Clinical biostatistics series: Non-compliance and Analysis sets

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Preamble: The perfect world

In a perfect world (of Randomized Controlled Trials), we would:

1. Have a strong trial design including:
   - Randomization
   - Blinding
   - Concealment etc
2. All patients would attend all visits and remain in the trial until it was completed: no missing values and no loss-to-follow-up(LTFU);
3. And all patients would comply with their allocated treatments as per protocol (i.e. as defined by the treatment protocol of their allocated group)

BUT THERE IS A PROBLEM....

Preamble: When reality bites

OFTEN, THEY DON'T

But so what? What if patients fail to turn up, or to comply with their allocated treatment protocol??

What problems does this cause to the results of our analysis, and more importantly, the quality of evidence our study produces?

Preamble: Investigators are a 'shady' bunch

To answer this question we must work on certain assumptions:

- We (as investigators) are *potentially* dishonest
- We often have SOME conflict of interest in showing the efficacy of our new treatment (whether it be $$$ or publishing in the NEJM)
- To clarify, we often want differences, and for these differences to be in a certin direction (i.e. New treatment superior)
- Our only protection against this mistrust is to codify the decisions we make to ensure a fair trial using good clinical practice and established methods for dealing with the problems that arise

Preamble: Missingness vs compliance

At this stage it is important I make an important distinction:

- **Missingness** is where a patient periodically or permanently exits the trial (resulting in missing values in our dataset)
- **Compliance** is about a patient's compliance with their treatment protocol. A patient who does not take their medication as prescribed (i.e. violates the treatment protocol), but is still present in the trial (and still yields data)

Missingness vs compliance

Although the issues of missingness and compliance are related (they both lead to biases and noise in our trial data), how to deal with these two problems is quite different

What we will cover today...

Of the three issues I raised in the first slide (Trial design, Missing values and Compliance), I will cover the last, **Compliance**, today .

Incidentally, dealing with missing values and loss-to-follow-up (a strongly related topic) will be dealt with in the next lecture.

In this series, I don't cover too much on trial design (e.g. different randomization protocols) although I am happy to answer questions about best practice in this area at any time.

Control in randomized *controlled* trials

Before we can talk about how we deal with non-compliance in our analysis, we need to discuss the different types of non-compliance, and how it might manifest itself.

First, we need to differentiate between the different ways we gauge the efficacy of our treatment. I will discuss two different types of comparisons:

1. Comparing our (new) treatment with a **Placebo-controlled** group
2. Comparing our (new) treatment with a **Active-controlled** group

Placebo-controlled trials

In a 'traditional' placebo-controlled trial, the control group patients receive no treatment except for a placebo. However, as you would expect, in many clinical situations this is unethical.

In many modern trials, placebo-controlled trial allow both types of patients receive the same level of care (e.g. usual care) except the treatment arm **also** receive the new treatment; the control group **appears** to receive the same but without the **active 'ingredient'**

Placebo controlled trials:

- The main point is that patients are blinded to their treatment membership
- However, hiding treatment membership from the patient in many situations is often impractical or even impossible.

Active-controlled trials

In these types of trials, the control arm usually receives standard care, whereas the treatment groups receives a new and alternative treatment (instead of standard care). In this respect it is harder to isolate the **active ingredient** effect.

So why I am focusing on these rather subtle differences between different types of RCTs? The answer is because protocol violation by participants through non-compliance may have different implications in these different types of studies.

This is probably best considered in terms of a couple of examples.

Ex1: Treating peri-menopausal symptoms

We would like to trial the efficacy of new product (a plant extract) to alleviate symptoms in peri–menopausal women

- We conduct a parallel, placebo-controlled superiority trial determine whether the new product helps
- We develop a placebo with the same 'look and feel' as the active drug and randomize women to one of the two treatment arms
- We use pill count and participant interview to gauge protocol compliance
- Incidentally, our outcome variable is a symptoms severity score (out of 10) based on the number, frequency and severity of a set of symptoms

Ex2: Improving disease self management in T2DM patients

In this study, we want to improve patients attitudes to managing their Type 2 Diabetes Mellitus (through monitoring blood sugar, diet, exercise, prescribed treatment adherence)

- We conduct a parallel, active-controlled superiority trial determine whether a cognitive behavior therapy (CBT) intervention helps
- As a placebo is impractical in this study (no patient blinding possible), controls are just given the standard educational intervention (which emphasizes diabetes knowledge)
- We should also note that the treatment group also receive this standard educational intervention
- Compliance (treatment arm) is based on completion of all CBT sessions

The nature of non-compliance

Many reasons exist for patients not adhering to prescribed therapies. But, the reasons for patient non-compliance is very important in clinical trials. We need to ask:

1. Is non-compliance associated with the study outcomes (are more/less severe patients more/less likely to comply)
2. Is non-compliance associated with allocated treatment: Are control-arm patients less/more likely to comply than those in the intervention-arm
3. If both arms' participants are non-compliant, is it for the same reasons (or is it 'modified' by treatment arm)
4. If the trial is longitudinal, does level of compliance vary over the course of treatment.
5. What mechanisms are there for patients to take 'treatment' into their own hands (i.e. administer their own co-interventions)

The nature of non-compliance

This is all very subtle and complex. To illustrate this, I would like us to think about the two examples above Think about:

- Mechanisms allowing the 'study' group to behave more like controls
- Mechanisms allowing controls to behave more like the treatment arm
- What might lead to differential non-compliance

1. Alleviation of symptoms in peri-menopausal women
2. CBT therapy to improve diabetes management self efficacy

What can we do?

Now what can we do about these problems? Where we can't anticipate them and 'design them out', our only choice is to control for them in the analysis.

In the end, our only real control we have is who should stay in the set of data to be analyzed. We call this the **Analysis set**.

Definition: The analysis set

The analysis set represents the sample (the patients) that we choose to keep in our analysis

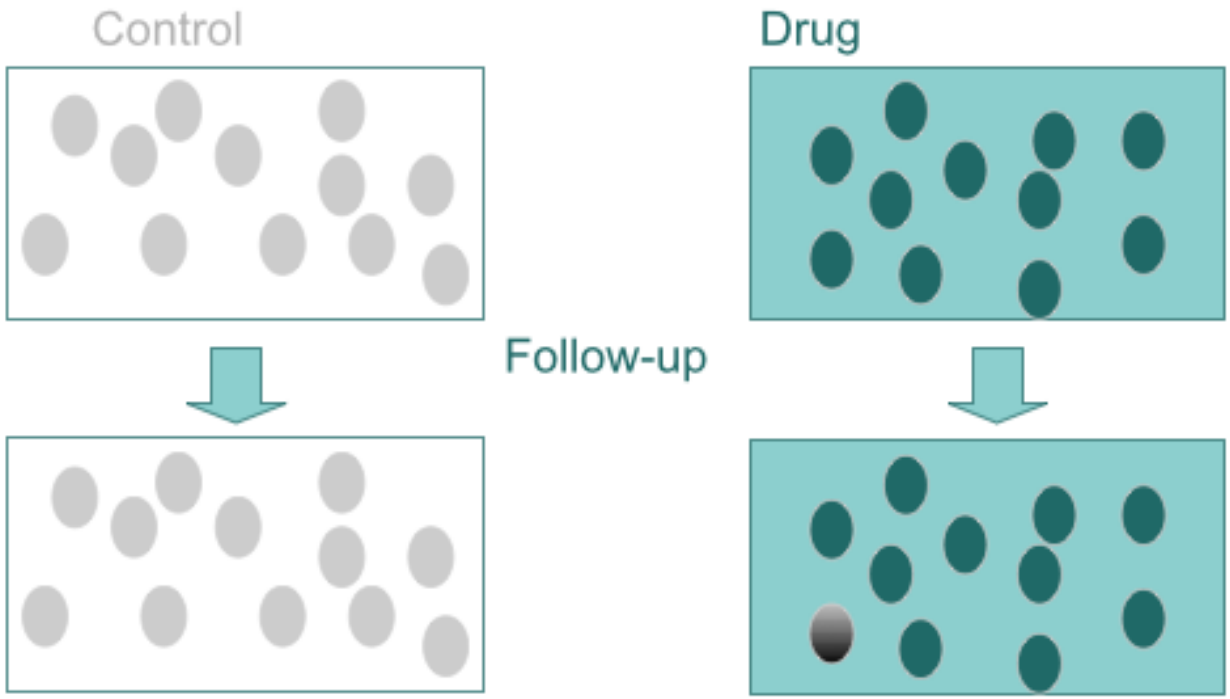
Analysis sets.

The analysis set is a pretty simple idea: **For non-compliant patients, should we....**

1. **Keep them** (as allocated)
2. **Drop them** (retain only well behaved patients)
3. **Swap them** (change their treatment arm)

Keep them: the 'Intention to treat' (ITT) set

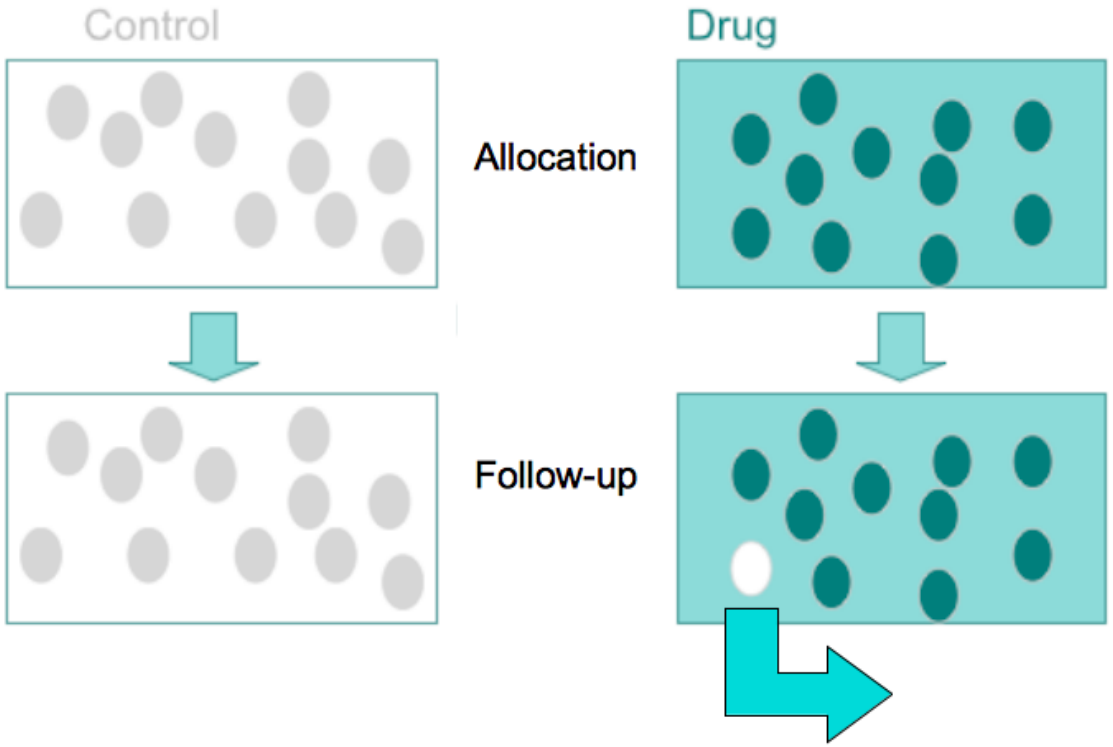
For intention to treat we will analyze the patients as they were allocated (regardless of how well they followed protocol).



The grey individual did not follow the treatment as prescribed, but we keep them in their original group.

Drop them: the 'Per protocol' set

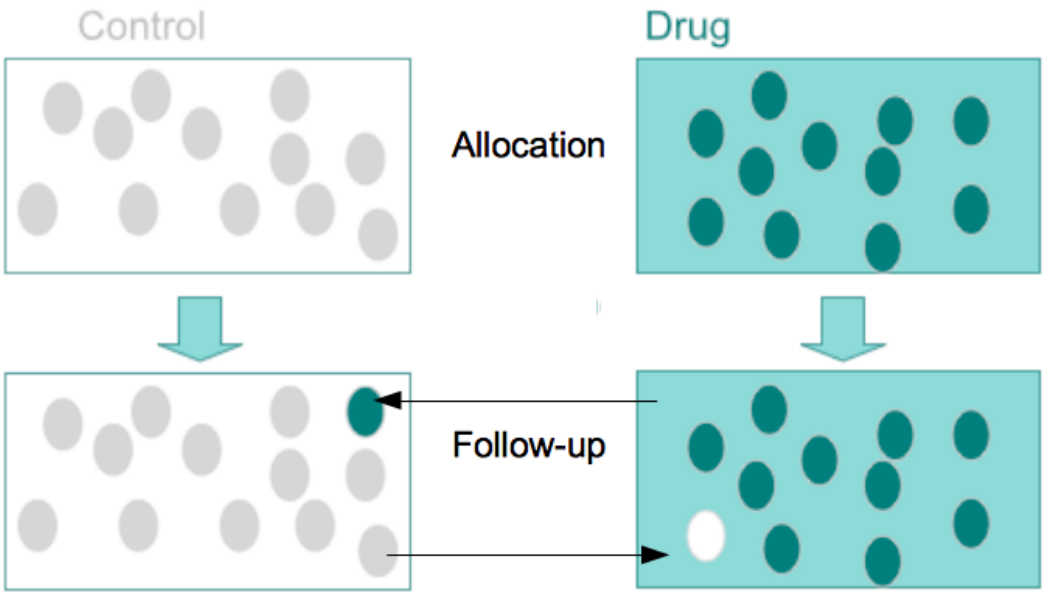
For per protocol we will only analyze patients who followed the protocol. Otherwise they are **excluded** from the analysis.



The white individual did not follow the treatment as prescribed, so they are removed from the dataset

Swap them: the 'As treated' set

We can also analyze patients AS THEY WERE TREATED. A patient in the treated group who behaved like a control (e.g. didn't take the drug) could be moved into the control group.



Above, the white (control)patient behaves more like a 'treated' , and one allocated as 'treated' acts more like a control $\Rightarrow$ swap their groups

Representation in our dataset

These three 'analysis sets' can be very simply represented in our dataset. Consider our symptoms in peri-menopausal women study...

PID	SympScore10	ITT (allocated)	PP	AT
1	2.8	Tx	Tx	Tx
2	3.3	Tx	Tx	Tx
3*	5.8	Tx	**NA**	**Tc**
4	2.7	Tx	Tx	Tx
...	...	...	...	...
101	6.7	Tc	Tc	Tc
102*	3.3	Tc	**NA**	**Tx**
103	5.9	Tc	Tc	Tc
104	8.1	Tc	Tc	Tc
...	...	...	...	...

*-non compliant patients, Tx-Treatment, Tc-Control

Which approach should we use.

Now the very important question arises: *Which is the best analysis set to use???*. **ANS: IT DEPENDS....**

- **Research objective**:
  - Are we trying to establish treatment **Superiority** or **Non-inferiority/Equivalence**?
  - Is this an effectiveness (pragmatic) or efficacy trial: Are we interested in the 'usefulness' of the treatment as a prescribed therapy, or more the impact of the 'biological agent'.
- **Likely impact of non-compliance**:
  - Did the protocol violations lead to breaking blind?
  - Was departure from protocol associated with treatment allocation (e.g. side effects), or the outcome (e.g. feeling better)

In the end: How did the non-compliance affect the plausibility of our findings AND our recommendations?

So? Which is the best analysis set?

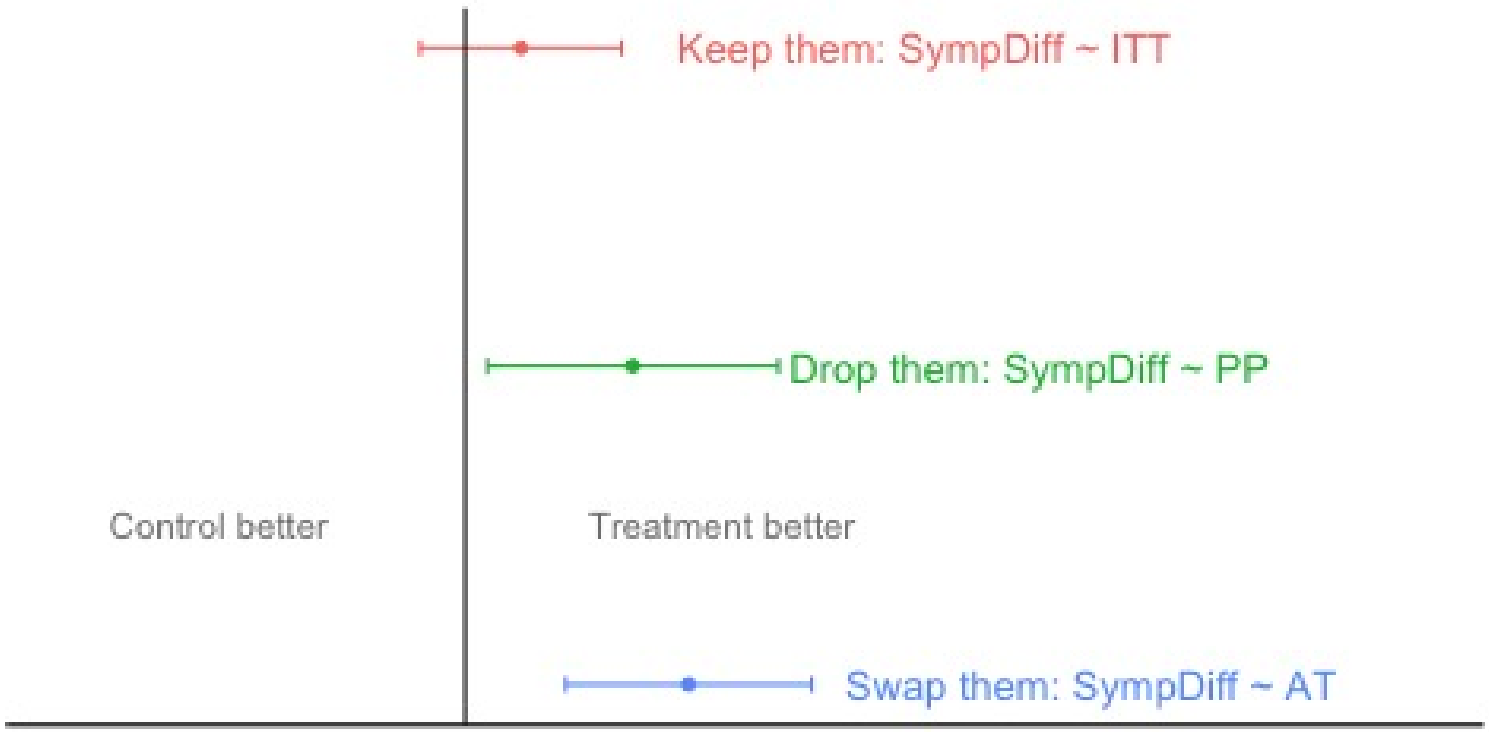
There are some basically well established prinicples that have been laid down. *For example see GUIDELINE FOR GOOD CLINICAL PRACTICE - ICH appendix E9 (statistical principles)*. Probably the best known is:

- In superiority trials, Intention to treat (retaining patients as allocated, regardless of level of compliance) should represent the primary analysis.
- Generally, as treated is to be avoided (unless we have compelling reasons to present this analysis)

Why is this? Before we discuss the reasons let go back to our example:

Illustration: Peri-menopausal Symptoms severity

Here the X axis represents **Reduction in symptom severity**



Now: What does it mean, and which should we trust??

Scenerio 1: Effectiveness, superiority trial

In this first case, let consider that the reason we did the study:

- RQ: Does our plant extract represent an **effective** therapy for reducing peri-menopausal symptoms
- (Inactive) Placebo-controlled RCT
- We note many women in the treatment arm violated protocol (high pill counts) due to side effects (**green pee**)

Which result (analysis set) would you choose? Also think about:

- The magnitude of the effect
- Width of 95%CIs

Scenerio 1: What would I do

Here, my primary analysis would be *ITT*. Although I would often also present the *PP* results (secondary analysis) **WHY?**

1. **Usefulness**: Our trial is a pragmatic trial, we want to know if this drug (as is it currently packaged) will help alleviate symptoms in these women. If many women are unwilling to use it, its unlikely to be a viable therapy
2. **Disclosure**: Remember, we (as investigators) can not be fully trusted (If we were, we wouldn't have to present any results). There is ALWAYS a conflict of interest (not always about $$$) and **ITT is conservative**
3. **Controlling bias**: Randomization, concealment and blinding are very important in RCTs (its why they are the gold standard). To change or omit membership of patients after randomization is likely to lead to biases that change our results (and their credibility)

Scenerio 2: Efficacy, superiority trial

Now we are running a trial for a pharmaceutical company...

- Still a phase III trial, but now...
- RQ: Does our plant extract reduce peri-menopausal symptoms (in those that take it)
- (Inactive) Placebo-controlled RCT
- Again 'treated' patients had low compliance (**green pea**)
- We note that some of the 'control' patients took over-the-counter alternative medications to alleviate symptoms (co-intervention)

Which would be your primary analysis now?

Scenerio 2: What would I do?

Even though it would be a hard sell, I would probably present my per protocol (perfect patient) analysis as my main results (but also include ITT as secondary)

- **Remember the research objective:** We have to acknowledge that it is the active ingredient (rather than how it is delivered) that is our primary objective. Here we want to emphasize the biological effects. How the drug might be better delivered would be left to later research.
- **Statistical considerations:** As I am using the PP set, there may be a lack of balance in potential confounders between arms. So for this type of study I would identify and statistically control for these confounders.

What would you do? Do you agree?

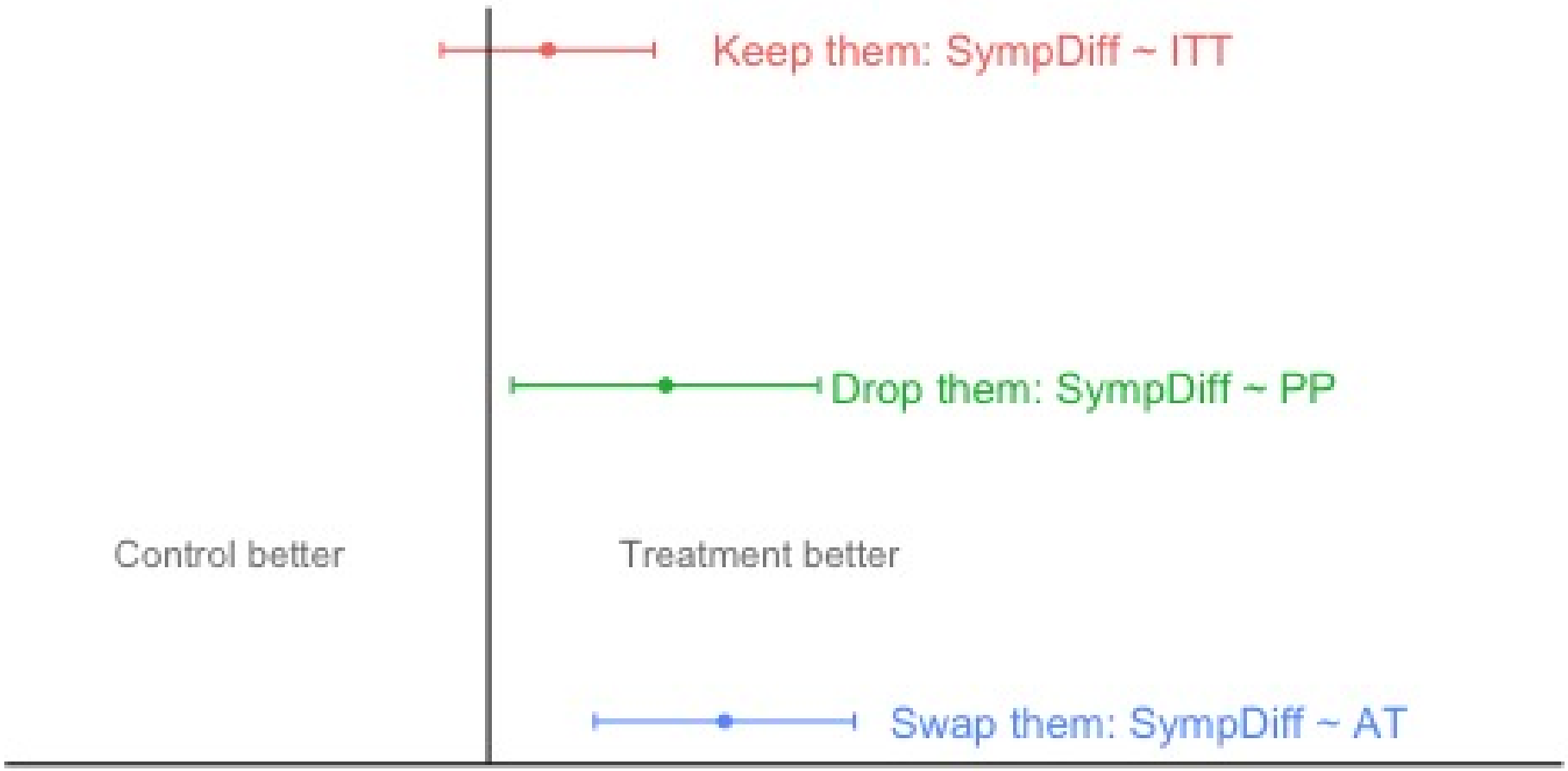
Sensitivity analysis

In both of the above cases I have presented multiple analyses. I think this is a very important part of the process. For example,

- If our conclusions are similar across both analysis (e.g. drug is superior), then this represents stronger evidence than any one analysis. It can also show that protocol violations due to non-compliance had no major (or sometimes even discernible) effect
- However, if our results do differ across the analysis sets (they are sensitive), we might to also talk about the reasons why this might be, and still salvage some useful findings.

Think about our figure.

Illustration: Peri-menopausal Symptoms severity



Non-inferiority and equivalence trials

Finally, I would like to talk about which analysis set is the best to use when we are conducting a non-inferiority (or equivalence) trial.

- First, we need to remember one of the reasons ITT is recommended in superiority trials is that ITT is conservative; it tends to err on the side of caution (failure to detect a superior treatment = Type II error)
- However, in non-inferority trials, ITT is likely to be too liberal. That is, it will often lead to us falsely conclude non-inferiority (Type I error)

Analysis set and type of trial

ITT tends to lead to type II errors in superiority trials (works against us), whereas ITT works for us in NI and equivalence trials. **Upshot: ITT often not trusted in NI trials**

Non-inferiority and equivalence trials

So which analysis set should we use in NI and equivalence trials????

Controversial: The jury is still out

My advice is to (again) conduct both PP and ITT analysis and make your decisions based on:

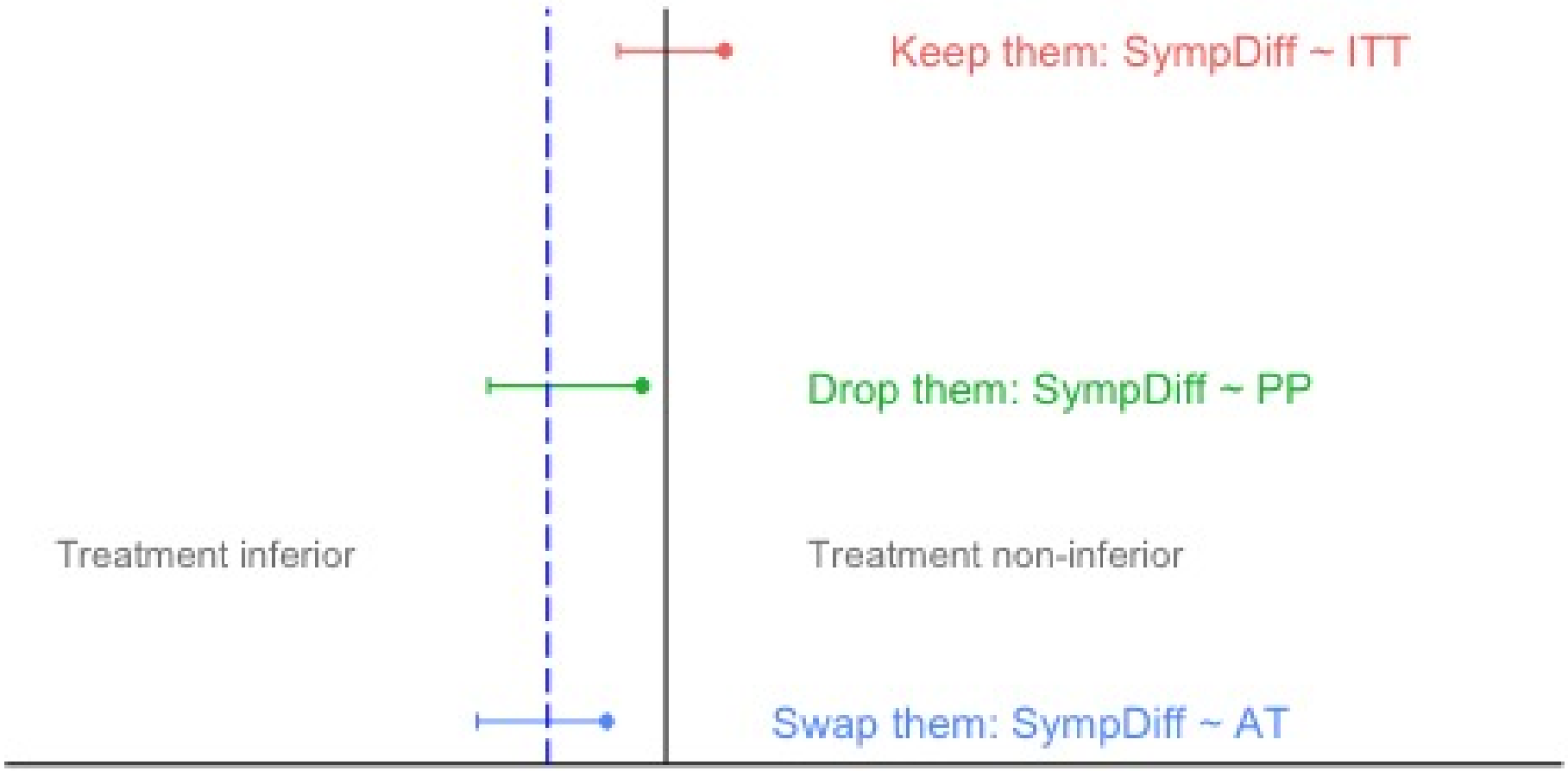
1. Your research objective,
2. The 'mechanics' of the non-compliance

Example

Let's go back to our peri-menopausal symptoms study. **BUT THIS TIME:**

- We are now considering an active control group (existing therapy)
- BUT the existing therapy tends to be expensive and is often unavailable (hence we need a non-inferior alternative).
- We want to conduct a trial to demonstrate (hopefully) that our plant extract (the experimental treatment) is non-inferior to the existing (standard) therapy.
- As before, we have similar compliance issues (side effects etc)

Peri-menopausal Symptoms severity: NI trial



What would you do?

Bringing it home...

So which is the best analysis set? There is no simple answer. However, we need to consider:

- Is it a superiority or NI/Equivalence trial?
- Is effectiveness or efficacy of primary importance
- What are the mechanics driving non-compliance:
  - Are they more or less random across the treatment groups, for the entire scale of the outcome
  - Or does it differ between treatments or at different spectra of the outcome

The fact is that one size does not fit all. A single analysis set is not always best. My recommendations is to conduct analyses on both ITT and PP sets (probably not AT), and examine differences in results. I would present both sets of results discussing the implications of each.

THANK-YOU

Questions?????