Adverse Events (Effects)

Adverse *Events or Adverse Effects* (AE) are harmful or undesirable consequences of a medication or treatment. In clinical trials, researchers must always report adverse *events*, even if they are not likely to be caused by the study medication or treatment, because not all adverse effects can be anticipated in advance. Useful information on possible risks can sometimes be gained by comparing the kind and number of *AE* in the control group with those in the intervention group. Serious Adverse *Events or Serious Adverse Effects* (SAE) are *events* that cause death, permanent damage, birth defects, hospitalization, or are life threatening.

Bias

Bias is an error that distorts the objectivity of a study. It can arise if a researcher doesn't adhere to rigorous standards in designing the study, selecting the subjects, administering the treatments, analysing the data, or reporting and interpreting the study results. It can also result from circumstances beyond a researcher's control, as when there is an uneven distribution of some characteristic between groups as a result of randomization.

Biomedical Research

This type of research studies normal and abnormal human function from the level of cells and molecules all the way up to the whole body. Basic biomedical researchers do their work in a laboratory using test tubes, cell samples, microscopes, chemical analysis, and other applicable tools or methods.

Blinding
Blinding is a method of controlling for bias in study by ensuring that those involved are unable to tell if they are in an intervention or control group. For example, this can be accomplished in a drug study by making the active drug and the placebo identical in appearance. In a single blind experiment, subjects are unable to tell whether they are receiving the active drug or a placebo. In a double blind experiment, neither the subjects nor the persons administering the treatments know which subjects are receiving the active drug. In a triple blind experiment, the subjects, the persons administering the treatments, and the persons evaluating the results are blinded. Triple blinding is considered to be the most objective way to conduct a study, although it is not always possible to achieve.

Citizen
Encompasses interested representatives of the general public, consumers of health services, patients, caregivers, advocates and representatives from affected community and voluntary health organizations.

Citizen Engagement
The meaningful involvement of citizens in its activities, from agenda-setting and planning to decision making, implementation and review

Clinical Research
Clinical research is health research on people, typically to evaluate the effectiveness of drugs, medical devices and practices. It may involve researchers asking questions, administering drugs, taking blood or tissue samples, or checking the progress of patients as they take a treatment according to a study's protocol. Clinical research studies often have specific criteria to define who can be recruited or enrolled in a particular study.

Clinical Trial

Clinical trials are pre-planned studies used to evaluate the safety and effectiveness of a treatment. For example, a clinical trial might compare a new drug to a placebo, or to a drug already used to treat the condition (a ~~comparator~~), if one exists. Once the safety of the new drug has been demonstrated in tests on animals, it goes through a multi-phase testing process to determine its safety and efficacy in treating human patients. If a drug shows success in one phase, the evaluation moves to the next phase, with successful completion of Phase /// being the point where the drug is considered ready to be marketed. These phases test a single drug but usually involve different researchers and different patients, and may be carried out several years apart. All clinical trials conducted in Canada must first have Health Canada approval.

- **Phase I trials** test a drug on a very small number of healthy volunteers to establish overall safety, identify side effects, and determine the dose levels that are safe and tolerable for humans.
- **Phase II trials** test a drug on a small number of people who have the condition the drug is designed to treat. These trials are done to establish what dose range is most effective, and to observe any safety concerns that might arise.
- **Phase III trials** test a drug on a large number of people who have the condition the drug is designed to treat. This phase is usually structured as randomized controlled trials, to see how much better the new product is than no treatment (placebo) or the best existing treatment (comparator). Adverse effects are noted and investigated. After successful Phase /// trials, the drug can be approved by Health Canada for release to the public.
- **Phase IV trials** can investigate uses of the drug for other conditions, on a broader patient base (e.g. elderly patients), or for longer term use. Recommended uses can be amended as a result of these studies.

Comparator

When a treatment for a specific medical condition already exists, it would be unethical to do a randomized controlled trial that would require some participants to be given an ineffective substitute. In this case, new treatments are compared to the best existing treatment, known as the 'gold standard'. The existing treatment is considered a comparator, and the trial will test the new treatment against the comparator.

Control

The goal of a clinical trial is to determine how a new treatment will affect the course of a patient's disease. To do so, researchers must design their study so that it "controls for" other factors that may influence the disease. Researchers address this problem by assembling a group of patients with similar characteristics and dividing them randomly into groups. If one group receives the treatment and another doesn't, any difference in the course of their disease can then be attributed to the treatment, since it is the only factor that is different between them. The untreated group, known as the control group, answers the question, "What would happen to the people in the intervention group if they had not received any treatment?"

Efficacy and Effectiveness

Efficacy is a measure of how effective a treatment is under ideal conditions, such as those within a clinical trial. Most clinical trials try to isolate the disease condition being treated from other factors, which means that the subjects they select will be motivated adults with no other medical conditions. Once enrolled, clinical trial participants are also monitored to ensure that they are compliant with dosages. Although these constraints are imposed to make sure that the maximum effect of the drug is achieved, typical, real-life patients are unlikely to do as well as those in a clinical trial. The term effectiveness is applied to the success of the treatment when typical patients are evaluated.

Epidemiology

Epidemiology is the study of how and why different patterns of health and disease occur among various subgroups in a population. Epidemiological methods are important in understanding infectious diseases, like influenza, but they are also widely applied to other population health issues, including sociological (e.g. How does income affect diet?) or environmental (e.g. Do people in cities develop more respiratory illnesses?) studies. Knowledge gained from epidemiological studies can help researchers design more structured studies of public health questions and help governments to improve health on a community or national level.

Ethics

CIHR-funded research that involves people must follow the ethical standards for research that are laid out in its *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (http://www.pre.ethics.gc.ca/eng/policy-politique/initiatives/tcps2-eptc2/Default/). This policy states that health research must be based on a fundamental moral commitment to protecting and advancing human welfare, knowledge, and understanding, while also examining cultural dynamics. The policy contains Guiding Ethical Principles indicating that research should respect free and informed consent, vulnerable persons, privacy and confidentiality, and justice and inclusiveness. Ethical health research should always work to maximize benefits while minimizing harm.

Evaluation

Evaluation is the careful and complete collection of information about a program or process in order to determine whether it achieved its goal. Both research and evaluation have features that center on answering a question but the purpose of evaluation is essentially to improve an existing program, while research is intended to provide support for a theory or hypothesis.

Experiment

An experiment is an orderly procedure carried out with the goal of confirming, refuting, or establishing the validity of a hypothesis. Experiments provide insight into cause-and-effect by demonstrating what result occurs when a particular factor is manipulated. Experiments always rely on repeatable procedures and logical analyses of results.

Gender

Gender refers to the socially constructed roles, behaviors, expressions and identities of girls, women, boys, men, and gender diverse people. It influences how people perceive themselves and each other, how they act and interact, and the distribution of power and resources in society. Gender is usually conceptualized as a binary (girl/woman and boy/man) yet there is considerable diversity in how individuals and groups understand, experience, and express it.

Health Systems and Health Services Research

This is a type of research that seeks to improve the efficiency and effectiveness of health professionals, such as doctors, nurses, or physiotherapists, or the health care system itself through changes to practice and policy. Health services researchers often use surveys, focus groups, randomized controlled trials, and comparisons of data from health records and other sources in their studies.

Hypothesis

A hypothesis is a proposed explanation for some event or phenomenon when the actual cause is either not known or does not adequately explain what is observed. A scientific hypothesis must explain all of the results of a study, and be testable, repeatable, and refutable (capable of being proven wrong). However, a scientific hypothesis can never be absolutely proven correct, because there is always the possibility that the real explanation is beyond our present state of knowledge.

Informed Consent

In any study involving humans, it is crucial that the participants voluntarily agree to take part in the research, and that they do so with a full understanding of their rights and the possible risks associated with participating in the study. Throughout the entire study, the researcher has an ethical obligation to share plain-language information with all participants that will enable them to give their free and informed consent.

Intervention
In a clinical trial, the intervention is the treatment being studied. The intervention group consists of the study participants that have been randomly assigned to receive the actual treatment.

Knowledge Translation
Knowledge Translation (KT) has a range of definitions, but within the Canadian Institutes of Health Research (CIHR) it is described as a process of summarizing, distributing, sharing, and applying the knowledge developed by researchers to improve the health of Canadians, and strengthen the health care system through the use of more effective health services, products, and standards of practice. CIHR is committed to sharing the knowledge generated by its researchers with whoever can take advantage of it, by making it understandable and available to all Canadians.
Integrated KT is a form of KT where researchers and knowledge users (e.g. policymakers, clinicians) work together to determine research questions, decide on methodology, collect data, develop tools, interpret findings, and disseminate research results. This approach is intended to produce research findings that are more likely to be relevant to, and used by, the end users than studies designed and conducted by researchers alone.

Observational Studies – Case Reports, Case-Control Studies, Cohort Studies, Cross-Sectional Surveys
An observational study, as distinguished from a randomized study, is usually undertaken when it is impossible, impractical, or unethical to have a control group. They are useful for generating hypotheses that can be more rigorously tested in randomized controlled trials. Their major disadvantage is that

there is no assumption that participants are representative of others with that condition. The four most common forms of observational studies are case reports, case-control studies, cohort studies, and cross-sectional surveys.

- **Case Reports** describe a unique patient, group, or event that may be of interest to others.
- **Case-Control Studies** examine a disease in an attempt to identify risk factors. Two groups are identified. Everyone in one group has a particular condition and no one in the other group has that condition (e.g., heart disease). Both groups are studied to see if more people in one group have a particular event or behaviour in their history that could be associated with either causing the disease or protecting against it (e.g., smoking, exercise).
- **Cohort Studies** examine risk factors in an attempt to identify a disease. These studies follow two or more groups of people, or cohorts, over time. The people in each group are as similar as possible, except each group has an event, condition, or behaviour in their past that the other doesn't (e.g., smoking, exercise). Cohort studies can be either prospective or retrospective. A prospective cohort study begins at a certain date and then follows the subjects over time to see how the groups in the study differ in terms of developing certain diseases. A retrospective cohort study starts in the present when it is already apparent who has the condition being measured, and traces events backward in time to see if a particular behaviour or event that occurred previously that may have caused the condition.
- **Cross-Sectional Surveys** examine a large group of people at a point in time to see what proportion has a particular condition. Researchers then attempt to correlate the condition with other information about the subjects that was collected at the same time (e.g., diet, age). A census would be an example of a cross-sectional survey.

Patient SPOR

An overarching term that includes individuals with personal experience of a health issue and informal caregivers, including family and friends.

Patient Engagement SPOR

Meaningful and active collaboration in governance, priority setting, conducting research and knowledge translation. Depending on the context, patient-oriented research may also engage people who bring the collective voice of specific, affected communities.

Patient-Oriented Research SPOR

Refers to a continuum of research that engages patients as partners, focusses on patient-identified priorities and improves patient outcomes. This research, conducted by multidisciplinary teams in partnership with relevant stakeholders, aims to apply the knowledge generated to improve healthcare systems and practices.

Placebo

In clinical trials, a placebo is usually a tablet or capsule with no active ingredients, or a sham treatment that is meant to make the patient believe that a medical procedure has occurred. Placebos are used so that the subjects in the control group (and often researchers involved in administering or evaluating the trial as well) are unable to tell who is receiving the active drug or treatment. Using placebos prevents bias in judging the effects of the medical intervention being tested.

Placebo Effect

There is always a psychological component to being enrolled in a clinical trial designed to test a treatment that might improve an existing medical condition. It's natural for a participant to hope that they are in the group receiving the active treatment and that it will improve their condition. For this reason, even patients who are receiving placebo treatment will often report an improvement, particularly in short term trials, even if it is impossible that the effects are caused by the placebo.

Power

The power *of a statistical test* is *a* measure of a study's ability to detect a *statistically significant difference* between the *results of the* intervention group and the control group *in a randomized controlled trial*. A *difference* is considered statistically significant when it is highly unlikely to have occurred by chance. A study's power is *partly* determined by the size of the difference in scores between the groups, but it is also affected by how many people are included in the study and how much variation

there is within each of the groups. For example, if there are too few people in the study, even a large difference may not produce a statistically significant result.

Prevention - Primary, Secondary and Tertiary

- **Primary Prevention** means preventing a disease before it occurs. An example would be a healthy person with a family history of heart disease taking a blood pressure reducing medication to prevent a heart problem in the future.
- **Secondary Prevention** means preventing a worsening or future occurrence of a disease after evidence of the disease has already been found. An example would be a doctor removing a suspicious growth before it becomes cancerous and spreads.
- **Tertiary Prevention** means treatment for an ongoing disease. This type of prevention could include reducing the effect of symptoms, slowing the progress of the disease, or taking steps to cure the disease.

Prognosis

A medical prognosis is a prediction of the course of a disease and likelihood of recovery, disability, or death, based on medical expertise. It includes factors such as the patient's medical history, the course of treatment being followed, and the statistical likelihood of the outcome of the disease in other people..

Qualitative Analysis

The purpose of a qualitative analysis is to get a range of responses on an issue from a variety of perspectives, valuing unique responses as much as consistent ones. Qualitative analysis methods can include focus groups, individual observations, in-depth interviews, or documentary accounts. Qualitative assessments can often be used as a means of generating research questions and identifying themes that can later be used in a quantitative analysis. Qualitative analyses are subjective, meaning that they depend on the particular people included, and can be shaped by interactions with the researcher or other participants.

Quantitative Analysis

Quantitative analysis attempts to understand the world objectively, rather than as different individuals might perceive it. It relies on compiling numerical data from many individuals into a single value, such as an average, or mean, that can be assessed by statistical tests. The goal of quantitative analysis is to be unbiased, which is why control groups and blinding are important considerations in constructing quantitative research studies. Statistical analyses applied to quantitative data define exactly how likely a result is to have occurred by chance alone, which helps the user understand how representative the results are of the population as a whole.

Randomization

Most randomization in health research has to do with the selection of intervention and control groups for clinical trials. The process begins with a group of people who have been carefully selected to meet all of the criteria defined for the trial. These usually include people who have a disease at the same stage, along with other similar factors such as age or weight, and none of the study's exclusion factors, such as multiple diseases or pregnancy. Even within this group, no two people are identical so randomly dividing them into two (or more) subgroups ensures that the same characteristics of the larger group are likely to be represented in the subgroups. Most randomization is done by using computer-generated lists of random numbers based on the number of groups to be studied (e.g., 1s and 2s for two groups) and giving each person enrolled the next number on the list. This will usually result in nearly even numbers of people in each group.

Randomized Controlled Trial

A randomized controlled trial (RCT) is considered the most unbiased way of assessing the outcome of an intervention. In the simplest case, a relevant population is identified (e.g. patients with the disease the drug is designed to treat). The population is divided by some impartial method of assignment (ideally, random numbers generated by a computer program) into intervention and control groups. These assignments are kept secret from the patients, and in the best case, from the investigators and the evaluators as well. Patients receive their assigned course of treatment (either the active treatment or

the placebo) over a pre-specified period of time and are monitored to ensure that dosage schedules are followed and that any adverse effects are recorded. At designated times, outcome data is collected. When the trial ends, all data are analyzed to determine if a statistically significant difference exists between the groups. If so, it can be concluded that the difference is due to the intervention.

Risk Reduction

Risk reduction is a measure of how successful an intervention is, when compared to patients not receiving the intervention, in reducing the risk of a negative health outcome such as death, stroke, or bleeding. There are two measures of risk reduction – absolute and relative. Absolute risk reduction is the most important statistic because it answers the question, "Out of X number of people, ***how many*** more are saved by this treatment compared to no treatment?" However, particularly when an advertiser wants to convince people that their treatment offers a substantial benefit, they will cite the relative risk reduction, which answers the question "Out of X number of people, ***what percentage*** more are saved by this treatment compared to having no treatment?" Citing relative risk reduction is misleading because it can make the differences seem larger, but it tells you nothing about actual risk. *However if the relative risk is used, it is possible to claim that the risk of a stroke had been reduced by 50% in the treated group which is true, but misleading.*

Screening

Screening is a method of secondary prevention. Screening programs check large numbers of individuals who are otherwise healthy for known symptoms before a disease is established. Screening is presently offered through programs such as mammography for breast cancer or skin examinations for melanoma.

Social, Cultural, Environmental, and Population Health Research

This research works to enhance the health of Canadian populations (or subpopulations, such as those from a particular region or ethnic group) by understanding how social, cultural, environmental, work-

related, and economic factors affect people's health. It also involves the evaluation of certain health interventions such as the effect of tobacco control programs on populations.

Statistical Significance and Probability

Statistical significance is about the likelihood of findings being due to chance. Probability, or p-value, is a statistical calculation that is used to determine how likely a result could have occurred just by chance. Any statistical analysis begins with the assumption that there is no difference between the two groups being compared (e.g., the intervention and control groups in a clinical trial). This assumption is known as the null hypothesis. Researchers select a p-value in advance of conducting the study to represent how much of a difference they would expect between the intervention and control group results in order to be confident that the results represent a true, or statistically significant, difference. Although it is possible to set this value at any level, for most analyses the p-value is set at 0.05, or 5%. This means that such a result could have occurred by chance only 5 times out of 100. Probability and confidence are influenced by a number of factors including the size and consistency of a sample. A study with a large sample size and highly consistent results is much more likely to produce statistically significant results with 95% confidence than a study with a small sample size and variable results. A statistically significant result technically applies only to the sample measured, and may not generalize to other populations.

Subjects

In clinical trials, the people selected to take part are called subjects. The term applies to both those participants receiving the treatment being investigated and to those receiving a placebo or alternate treatment.

Surrogate Endpoints (Surrogate Marker)

A surrogate endpoint or marker is some change that is easy to measure and is expected to correlate with a more meaningful endpoint, although the actual relationship between the marker and event may not be known. As an example, a cholesterol lowering medication is expected to reduce cardiac deaths among patients with high cholesterol. However, it would take many years of costly follow-up to actually measure whether the medication reduced deaths in a clinical study, and the sample size would have to be unrealistically large before enough deaths occurred to give reliable differences between treated and untreated subjects. Instead, because cholesterol is known to be correlated with cardiac deaths, lower cholesterol levels in the intervention group is taken as a surrogate for fewer deaths from cardiac

disease. When surrogate markers are used as predictors, it is important to remember that all the experiment is actually confirming is that cholesterol lowering drugs lower cholesterol, so the relationship between lowering cholesterol and preventing actual deaths cardiac deaths may not have been established by the study.

Survey

Surveys can be either quantitative or qualitative. A quantitative survey provides a series of questions where the answers can be recorded as numerical answers on a scale. Results are combined for each question, and percentages of responses can be calculated. A qualitative survey can involve personal interviews, participation in a focus group, or answers written on a questionnaire. These may be analyzed by identifying themes and consistencies, but individual perspectives make important contributions as well.

Systematic Review and Meta-analysis

A systematic review consists of a methodical search for all published literature on a single topic that meet specific selection criteria. By compiling results from every study investigating the same question, it is possible to extract a much more reliable and accurate picture of the significant findings and to get a sense of their consistency. Meta-analysis is a way of statistically analyzing the results of a systematic review. In a meta-analysis, the subject populations of all similar studies are combined, giving much more statistical power to the result than any individual study would have on its own. It can also show the degree of similarity (homogeneity) or difference (heterogeneity) in the studies included. If the studies being combined are very different, the overall result is less trustworthy, but an examination of the data might show what particular feature of a subset of the data makes it different.

Valley 1 (T1) and Valley 2 (T2) SPOR

These terms metaphorically represent two gaps that have been identified in Canadian medical research. If we picture the continuum of research as extending from laboratory discoveries (Basic Biomedical Research) through the development of drugs and treatments for patients (Clinical Research) and from

there to improvements in medical systems, staffing, and decision making (Health Services and Health Systems Research), we see that there are places along the continuum between these three "peaks" where the capacity of the healthcare system to make use of research discoveries is much weaker. These have been identified as "Valleys" or gaps between these divisions and CIHR recognizes that they are also need attention. Valley 1 (T1) refers to the gap between laboratory (Basic Biomedical) research and the application of laboratory research to patients (Clinical Research), as well as the commercial development of these discoveries for international use. Valley 2 (T2) refers to the gap between the application of research discoveries to patients (Clinical Research) and its broader application by clinical practitioners and healthcare decision makers (Health Services and Health Systems Research).

Variable – Independent and Dependent

Any factor in an experiment that can be changed is considered a variable. There are three kinds of variables in an experiment:

- **An independent variable** is a factor in the experiment that is manipulated by the experimenter. An example could be three dose levels of the same drug.
- **A dependent variable** is something over which the experimenter has no control, but that is expected to change in a systematic way, depending on the independent variable, for example a decrease in coughing at higher dose levels of the drug. The change in the dependent variable is what gets recorded as data in a research study.
- **A controlled variable** is something that does not change, for example, the number of times per day that each subject is expected to take the trial medication.

By manipulating only one independent variable at a time, the resulting difference between groups can be reliably attributed to that variable.