Chapter 47 - How are the benefits of new medications documented?
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The first hint of a possible benefit of a new medication often appears in the research laboratory. If the goal is to develop a new antibiotic, scientists examine whether a new chemical compound can slow the growth of bacteria. Similarly, if the objective is to find a new medication for cancer, researchers may grow human cancer cells and determine whether the medication has the ability to slow, halt or reverse the growth of these cells. In this screening process, the hope is to identify promising chemicals worthy of further study in animals and, eventually, in humans.

What is the purpose of animal studies?
Exposing animals to a new chemical in the laboratory represents an early step in determining how safe it will be for humans. Animal studies may also provide some information about benefits to people, since some animal disease models offer insight into how new compounds may work in the treatment of humans.

What is a Phase 1 study?
Following years of laboratory and animal (preclinical) testing, during which hundreds or thousands of chemicals are evaluated and rejected, the time comes to expose the most promising compounds to human subjects. Such studies must first be reviewed by the FDA. New compounds are typically (and cautiously) tested in a small group of healthy volunteers. The treatment is given over a short period of time and the volunteers are usually observed around the clock. These studies provide information about what happens to the compound in the human body (absorption, tissue distribution, metabolism [breakdown] of the product and elimination), and they may also give early indications about safety, tolerability and whether the compound has the desired effect (for example, lowering of blood pressure or blood sugar levels).

What is a Phase 2 study?
If the results from Phase 1 studies are encouraging, the next step is Phase 2 testing. In this phase, the experimental compound is given to a small group of patients who have the condition or disease that the “drug” is intended to treat. The goal is to gather as much information as possible about beneficial effects,
adverse effects and dosing. These studies typically involve a few hundred patients. While it may sound risky to be among the first to test a brand-new compound, there are many precautions taken to ensure patient safety.

What is a Phase 3 trial?
The main objective of Phase 3 trials is to confirm on a larger scale that the experimental compound or medication provides benefits to patients, and that these benefits outweigh any adverse effects. Participants in this phase are assigned to one of two “intervention” groups to measure the favorable and unfavorable effects of the investigative medication. One group receives the new compound and the second group is given either a placebo (see Chapter 27) or an approved drug that is used in standard medical care to treat the condition or disease. With the exception of very rare diseases, Phase 3 trials typically involve thousands of patients. If the medication is intended for long-term use, government regulations require a few hundred patients be treated for at least one year. After the completion of all Phase 3 trials, the pharmaceutical company producing the medication studies analyzes the collective data on quality, efficacy and safety, and submits an application for drug approval to the FDA called a New Drug Application (NDA).

Phase 3 trials represent the most costly part of drug development for a company. Because of the huge expenses involved, it is primarily the big, well-established companies that can afford to conduct a three-phase drug trial program. Smaller pharmaceutical companies often test their investigational products through Phase 2, then try to enter into agreements with bigger companies for the more ambitious Phase 3 trial testing and the subsequent regulatory approval process and marketing.

What are the benefits and risks of trial participation?
Participation in a Phase 3 trial is often seen by study participants as an advantage, even if the new medication does not turn out to be better than current products. The advantages include cost-free, high-quality care given by a research physician/nurse team with special interest and expertise in the disease being treated. Such care continues throughout the duration of the trial and usually involves communication between the study physician and participants’ personal physicians. Other advantages include repeated medical examinations and careful evaluation of favorable and unfavorable medication effects.

There are also potential risks in participating in clinical trials. There is little definitive information on the number of injuries resulting from participation in these experimental studies, in part because there is no single government agency that oversees all of them. Another downside is that federal law does not require researchers to compensate subjects harmed in such trials.
**How relevant are the Phase 3 trials to clinical practice?**

The purpose of Phase 3 trials is to learn how well a new medication will do in regular clinical practice. The drug sponsor wants the best possible conditions during the trial, in order to increase the likelihood of obtaining beneficial effects. This typically means that patients enrolled in Phase 3 trials are carefully scrutinized and selected. They should not be too old, should not have other major medical conditions, and should not use more than a few other medications. They should also be good “compliers,” meaning that they will take the new medication exactly as prescribed by the study staff, will reliably show up for all study visits, and will submit to all study procedures and tests. Ironically, the largest segment of consumers using approved medications are elderly patients, and they are excluded from participation in many Phase 3 trials. As a consequence, it can be difficult to predict how well a new drug works in the elderly when it has been tested on younger, healthier, more independent and mobile people.

**What is a Phase 4 trial?**

Additional trials may be conducted by drug companies after regulatory approval by the FDA in order to learn more about a drug’s benefit-harm balance (see Chapter 46). For approval, it may be enough to document that a medication has a favorable effect on a surrogate (intermediate or substitute) outcome such as measurement of blood pressure reduction (rather than waiting much longer to determine how many people suffer a stroke). Pharmaceutical companies conduct Phase 4 trials, in large part, to strengthen their marketing arguments concerning the benefits of a newly approved drug (for example, to what extent does blood pressure reduction lead to fewer complications of high blood pressure, such as strokes, heart attacks and heart failure). Phase 4 trials have an important role in the evaluation of drug safety post-approval (Chapter 48). At the time of regulatory approval, it is very common to scrutinize possible safety signals. In order to get FDA approval for marketing, the sponsor typically commits to conduct a post-marketing study to determine whether the safety signal was true or not. Commitments to conduct post-marketing safety studies are very common and apply to more than half of all approved medications. For some medications, there may be several such commitments. The disappointing fact is that most industry commitments are not met. According to the latest update in the Federal Register, there were approximately 900 unmet commitments. Because there are no consequences for the pharmaceutical companies when they ignore their commitments, the number remains high. In addition, many commitments lack deadlines, which will be addressed with the new FDA Amendments Act, which requires firm deadlines and financial penalties for companies that violate their safety commitments.
Key messages

✓ Prior to regulatory approval and marketing, a new medication is rigorously tested in laboratories, animal studies, healthy volunteers and patients.
✓ Approval of a new medication must involve testing in a few thousand patients.
✓ Participants in drug evaluation trials are often carefully scrutinized and chosen.
✓ Medications expected to be used by patients for chronic treatment are often inadequately tested for long-term safety.