Defining Treatment Effects

Thomas Permutt

FDA Topic Leader

ICH E9(R1) Expert Working Group

Treatment Effects

- Abigail
  - If placebo, 15
  - If test, 17
  - What is treatment effect?

Treatment Effects

- Abigail
  - If placebo, 15
  - If test, 17
  - What is treatment effect?
- Treatment effect is 2

Treatment Effects

- Bert
  - If placebo, discontinue for lack of efficacy
  - If test, 18
  - What is treatment effect?

Treatment Effects

- Bert
  - If placebo, discontinue for lack of efficacy
  - If test, 18
  - What is treatment effect?
- Treatment effect is to keep Bert in study (with outcome 18)

Treatment Effects

- Carmen
  - If placebo, 14
  - If test, drop out for adverse event
  - What is treatment effect?
- Treatment effect is to make Carmen drop out

Treatment Effects

- Donald
  - Drops out in either group
  - What is treatment effect?
- Treatment effect is zero (maybe)

Four Kinds of Subject

	Placebo	Test
Abigail	15	17
Bert	X	18
Carmen	14	X
Donald	X	X

When Everyone Is Like Abigail

	Placebo	Test	Effect
Abigail 1	15	17	2
Abigail 2	14	19	5
Abigail 3	16	15	-1
Average	15	17	2

When Everyone Is Like Abigail or Donald

	Placebo	Test	Effect
Abigail 1	15	17	2
Abigail 2	14	19	6
Abigail 3	16	15	-1
Donald I	X	X	0
Donald II	X	X	0
Donald III	X	X	0
Average	(15 + X)/2	(17 + X)/2	1

But …

- Two distinct things happening, why average?
- Average effect doesn't depend on X, but significance does …
  - And it shouldn't, because …
  - There is an effect, if there's an effect in Abigails

But …

- Not Everyone is like Abigail or Donald

- Where in the world are Bert and Carmen?

- When statisticians say "missing at random," I say …

  – We haven't randomized yet, so nothing is random

  – Nothing is missing

  – Where have you hidden Bert and Carmen?

    - They don't exist?

    - They're "the same"?

Finding Bert and Carmen

- Everyone is like Abigail
  - Because the actual value is the outcome
  - Because dropping out is the outcome
- Who is Abigail?
- Everyone could be like Abigail if …
- Everyone was like Abigail for a while

Finding Bert and Carmen

- Everyone is like Abigail
  - Because the actual value is the outcome
  - Because dropping out is the outcome
- Who is Abigail?
- Everyone could be like Abigail if …
- Everyone was like Abigail for a while

Actual Value Is the Outcome

- Common when outcome is life or death
- Not common in "symptom" studies
  - Value "not relevant" (?)
  - OK, but why not?

Finding Bert and Carmen

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  - Because the actual value is the outcome
  - Because dropping out is the outcome
- Who is Abigail?
- Everyone could be like Abigail if …
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Dropping Out Is the Outcome

- Retrieved value not relevant because …
- The treatment (or control) failed this subject
  - Toxicity
  - Lack of efficacy
  - Unrelated to treatment
- Outcome is not missing, it's just not a number

Finding Bert and Carmen

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  - Because the actual value is the outcome
  - Because dropping out is the outcome
- Who is Abigail?
- Everyone could be like Abigail if …
- Everyone was like Abigail for a while

Who Is Abigail?

- What if all the men drop out in both groups …

- And all the women adhere in both groups?

- Then all the men are Donald
  - Because if some were Bert they would have adhered in the active group

- And all the women are Abigail
  - Because _____

When Everyone Is Like Abigail or Donald

	Placebo	Test	Effect
Abigail 1	15	17	2
Abigail 2	14	19	6
Abigail 3	16	15	-1
Donald I	X	X	0
Donald II	X	X	0
Donald III	X	X	0
Average	(15 + X)/2	(17 + X)/2	1

- Effect is 2 or 1
- I'd say effect is
  - In women, 2
  - In men, makes them drop out
  - Average effect is not very meaningful

What Color Is Abigail?

Sex	Color	Test	Placebo
F	Green	Adhere	Adhere
F	Blue	Drop out	Adhere
M	Green	Adhere	Drop out
M	Blue	Drop out	Drop out

Finding Bert and Carmen

- Everyone is like Abigail
  - Because the actual value is the outcome
  - Because dropping out is the outcome
- Who is Abigail?
- Everyone could be like Abigail if …
- Everyone was like Abigail for a while

If …

- If no rescue
  - Akin to noninferiority study
  - Can't do for ethical or practical reasons
  - But answer is of interest
- If perfect adherence
  - Can't do for fundamental reasons
  - And answer is not of interest
    - "Will have the effect it purports or is represented to have"

Finding Bert and Carmen

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  - Because the actual value is the outcome
  - Because dropping out is the outcome
- Who is Abigail?
- Everyone could be like Abigail if …
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While on Treatment

- Everyone (?) has some measurements
- Average while on treatment
- Palliation in terminal disease
  - Short, comfortable life good
  - Long, comfortable life good
- Smoking cessation
  - Only smoked off treatment!
  - Failure
- Where are you in between?

Strategies for Defining Treatment Effects

- Everyone is like Abigail
  - Because the actual value is the outcome—treatment policy
  - Because dropping out is the outcome—composite
- Who is Abigail?—principal stratification
- Everyone could be like Abigail if—hypothetical
- Everyone was like Abigail for a while—while on treatment