogate marker, resulted in shorter life expectancy for many patients. Regulatory statements and guidelines following the BELLINI trial emphasized that venetoclax should be avoided in general populations of relapsed/refractory multiple myeloma patients, except potentially for those with genetic features, such as t(11;14) translocation or high BCL2 gene expression who may have had more favorable survival outcomes.

Kumar SK, Harrison SJ, Cavo M, et al. Venetoclax or placebo in combination with bortezomib and dexamethasone in relapsed or refractory multiple myeloma (BELLINI): final overall survival results from a randomised, phase 3 study. Lancet Haematol. 2025;12(8):e574-e587. doi:10.1016/S2352-3026(25)00139-5

[2] Ciani O, Manyara AM, Davies P, et al. A framework for the definition and interpretation of the use of surrogate endpoints in interventional trials. EClinicalMedicine. 2023;65:102283. doi:10.1016/j.eclinm.2023.102283

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8.2. Patient Reported Outcome Measures (PROMs)

Patient-Reported Outcome Measures (PROMs) are standardized questionnaires or tools that directly collect information from patients about their health status, symptoms, functioning, and quality of life, without interpretation by clinicians or others. PROMs are designed to capture what matters most to patients, how a disease or treatment affects their daily lives, as opposed to relying solely on clinical or laboratory measures.

At the heart of this concept is the patient-reported outcome (PRO): **any report of a patient's health condition, well-being, or health-related behavior provided directly by the patient**. Examples include self-assessments of pain severity, fatigue, mobility, emotional functioning, or overall quality of life. PROs are valuable because they reflect the subjective experience of living with illness or receiving treatment.

Clinical trials and observational studies have traditionally relied on so-called 'hard' outcomes such as survival, laboratory biomarkers, or imaging results. These are typically reported by clinicians or measured objectively. PROMs, in contrast, put the patient's voice at the center, because they are not interpreted or filtered by clinicians. They focus on subjective but clinically meaningful domains such as pain intensity, physical limitation, social participation, emotional well-being, and treatment side effects, which may not be visible through lab tests or clinical examination. PROMs can be **general** (enabling comparisons across conditions) or **disease-specific** (addressing symptoms and impacts unique to a particular illness).

Patient-reported measures have become a cornerstone of person-centered and value-based care, providing evidence that complements traditional outcome measures. By systematically including PROMs in research and practice, healthcare teams can better understand and address issues affecting patients' daily lives, improve communication, and guide shared clinical decision-making.

By systematically measuring symptoms, functioning, and quality of life from the patient's perspective, PROMs reveal benefits and harms of interventions that often go unnoticed if only clinical, imaging, or laboratory endpoints are used. For example, changes in biomarkers like FEV1 in COPD or radiographic arthritis severity in osteoarthritis frequently correlate poorly with patient-reported symptoms or day-to-day functioning, highlighting the added value of PROMs in capturing patient-important changes.

PROMs encompass several types of instruments, each designed to capture specific domains of a patient's health experience. The most common domains measured by PROMs are symptoms, health-related quality of life (HRQoL), and functioning.

- **Symptom-based PROMs** focus on the patient's subjective experience of disease or treatment-related symptoms, such as pain, fatigue, nausea, or breathlessness. These tools allow patients to quantify symptom severity, frequency, and impact, often providing information that clinical examination alone cannot reveal.
- **Quality of Life PROMs** aim to capture broad aspects of a person's well-being that go beyond mere symptom control. HRQoL instruments, such as the SF-36 or EQ-5D, include items related to physical, emotional, and social functioning. They measure the

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overall impact of health status on daily life, reflecting the patient's perspective on physical, psychological, and social domains.

- **Functioning PROMs** assess how well an individual performs daily activities or specific roles, such as mobility, self-care, work participation, and social engagement. Functioning is a critical outcome dimension, especially for chronic diseases and rehabilitation, and is typically addressed in both generic and disease-specific PROMs.

Patient-Reported Outcome Measures in Cancer Care

Balitsky et al. (2024) investigated whether systematically integrating patient-reported outcome measures (PROMs) into cancer care improves key clinical and patient-centered outcomes for adults undergoing anticancer therapies. Spanning 45 randomized clinical trials and including 13,661 patients with solid and hematologic malignancies treated worldwide, the review evaluated the impacts of PROMs on survival, health-related quality of life (HRQoL), and healthcare resource utilization. This review underscores persistent discrepancies between clinician-reported and patient-reported outcomes, especially for symptoms and treatment side effects, and positions PROMs as an essential tool for accurate assessment and management in oncology.

Findings showed that systematic use of PROMs clearly benefits survival: cancer patients whose symptoms and concerns were monitored via PROMs and shared with their healthcare teams had lower overall mortality than those receiving usual care (HR 0.84; 95%CI: 0.72–0.98, moderate certainty). The most influential studies achieved this by facilitating early detection of symptom worsening and prompt intervention, suggesting a causal link between symptom management and improved survival.

Implementation approaches varied across studies, with many employing electronic platforms and remote monitoring systems, reflecting current trends in digital health and telemedicine. The meta-analysis emphasizes that symptom monitoring, rather than quality-of-life surveys alone, was particularly impactful. Completing PROMs often prompted patients to reflect on their symptoms and facilitated more open communication with their care teams.

Balitsky AK, Rayner D, Britto J, et al. Patient-Reported Outcome Measures in Cancer Care: An Updated Systematic Review and Meta-Analysis. JAMA Netw Open. 2024;7(8):e2424793. doi:10.1001/jamanetworkopen.2024.24793

8.3. Patient-Reported Experience Measures (PREMs)

Patient-Reported Experience Measures (PREMs) are structured questionnaires designed to capture patients' **perspectives on their experiences** while receiving healthcare services. PREMs assess the process of care, asking patients to objectively report on various aspects of their interactions with healthcare providers and systems.

PREMs gather critical information on topics like communication with staff, feeling respected and involved in decision-making, timeliness of care, the clarity of information provided, and the physical environment of care. Two main categories exist: **functional PREMs**, which evaluate practical aspects such as facilities and organization; and **relational PREMs**, which assess the interpersonal dimension, including empathy, trust, and shared decision-making. Unlike patient satisfaction surveys, which measure subjective satisfaction based on expectations, PREMs are

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designed to elicit factual reports of care processes, often using frequency-based response options (e.g., “never” to “always”), making them more actionable for quality improvement.

The main value of PREMs is in illuminating areas where healthcare excels or falls short from the patient perspective, which can drive targeted improvements in care delivery, foster a culture of patient-centeredness, and support accountability in health systems. Regular use of PREMs helps organizations monitor trends in patient experience, benchmark performance, and ultimately enhance the overall quality of care.

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