Discuss the information that should be reported in the results section of an article about a clinical trial regarding subjects

Define ITT and PP analysis and list advantages and disadvantages of each

Review primary versus secondary endpoints and surrogate versus clinical endpoints

State the points that should be evaluated regarding endpoints and safety when evaluating a clinical trial

Define subgroup analysis and state the pre-requisites for subgroup analysis

Define ancillary versus adjunctive therapies

List the information that should be included in the discussion and conclusion sections of a clinical trial article

State what information is usually included in the acknowledgements sections of a clinical trial write up

List traits to look for when evaluating the bibliography/reference list associated with an article about a clinical trial

State the usual sources of funding for research studies and discuss bias related to funding source

Describes the average subject enrolled (usually in table format)

Average age, male to female ratio, disease states, other drug therapies (other than intervention being done or control) at time of enrollment, number who smoke, etc...

Look for groups to be as similar as possible (proper randomization helps make this possible)

Significant dissimilarities that could have an impact on the outcome(s) being measured should be scrutinized
Table 1: Summary of baseline demographic and clinical characteristics among hospitalized patients who received inhaled ipratropium (ITT) or inhaled ipratropium with or without anticholinergic (ITT + DPI) for treatment of community-acquired pneumonia.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ITT</th>
<th>ITT + DPI</th>
<th>ITT</th>
<th>ITT + DPI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Validated per-protocol population</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Characteristics</td>
<td>N</td>
<td>CTM ± SD</td>
<td>N</td>
<td>CTM ± SD</td>
</tr>
<tr>
<td>Main sex</td>
<td>102</td>
<td>81.6 ± 0.5</td>
<td>102</td>
<td>81.6 ± 0.5</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>48</td>
<td>48.2 ± 3.2</td>
<td>48</td>
<td>48.2 ± 3.2</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>70</td>
<td>70.6 ± 3.8</td>
<td>70</td>
<td>70.6 ± 3.8</td>
</tr>
<tr>
<td>Comorbidity score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ITT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Results from all randomized subjects included in analysis

Most real world applicability

Beware bias this can cause (example: treatment being studied for a disease known to progress like dementia)

Table 1 (15 December) • Vito et al.

Subject Demographics

- After baseline demographic info presented, you will have data regarding follow up presented
- Subject dropout and Compliance should be discussed
  - Reasons for discontinuation of therapy should be presented

Results Analysis

- **ITT** = Intention To Treat
  - Results from all randomized subjects included in analysis
- Most real world applicability
- Beware bias this can cause (example: treatment being studied for a disease known to progress like dementia)

Endpoints and Safety

- **ITT** = Intention To Treat
  - Results from all randomized subjects included in analysis
- Most real world applicability
- Beware bias this can cause (example: treatment being studied for a disease known to progress like dementia)

Primary endpoints
- Studies powered to detect a difference in primary endpoint
- Main objective of the study (study designed to address this objective)

Secondary endpoints
- Power calculations not done based on secondary endpoints
- Significant differences could be due to chance
- Sometimes a result of post-hoc analysis (after the end of the study)
### Example of Risk

<table>
<thead>
<tr>
<th>Groups</th>
<th>No Heart Attack</th>
<th>Heart Attack</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug A</td>
<td>40</td>
<td>10</td>
<td>50</td>
</tr>
<tr>
<td>Drug B</td>
<td>48</td>
<td>2</td>
<td>50</td>
</tr>
<tr>
<td>Total</td>
<td>88</td>
<td>12</td>
<td>100</td>
</tr>
</tbody>
</table>

### Evaluating the Results

**Risk**
- The percentage of patients in a given group undergoing the same treatment who will experience the outcome/event

**Absolute Risk Reduction (ARR)**
- The absolute difference in the outcome between the two studied groups
- The percent of patients who were saved/harmed by the treatment vs the control group
- Value (%) is ALWAYS smaller than the value (%) of observed outcome in either group
- An ARR of zero denotes no difference in risk between the two groups (if A-B = 0, then A=B)

### Example of ARR

<table>
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<tr>
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</tr>
</tbody>
</table>

### Evaluating the Results

**Relative Risk (RR)**
- Ratio of the risk of one group divided by the other (usually treatment group divided by control)
- RR value is never “Zero”
- RR of “1” denotes not difference in risk between groups (A/B = 1, then A=B)
- If RR < 1.0, then risk is reduced vs control
- If RR > 1.0, then risk has increased vs control
### Example of RRR

<table>
<thead>
<tr>
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### Evaluating the Results

**Relative Risk Reduction (RRR)**
- The % of risk removed by the more effective therapy compared to control
- Value is always EQUAL OR LARGER than ARR
  - False sense of significance of a result
  - Only significant to group which reduces risk
  - $0 < RRR < 1$

**Odds Ratio (OR)**
- Similar to RR but used in the setting an observation of two different populations rather than two different interventions/medications
- Odds of exposure in the intervention group divided by the odds of exposure in the control group
- Similar to RR, if OR = 1, then no difference in odds between the two groups

**Hazard Ratio (HR)**
- The hazard ratio is an expression of the hazard or chance of events occurring in the treatment arm as a ratio of the hazard of the events occurring in the control arm
- Similar to RRR but differs with regard to:
  - Identified hazard and not avoidance of hazard such as RRR
  - Specific to a given time

### Evaluating the Results

**Confidence Interval**
- A confidence interval calculated for a measure of treatment effect shows the range within which the true treatment effect is likely to lie
- 95% CI is a range of data which is Mean +/- 2 SD
- Allows one to see the magnitude of the effect
- Narrow vs broad CI
Range significance depends on which statistic is used to analyze data:

- ARR: if CI includes zero then a conclusion on whether the treatment has an effect or not cannot be drawn.
- For all “ratios” if “1” is included, then a conclusion on whether the treatment has an effect or not cannot be drawn.

The p-value is the probability we would observe the outcome (with the given magnitude) if there was really no difference between the groups/treatments.

Statistically significant outcomes are when there is a <5% chance that the results were due to chance (p-value <0.05).

- Reproducible results

Factors Affecting p-value

- Magnitude of the main event/outcome
  - 50% decrease in HA vs 2% decrease in HA
  - The smaller the magnitude, the larger the p-value

- Number of observations
  - Larger number of observations will result in a smaller p-value (more significant)

- Spread of the data
  - The smaller the spread the smaller the p-value (more significant)

No Effect vs Total Effect with CI

P-value

<table>
<thead>
<tr>
<th>Common Language</th>
<th>Statistical Statement</th>
<th>Conventional Test Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Statistically significant” “Unlikely due to chance”</td>
<td>The null hypothesis was rejected.</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>“Not significant” “Due to chance”</td>
<td>The null hypothesis could not be rejected.</td>
<td>P &gt; 0.05</td>
</tr>
</tbody>
</table>
Number Needed to Treat (NNT)

- The number of patients needed to be treated with intervention to prevent one event
- ALWAYS round up next to full integer
- NNH: same as NNT but used when assessing ADR and harmful outcomes of interventions
- Would always prefer an intervention when:
  - NNH >> NNT

\[
\text{NNT} = \frac{1}{(\text{proportion benefiting from experimental intervention}) - (\text{proportion benefiting from a control intervention})}
\]

Example of NNH/NNT

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NNT = 1/ARR = 1/0.06 = 16.67 = 17
Since ARR is 6%, thus for every 100 patients treated with TX, 6 will be saved... Thus for every 17 treated with TX, 1 will be saved

ARR (6%)

Deaths (%)

Kaplan Meier Survival Curve

- A graphical illustration depicting survival of patients at a given time along an observed period of time
- Use in studies which assess survival of patients in terminal diseases

Constructing a K-M Curve

K-M Survival Curve Censorship
Was medication titration allowed? If so, are both groups maximized?

Safety and assessment of tolerability should be assessed and presented
- Study probably not powered to detect differences

Trial duration
- Sample size included/analyzed
- Exclusion of subjects from being enrolled in trial

Example: Cholesterol lowering medication trial
- Surrogate marker: LDL-C
- Clinical endpoint: MI, stroke, death

Investigators often analyze the results of subsets of study subjects as divided into various groups such as gender, age, presence of diseases or other complicating factors

Pre-requisites for subgroup analysis:
1. Trial should be well-designed with sound methods
2. Multiple sub-group analyses should generally be avoided; the more that are done, the higher likelihood of a statistically significant difference being reported that is due to chance alone (Type I Error)
3. Power reduced by analysis of smaller groups
4. Primary endpoint should be of statistical significance
5. Reason for sub-group being analyzed should be stated before outset of study or be justifiable (prior studies have suggested an effect in this particular group)
6. Outcomes that can be influenced by either the intervention or control group should not be selected for subgroup analysis

Keep primary outcome your focus
Ancillary versus Adjunctive Therapy

- **Ancillary:** An additional therapy not equally distributed between intervention and control groups
  - Example: allowing antacid use in a trial examining a new proton pump inhibitor
  - Can affect outcomes potentially
  - Could be a rescue therapy

- **Adjunctive:** An additional therapy equally distributed between intervention and control groups
  - Example: Low cholesterol diet in a trial examining a new drug for high-cholesterol

Discussion/Conclusion

Discussion Should Include:

- Summary of key findings
- Possible explanation of findings
- Internal and external validity discussion
- Interpretation/comparison of findings in relation to other similar clinical trial findings
- Identification of and discussion of clinical trial limitations
- Discussion of clinical importance of results and how they should be used in practice

Conclusion Should:

- Provide investigators’ overall recommendation
  - Should focus on primary endpoint results

  - No new info should be presented in this section

  - Conclusions should be aligned with results of the trial/supported by trial results

Bibliography/References

- Should be up to date

  - Investigators/Authors should avoid extensively referencing their own prior work

Bibliography and Acknowledgements
**Acknowledgements**

- Includes recognition for persons contributing to the article but who do not meet criteria for authorship.
- May also include information about funding.
- May also include information about when paper was received, revised, and/or accepted.

**Funding**

- Section outlining where any monetary support for study may have come from and the role of the funding source in the research.
  - Examples of funding sources:
    - Pharmaceutical companies
    - Government agencies (such as National Institutes of Medicine)
    - University grants
    - National organizations (such as the American Cancer Society)
- Not all pharmaceutical company sponsored studies will be biased by this support, but reader must assess methods, results, etc for themselves.