Understanding Clinical Trials
Introduction and Objectives

Introduction

• This module provides learners with an educational resource that focuses on understanding both why and how clinical trials are conducted as well as the importance of clinical trial results

Objectives

• Understand basic concepts of the drug approval process
• Describe the types and variations of clinical trials
• Review outcome measures in multiple sclerosis (MS) clinical trials
• Understand statistical measures
• Understand challenges involved in designing and conducting MS clinical trials
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Summary
Chapter 1

Regulatory Pathway
Drug Approval Process

Preclinical¹
- Drug discovery
- Preclinical testing
- Submit an investigational new drug application (IND) to FDA

Clinical Review¹,²
- Phase I studies
- Phase II studies
- Phase III studies

NDA¹-³
- Submit new drug application (NDA) to FDA
- Initial NDA review (FDA decides whether to accept NDA for review)
- Application reviewed
- Receives approval or a complete response letter

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Therapeutic Biologic Application

Therapeutic biologic application (also known as biologic license application [BLA])

- Required by the FDA for therapeutic biologic products
- Approval processes for BLAs and NDAs are essentially the same
- Reviewed by the FDA’s Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER)

<table>
<thead>
<tr>
<th>Traditional Drug Treatments</th>
<th>Biologic Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemically synthesized</td>
<td>Derived from living material</td>
</tr>
<tr>
<td>Smaller, well-defined structure</td>
<td>Complex structure</td>
</tr>
<tr>
<td>NDA</td>
<td>BLA</td>
</tr>
</tbody>
</table>

Categories for therapeutic biologics¹

- Monoclonal antibodies for in vivo use
- Cytokines, growth factors, enzymes, immunomodulators, and thrombolytics
- Proteins intended for therapeutic use that are extracted from animals or microorganisms, including recombinant versions of these products (except clotting factors)
- Other non-vaccine therapeutic immunotherapies

MS disease-modifying products considered by FDA to be biologics²

- Avonex® (interferon beta-1a)
- Betaseron® (interferon beta-1b)
- Copaxone® (glatiramer acetate)
- Extavia® (interferon beta-1b)
- Glatopa® (glatiramer acetate)
- Lemtrada® (alemtuzumab)
- Plegridy® (peginterferon beta-1a)
- Rebif® (interferon beta-1a)
- Tysabri® (natalizumab)
- Zinbryta® (daclizumab)

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Drug approval process

- Similar to drug approval process in the United States
  - Begins with a clinical trial process followed by approval to market and sell the drug
- Two drug approval procedures
  1. Centralized\(^1\)
     - Commission approval of a new drug allows a pharmaceutical company to market its drug in all Member States without having to obtain separate approval in each Member State
  2. Decentralized\(^1,2\)
     - If a product does not meet the requirements for consideration under the centralized process, the application may be submitted under the decentralized process
     - Allows for simultaneous consideration by Member States that have not yet approved the product
The centralized process is mandatory for all:

- Human medicines for the treatment of HIV/AIDS, cancer, diabetes, neurodegenerative diseases, autoimmune and other immune dysfunctions, and viral diseases
- Veterinary medicines for use as growth or yield enhancers
- Medicines derived from biotechnology processes, such as genetic engineering
- Advanced-therapy medicines, such as gene therapy, somatic cell-therapy, or tissue-engineered medicines
- Officially designated “orphan medicines” (medicines used for rare human diseases)

HIV, human immunodeficiency virus.

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Chapter 2

Types of Clinical Trials
Clinical Trials

Clinical trials\textsuperscript{1,2}

- “Investigational” trials or experiments conducted in humans during which researchers will test the effects of a treatment or prevention strategy on pre-specified outcomes
- Determines a treatment’s safety and/or efficacy based on pre-specified outcomes
- Categorized as:

  \begin{itemize}
  \item \textbf{Interventional}\textsuperscript{2}
  \begin{itemize}
  \item Participants take a drug or undergo therapy
  \item Investigators record results and events that occur
  \end{itemize}
  \item \textbf{Retrospective}\textsuperscript{3}
  \begin{itemize}
  \item Investigators look at medical records to determine what happened to 2 or more groups in the past
  \end{itemize}
  \item \textbf{Observational}\textsuperscript{2}
  \begin{itemize}
  \item Investigators assess health outcomes and record these observations in the absence of investigator-induced intervention
  \end{itemize}
  \item \textbf{Prospective}\textsuperscript{3}
  \begin{itemize}
  \item Investigators follow patients into the future for various periods
  \end{itemize}
\end{itemize}

## Types of Clinical Trials

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment trials</td>
<td>Test experimental treatments, new combinations of drugs, new devices, or new approaches to surgery or radiation therapy</td>
</tr>
<tr>
<td>Prevention trials</td>
<td>Seek better ways to prevent disease in people who have never had the disease or to prevent a disease from reoccurring</td>
</tr>
<tr>
<td>Diagnostic trials</td>
<td>Conducted to find better tests or procedures for diagnosing a particular disease or condition</td>
</tr>
<tr>
<td>Screening trials</td>
<td>Test the best ways to detect certain diseases or health conditions</td>
</tr>
<tr>
<td>Quality of life trials</td>
<td>Explore ways to improve comfort and quality of life for individuals with a chronic illness</td>
</tr>
<tr>
<td>Genetic studies</td>
<td>Improve prediction of disorders by identifying and understanding the relationship between genes and illnesses</td>
</tr>
<tr>
<td>Epidemiology studies</td>
<td>Identify patterns, causes, and control of disorders in groups of people</td>
</tr>
</tbody>
</table>

US Food and Drug Administration. [https://www.fda.gov/ForPatients/ClinicalTrials/Types/default.htm](https://www.fda.gov/ForPatients/ClinicalTrials/Types/default.htm). Accessed [March 15, 2017].
Benefits and Challenges of Clinical Trials

Benefits
• Provide the strongest evidence supporting cause-effect relationships
• Form the basis for clinical practice and public health policy
• Minimize or eliminate bias and confounding factors

Challenges
• Expensive and time-consuming
• Ethical concerns
• Difficult to recruit patients into study
• Logistically complex
• Many research questions cannot be answered due to study design restrictions

Placebo-Controlled and Superiority Trials

Placebo$^{1,2}$
- Substance with no known treatment value that is given to a study participant
- Made to appear, smell, and/or taste similar to the actual treatment

Placebo-controlled trial
- Determines whether a drug of interest is better than a placebo$^3$
- Blinding so that study participants and investigators do not know who is receiving the active treatment and who is receiving the placebo$^2$

Superiority trial$^3$
- Tests whether a new treatment is superior to the existing treatment, which may be the current standard of care
- May include placebo-controlled efficacy trials, because the new treatment is being tested for superiority to placebo

Non-inferiority Trials

Non-inferiority trial\(^1,2\)

- Shows that an experimental treatment is *not worse* than an active control by more than the equivalence margin
- If non-inferiority is established, a treatment may be preferred based on other considerations such as easier to use, fewer side effects, less costs, etc\(^2,3\)

Dose Comparison or Dose-Ranging Trial

Method

• Used to determine a reasonable initial dose
• The initial dose is the lowest dose tested that has a response that is statistically greater than the response after a placebo test
• Placebo periods may follow the active drug period in trials designed with more than one active drug period

**Combination Trial**

**Method**

- Tests the effects of using 2 or more drugs in combination to determine whether the drugs may work together and be more effective, or more toxic, than using either drug as monotherapy

**Three variations of a combination trial**

1. **Combination therapy**
   - When 2 or more drugs (or a drug plus a immunomodulator or antibody) are administered together to a patient who had not received any part of the combination previously

2. **Add-on therapy**
   - When 1 drug is administered for some period and then a second drug is added to the regimen

3. **Sequential therapy**
   - When the first drug that is administered is discontinued before initiation of therapy with a second agent

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Cross-sectional or Prevalence Study

**Method**¹

- Simultaneously measure exposure and disease status in a given population
- Cannot be used to determine the following
  - Whether the exposure preceded or followed the disease
  - Cause-and-effect relationship

**Advantages**²

- Results can be highly generalizable, if the sample is representative of the population of interest
- Inexpensive
- Can be completed quickly

**Disadvantages**¹

- Can only identify patterns or trends in disease occurrence, but cannot differentiate between an association and a causal effect

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Case-Control or Retrospective Study

Method

• Observational study that does not involve an intervention or an attempt to alter the disease course
• Compares patients who have a disease or outcome of interest (cases) with patients who do not have the disease or outcome (controls)
• Retrospective analysis to compare how frequently a specific exposure to a risk factor is present in each group

Advantages

• Good for studying rare conditions or diseases
• Less time is needed to conduct the study
• Allows researchers to simultaneously look at multiple risk factors
• Useful as initial study to establish an association

Disadvantages

• Difficult to find a suitable control group
• Greater chance of bias than experimental studies
• Difficult to establish temporal relationship between exposure and disease

Diagram of a Case-Control Study

Study individuals

Selected cases

Exposed

Not exposed

Selected controls

Exposed

Not exposed

Cohort, Prospective, or Longitudinal Study

Method

- Follows prospectively over time one or more populations (or cohorts)
- Determines which patient characteristics or risk factors are associated with the development of a disease or outcome

Advantages

- Easier and less expensive than a randomized controlled trial
- Best way to ascertain both the incidence and natural history of a disorder
- Time sequence between putative cause and outcome is usually clear
- Other outcomes, besides the pre-determined outcomes, are discovered
- May be useful in the study of rare exposures

Disadvantages

- Cohorts can be difficult to identify due to confounding variables
- No randomization, which means an imbalance in patient characteristics could exist
- Blinding or masking is difficult
- Outcome of interest could take time to occur

Diagram of a Prospective Cohort Study

Method

- Hybrids of retrospective and prospective analyses
- Participants are often selected from ongoing cohort studies
- Compares the course of individuals who develop the disease (case) with those who do not develop the disease but are at risk of developing the disease (control)

Diagram of a Nested Case-Control Study

**Method**
- Uses statistical methods to combine results of individual studies that are focused on related research

**Advantages**
- Makes it possible to see the results of several studies at one time
- Can see treatment effects in a more diverse population with a larger number of people
- Higher statistical power than individual studies

**Disadvantages or weaknesses**
- Difficulty in selecting which studies are included or excluded in a meta-analysis
- Not all studies may have subject characteristics and data suitable for inclusion and analysis
- Requires advanced statistical techniques

Chapter 3

Trial Design and Terminology
Goals of well-designed clinical trials

- Differences observed between different intervention groups may be attributed to the treatment under investigation\(^1\)
- Generalizable results\(^1\)
  - Results are applicable to real people outside of the study
- Fair to the participants\(^2\)
- Ethical to the participants\(^2\)

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Why are participants randomized?
• To avoid bias on the part of investigators\(^1\)
  o Bias consists of any effect or interference that can affect a clinical trial’s results\(^2\)
• To facilitate blinding of study investigators and participants\(^1\)

Goals of randomization\(^1,3\)
• To produce comparable groups in terms of general participant characteristics
  o Characteristics may include age, gender, duration of disease, and disability status
• To conclude that study results are valid and cannot be attributed to assignment arm bias

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**Randomization**

Randomization occurs when trial participants are randomly assigned to a particular treatment arm of a trial, rather than someone deciding which arm they should be in\(^1\)

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Blinding

Blinding means that investigators and/or participants do not know which treatment arm a participant is in\(^1\)

Blinding prevents\(^1\)

- Response bias from patients
  - The tendency for patients to report symptoms differently, based on the treatment they are getting

- Behavior changes in patients that will affect the trial
  - Attrition
  - Secretly adding in medication or other therapies if the patient thinks they are receiving placebo

- Bias on behalf of the people collecting and reporting the data

How is blinding done?\(^1,2\)

- By randomization
- By making all the interventions received by each arm look identical and be dosed identically

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Types of Blinding

Single-blinded\textsuperscript{1,2}
- Either the investigator or the participant is unaware of which medication the participant is taking or which intervention they have been exposed to.

Double-blinded\textsuperscript{1,3}
- Neither the investigator nor the participant knows which drugs are being taken.
- Participants are randomized to one of two or more study groups.
- All medications and procedures that are given are designed to look identical.

Double-dummy\textsuperscript{4}
- Each group of participants receives one of the active interventions and a placebo (or dummy) that looks and tastes the same as the other intervention.
- Used to compare interventions that are administered by different routes or on different schedules.

Double-blind trials are considered the most objective type of study and are known as the “gold standard” of drug trials\textsuperscript{5}

Crossover Study

Method\(^1,2\)

- Allows each patient to act as their own control
- Ensures that patients in different arms of a study are similar enough to compare results
- May be used to compare the effects of two drugs to one another
- Most appropriate for short-term studies

Two main issues regarding crossover trials\(^1,2\)

1. Order effects
   - When the order in which the treatments are given impact the outcome

2. Carryover effects
   - When beneficial effects and/or negative side effects carry over from the first treatment
   - May be minimized by adequate washout periods

Diagram of a Crossover Study

Patients participate in each arm of the study, usually in random order

Visit 1

Drug A

Drug B

Eligibility

Informed consent

R

Washout

Washout

Single dose

Single dose

Inclusion/exclusion criteria\(^1\)

- Characteristics of a person or illness that researchers use to determine who is eligible to participate

Baseline data\(^1\)

- Patient information collected before randomization

Adverse effects\(^2\)

- Any negative changes in health or side effects that occur in a person who participates in a clinical trial while the patient is receiving a study drug (active drug or placebo) or within a certain (specified) amount of time after the trial ends

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Chapter 4

Outcome Measures in MS Trials
Annualized Relapse Rate

Total number of relapses experienced by the group (the treatment or placebo arm) divided by the person/years at risk\textsuperscript{1}

The most common summary measure of relapses\textsuperscript{2}

Disadvantages

• Difficult to compare across studies, as different researchers adopt different methods and definitions to confirm relapses\textsuperscript{1}

EDSS\(^1\)
- Rating system that is used frequently for classifying and standardizing the physical condition of people with MS in clinical trials
- It is possible to move back and forth on the scale\(^2\)
- A composite scale based on multiple outcome measures, not on an individual measure\(^1\)

Calculating the EDSS score\(^3\)
- Based on neurological testing and examination of 8 functional systems

Advantages\(^3\)
- Familiar system for researchers
- Researchers and physicians understand the significance of changes in EDSS

Disadvantages\(^1\)
- Places emphasis on the ability to walk, when other symptoms could be impacting a person’s ability to function
- Insensitive to cognitive dysfunction
- Moderate inter-rater reliability
- Not a linear scale

A multidimensional clinical outcome measure consisting of 3 components

1. **Timed 25-foot walk**
   - Measure of leg function and ambulation

2. **9-hole peg test**
   - Measure of upper extremity (arm and hand) function

3. **Paced auditory serial addition test (PASAT)**
   - Measure of cognitive function that specifically assesses auditory information-processing speed and flexibility

**Advantages**
- Dimensions change relatively independently over time
- Measures are quantitative and standardized
- Easy to administer by a non-medical person
- Inter-rater and test-retest reliability are good

**Disadvantages**
- Many researchers are unfamiliar with the MSFC
- Clinical meaning of a 1-point change on the scale is not as clear as a change on the EDSS
- "Practice effect" can influence test results—scores tend to improve naturally after individuals take the tests on separate occasions

Results of MRI scans¹

- Provide a measure of disease activity in relapsing-remitting MS
- Show lesions indicative of breakdown of the blood-brain barrier and total lesion burden
- MRI measures have been used from pilot studies to phase III studies

Advantages²

- More sensitive in identifying disease activity than measures of relapse
- Easily blinded
- Objective and less prone to reporting bias on the part of the patient or bias on the part of the researchers
- Reliability and reproducibility are generally very good

Disadvantages¹

- Disease activity as seen on MRI scans does not correlate exactly with clinical signs or with disability

References:

Quality of Life Measures

Quality of life scales

• Are included in and required by the FDA for some trials

Health status questionnaire Short Form-36 (SF-36)

• Generic QOL scale covering 8 areas of health
• Used to compare QOL across different diseases

QOL scales for MS

• Multiple Sclerosis Quality of Life-54 (MSQOL-54)
  o 54-item scale that incorporates elements of the SF-36
• Multiple Sclerosis Quality of Life Inventory (MSQLI)
  o Covers some areas in more detail than the MSQOL-54
  o Includes subscales that study particular aspects of MS

Chapter 5

Statistical Measures Utilized in MS Clinical Trials
Statistical Significance and Statistical Power

**Statistical significance**

- The percent likelihood that a result obtained happened by chance alone
- Expressed as a probability value \((P\text{ value})\)
- Determined by the magnitude of the result and the sample size
- Does not necessarily suggest clinical significance
- A common cutoff for \(P\) values is 0.05
  - When there are multiple endpoints, this \(P\) value may be divided among endpoints
  - However, in some situations, endpoints are deemed “exploratory” and cannot be used to assess statistical significance

**Statistical power**

- Probability of a statistically significant result
- Increasing the probability of a statistically significant result is accomplished by increasing the sample size

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Relative Risk or Risk Ratio

**Example**

A cohort study reported that 280/1000 people who chewed gum every day for at least 10 years developed chronic jaw pain, and 48/1000 people who didn't chew gum developed chronic jaw pain.

\[
RR = \frac{\text{Incidence of chronic jaw pain in daily gum chewers}}{\text{Incidence of chronic jaw pain in non-gum chewers}} = \frac{280}{48} = 5.83
\]

This would translate to findings of "people who chew gum every day for at least 10 years are 5.83 times more likely to develop chronic jaw pain than those who do not chew gum."

**Relative Risk**

\[ \text{Relative Risk} = \frac{\text{incidence of disease in exposed population}}{\text{incidence of disease in non-exposed population}} \]

<table>
<thead>
<tr>
<th>Relative Risk</th>
<th>Meaning</th>
<th>Incidence of chronic jaw pain in daily gum chewers</th>
<th>Incidence of chronic jaw pain in non-gum chewers</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>There is no difference in risk between the 2 groups</td>
<td>280</td>
<td>48</td>
</tr>
<tr>
<td>&lt;1</td>
<td>The event is less likely to occur in the experimental group than in the control group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;1</td>
<td>The event is more likely to occur in the experimental group than in the control group</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Determine if using a computer keyboard for more than 6 hours per day contributes to hand pain. A case-control study compared 100 people with hand pain to 100 people without hand pain. We find out that 60 of the people with hand pain use a computer keyboard for more than 6 hours per day, while 20 people with hand pain use a computer keyboard for less than 6 hours per day. Here is the OR calculation:

\[
\text{OR} = \frac{60\%}{40\%} = 1.5
\]

Survival analysis

- Statistical method in which individuals are followed until the occurrence of a predetermined event
- Described in 2 different methods
  1. Life tables
     - Used when researchers do not know the exact survival time of each individual study participant but do know the total number of study participants who have survived at a succession of time points
  2. Kaplan-Meier estimate of survival curve
     - Curve is based on the exact time in the study that each individual study participant reaches the survival end point
- Primarily used to compare the survival patterns of different groups

Hazard ratio

- Measure of how often a particular event happens in one group compared with how often it happens in another group, over time
- HR = 1 means there is no difference in survival between 2 groups
- HR >1 or HR <1 means that survival was better in one of the groups

95% Confidence interval

- Range of numbers that represents the upper and lower 95% confidence limits for reported data

Intention to Treat

Method\(^1,2\)

- Preferred for the analysis of clinical trials
- Individuals are analyzed according to randomized assignment, independent of whether they remain on assigned therapy
- Provides an unbiased assessment of the efficacy of the intervention at the level of adherence that occurred in the trial

Figure is an example of modified intention to treat\(^3\)

- “Modified” because the study only included patients who received at least 1 dose of study drug

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### Mean Compared With Median

#### Mean\(^1,^2\)
- Mathematical *average* of a group of numbers
- Typically used for normal distributions

#### Median\(^1,^2\)
- The middle number of a data set when the set is *sorted in numerical order*
- Used for skewed distributions

<table>
<thead>
<tr>
<th>Mean example (set of 11 numbers)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[2 + 3 + 3 + 4 + 7 + 9 + 11 + 12 + 14 + 17 + 18 = 100/11 = 9.1]</td>
</tr>
<tr>
<td>Adding the numbers up, you get a total of 100. Divide this by 11 and you get a mean of 9.1 (median = 9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean outlier example (set of 11 numbers)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[2 + 3 + 3 + 4 + 7 + 9 + 11 + 12 + 14 + 17 + 86 = 168/11 = 15.3]</td>
</tr>
<tr>
<td>Adding the numbers up, you get a total of 168. Divide this by 11 and you get a mean of 15.3 (median = 9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median example (odd-numbered data set)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[2\ 3\ 3\ 4\ 7\ 9\ 11\ 12\ 14\ 17\ 18]</td>
</tr>
<tr>
<td>To find the median, choose the middle number (the 6th one in the list with 5 numbers on each side) and you get a median of 9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median example (even-numbered data set)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[2\ 3\ 3\ 4\ 7\ 9\ 11\ 12\ 14\ 17\ 18]</td>
</tr>
<tr>
<td>To find the median, choose the middle 2 numbers (the 6th and 7th ones in the list with 5 numbers on each side), add them and divide by 2, and you get a median of 10 ((9 + 11 = 20 \div 2 = 10))</td>
</tr>
</tbody>
</table>

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Standard Deviation

**Standard deviation**\(^1,2\)

- Shows how much variance is in the data or how different the points are from the mean
- For a normal distribution, nearly all values lie within 3 standard deviations of the mean

**Figure of a normal curve and standard deviations**\(^1-3\)

- Dark blue is +/- 1 standard deviation from the mean, which is approximately 68% of the set for a normal distribution
- Medium and dark blue are +/- 2 standard deviations from the mean, which is approximately 95% of the set for a normal distribution
- Light, medium, and dark blue are +/- 3 standard deviations from the mean, which is approximately 99% of the set for a normal distribution

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Chapter 6

Factors Affecting the Validity and Relevance of MS Clinical Trial Results
## Factors Affecting Validity and Relevance of MS Trial Results

<table>
<thead>
<tr>
<th>Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short duration of trials</strong>¹</td>
<td>• 1 to 2 years’ duration for disease-modifying agents</td>
</tr>
<tr>
<td></td>
<td>• Makes it challenging to detect effectiveness in prevention of long-term disability</td>
</tr>
<tr>
<td><strong>Duration of MS</strong>²</td>
<td>• Frequency of relapse tends to diminish the longer a person has had the diagnosis of MS</td>
</tr>
<tr>
<td></td>
<td>o Leads to difficulty interpreting ARR or other measures of relapse</td>
</tr>
<tr>
<td><strong>Randomization</strong>³</td>
<td>• Treatment arms <em>not</em> comparable in baseline characteristics may affect study results</td>
</tr>
<tr>
<td><strong>Seasonality</strong>⁴</td>
<td>• May impact MS symptoms, relapses, and the appearance of new lesions found in serial T2-weighted MRI</td>
</tr>
<tr>
<td><strong>Attrition and lack of adherence</strong>⁵,⁶</td>
<td>• May affect statistical power</td>
</tr>
</tbody>
</table>

Natural history classifications

- 5 classifications of disease course
  1. Clinically isolated syndrome (CIS)
  2. Relapsing-remitting MS (RRMS)
  3. Relapsing-progressive MS (RPMS)
  4. Secondary progressive MS (SPMS)
  5. Primary progressive MS (PPMS)

  - Reliance on only these 5 classifications for clinical trials limits the generalizability of the results across the entire MS spectrum and restricts FDA approval for other subtypes of MS

Placebo-controlled trials

- It is difficult to recruit and retain patients to take placebo because many approved therapies are available

- Ethical concerns

Common Categories of Bias

Selection bias
• Occurs when the groups to be compared are intended to be similar but are actually different
  o Volunteer or referral bias
  o Nonrespondent bias
    o Occurs when those who do not respond to a survey differ in important ways from those who respond or participate
    o This bias can work in either direction

Measurement bias
• Can occur when systematic error is introduced when data are collected
  o Instrument bias
  o Insensitive measure bias
  o Expectation bias
  o Recall or memory bias
  o Attention bias
  o Verification or workup bias

Intervention (exposure) bias
• Is generally associated with research that compares groups
  o Contamination bias
  o Co-intervention bias
  o Timing bias
  o Compliance bias
  o Withdrawal bias
  o Proficiency bias
    o When interventions or treatments are not equally applied to the subjects

Relapse reporting by patients
- Difficulty distinguishing a true relapse from a pseudoexacerbation
  - Relapses are over-reported
- Ignores worsening or new symptoms
  - Relapses are underreported

Non-standardized definition and counting of relapse
- Studies vary on the definition of relapse
- Interpretation of symptoms differ by examiner

EDSS limitations
- EDSS may not capture accruing disability in functional areas besides ambulatory disability
- Significant amount of inter-observer variation at the lower end of the scale

MRI measures and clinical correlation
- MRI measures cannot predict clinically relevant relapse(s) or long-term disability outcomes

Drug approval in the United States follows either an NDA process or a BLA process. Many pharmaceutical products used in MS require a BLA.

Clinical trials determine a treatment's safety and/or efficacy on pre-specified outcomes. Trials can be categorized as experimental or observational and prospective or retrospective. Well-designed clinical trials are planned to achieve valid results and eliminate bias. Trials are also designed to be fair and ethical to the participants.

There is no single ideal measure for MS outcomes. ARR is a common summary measure of relapses. EDSS remains the gold standard in clinical trials for measuring physical impairment from MS.

Statistical significance is the percent likelihood that the result occurred by chance. Statistical significance does not necessarily mean clinical significance.

In MS trials, evaluating efficacy can be challenging due to the nature of the disease. Clinical trial design ensures that results obtained are real and not due to unseen influences or problems in the research protocol.
