Critical Appraisal of a Scientific Article on Therapy

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Phases of Trials

- **Phase 1. In a small number of normal subjects**

- **Phase 2. In those with the disorder,
  few centers, moderate numbers**

- **Phase 3. Calculated sample size,
  multicentric, longer duration**

- **Phase 4. Post marketing, post-release**

- **Why conduct therapeutic trials?**

To Distinguish Harmful from Useful Therapy

Is the Trial really Randomized?

Why Randomize?

Elimination of bias

a) Balances known and unknown covariates (cofactors) on average across treatment groups.

b) Provided that each observation is independent of the others, validity of statistical test is assured without additional assumptions.

Nonrandomized trials:

False acceptance of treatment modality
Eg. Human insulin over
Porcine/Bovine insulin

Exception to randomization:
Marked reduction in mortality/
Universal response
eg.1.Introduction of SM in Tb meningitis
2. Acetaminophen in fever

Ensure that all <u>clinically relevant</u> outcomes are reported

Eg. Conclusion:
Folic acid reduces neural tube defects
Based on:
a) All sonological findings at the 14th week of GA.
b)All live term neonates on the 1st day of life.
Problem??

Ensure: Is the clinical statement relevant in your population

1.Statement:

Vitamin D prophylaxis helps in the prevention of hip fractures.

Question: Replicate the application of the study in the Indian population

Catch:

Mean age of patients at analysis: 83-86 years.

Sunlight factor in Tropical countries (?)

2.Statement:

A study in Japan shows that Drug M reduces the occurrence of Grave's disease with thyrotoxic periodic paralysis from 30 cases in 150- to 5 in 140.

Question: Conduct the study in India

Catch: thyrotoxic periodic paralysis is seen almost exclusively in oriental subjects.

Ensure that both clinical and statistical significance are considered in analysis

Statement:

In a randomized controlled trial in New Delhi, Losartan reduces blood pressure more than Atenolol in 7,000 patients. $p < 0.0001$.

Catch:

Losartan reduces diastolic by 3.2mmHg

> Atenolol: 79mmHg vs 82mmHg.

"Over-powering" can make the p-values high right across the board

In a randomized controlled trial in New Delhi, Losartan reduces blood pressure more than Atenolol in **7,000 patients. p<0.0001**.

Same study:

Total cholesterol. p <0.05

Fasting Plasma glucose. p<0.05

Weight . P<0.05

P-value Interpretation

- P< 0.01 very strong evidence against H0

- 0.01< = P < 0.05 moderate evidence against H0

- 0.05< = P < 0.10 suggestive evidence against H0

- 0.10< = P little or no real evidence against H0

Common Misinterpretations of the p-value

In a study where p<0.01 ………………………

There is a 1% chance of observing a difference as large as you observed even if the two population means are identical (the null hypothesis is true)

 - **Correct**

There is a 99% chance that the difference you observed reflects a real difference between populations, and a 1% chance that the difference is due to chance-

-**Incorrect**

Ensure that the therapeutic maneuver is feasible in your practice

Statement: Aspirin prophylaxis reduces the incidence of Myocardial infarction significantly.

Comment:

Cheap, Easily available.

Statement: Parathyroid hormone: 1-34 is effective in the therapy of osteoporosis, if used long-term

Catch: It costs 20,000/- per month in India

Involves daily injections

Ensure: Were all patients who entered the study accounted for at it's conclusion?

Were drop-outs,non-compliers and those who crossed-over handled appropriately ?

- eg: <u>Drop-outs</u> in drug trials in tuberculosis should be followed up and the morbidity/ mortality assessed.

<u>"Intention to treat" (ITT):</u>

Analysis includes all randomized subjects regardless of compliance with the protocol. ITT is the only analysis that preserves benefits of randomization.

As opposed to: "As treated"

Intention to treat

- Eg: In "ORIGIN":

  looking at cardiovascular morbidity and mortality with the impact of tight glycaemic control

  Drop outs may occur.

  Follow up drop outs with a phone call:
  - just one question: <u>are they alive</u>

Contamination:

Azidothymidine trials- controls started popping the cases tablets

(and vice-versa):

Solution: Check MCV in controls and cases.

- **Were phenomena like contamination and co-intervention accounted for?**

Co-intervention:

Therapeutic trials in patients with hypertension:

local doctors may start separate medications that effect the trial treatment.
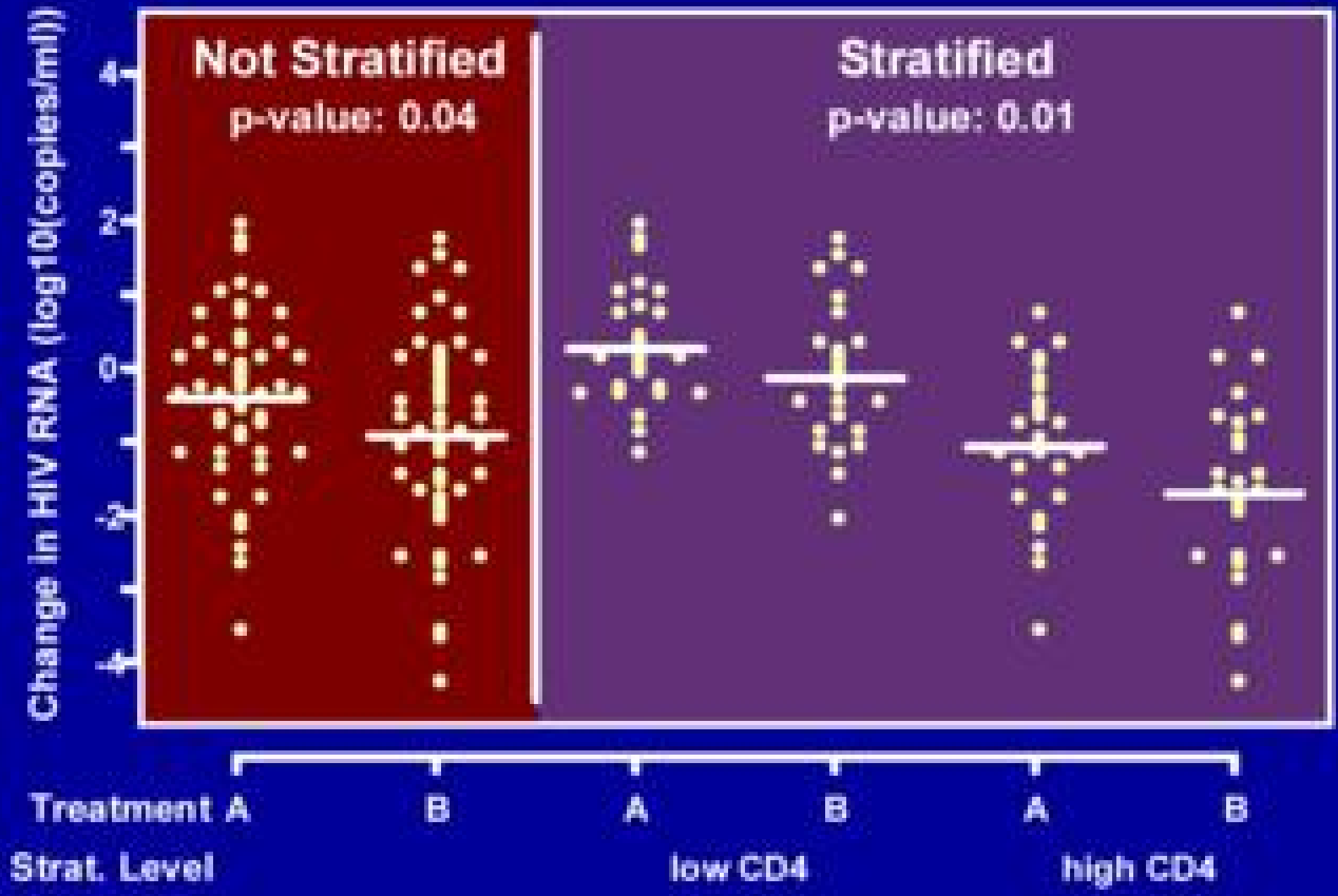
Have Strategies been used to optimize data usage and patient numbers?

- **Stratification**

- **Cross-over design**

- **Factorial design**

- **'Piggy-backing' questions**

Stratification at Randomization

Stratification to group patients who are similar

- **may reduce variability and increase power**

- **ensure treatment balance within important subgroups;**

Cross-Over Design

Cross-over studies in diabetes mellitus;

wash-out time to be accounted for in drugs with
   prolonged effect
    eg. Pioglitazone.
      Anti-neuropathic medications

Factorial Design

Cancer: <u>Beta Carotene</u>

Yes   No

Heart Disease: Yes

<u>Aspirin</u> No

"Piggy-back"…scientific questions to optimize data-extraction

eg.

In a study to assess diabetes therapy in Ramzan, other questions were asked:

A sub-study was performed to assess dietary intake comparing subjects behaviour:

pre-Ramzan and during Ramzan

Scrutinize the Data---carefully: look for flaws

Baseline Characteristics in a study…..

Parameters	Drug X	Placebo
Age	45 ± 9	45 ± 9
Duration of DM	8.0 ± 2	8.5 ± 2.2
Body Wt (Kgs)	66.99 ± 12	62.04 ± 8.4
BMI	29.8 ± 5.0	29.4 ± 5.4
S.Fructosamine	320.46 ± 80.16	330.64 ± 92.27
AC	157.47 ± 53.04	162.77 ± 55.19
2h PC	229.62 ± 73.45	247.03 ± 75.68

Weight between Placebo & Drug X……
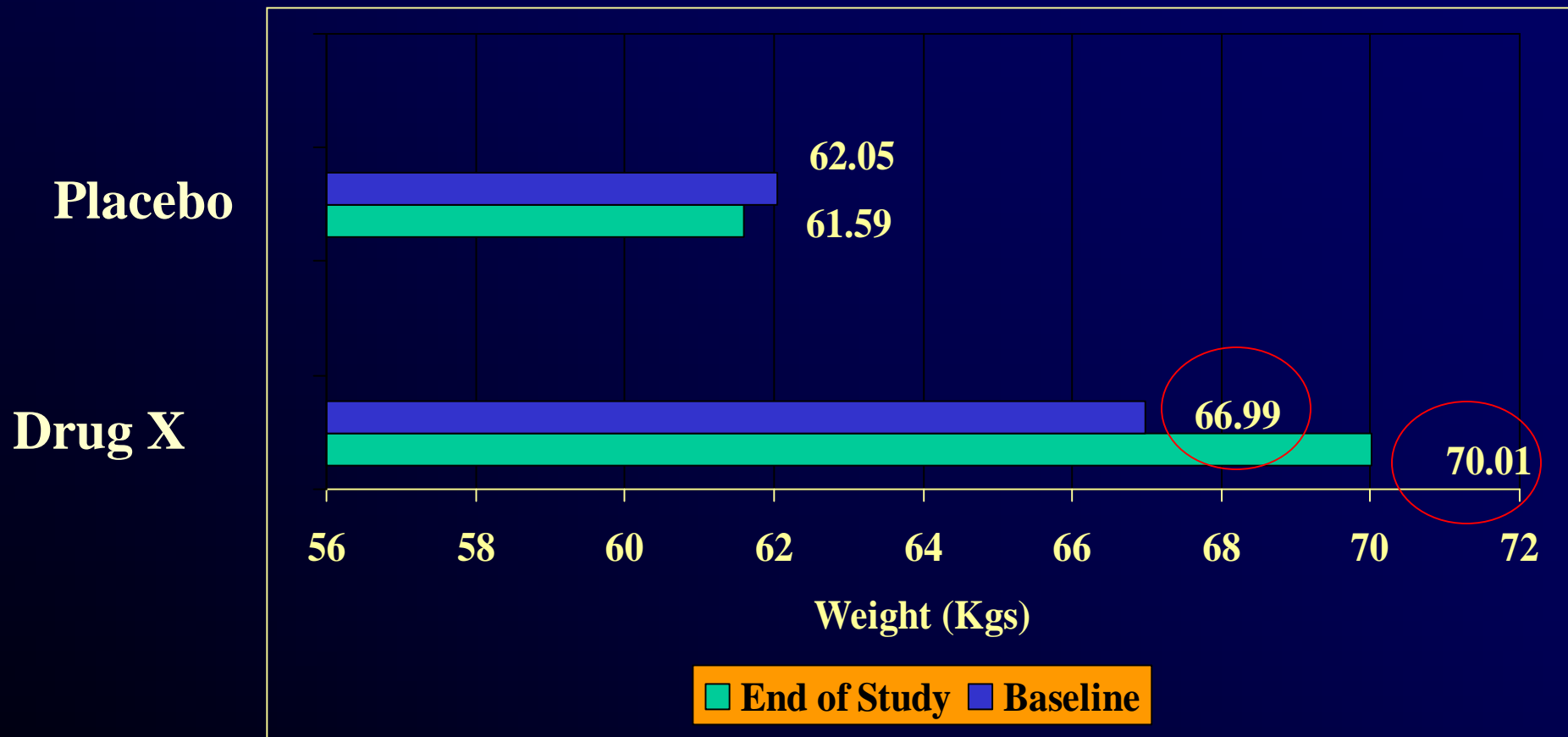
Has the Sample size been properly calculated?

- **Primary outcome measure:**
  eg. Patients with:
 Severe hypoglycaemic attacks with known
  Drug A= 30% in 12 weeks

 Severe hypoglycaemic attacks <u>expected</u> with drug X= 15%.

 If possible scrutinise the study where the <u>previous</u> study with drug A has been performed: look for:-

- frequency of glucose monitoring
- duration of study
- Nature of subjects: potential for hypoglycaemia unawareness

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 Ideally the situation should be similar

Assessment of Primary Outcome Measures

- Final conclusions should be based on the primary outcome measure:

  Eg: Drug A does not cause Hepatitis more than placebo in a 1 year study.

  But sporadic cases are seen.

  The 1 year study: is not powered to assess the potential of Hepatitis being a siginificant side effect of the drug.

  Longer study required.

  Sample size should be larger.

Cost Analysis should be performed

Direct cost per month per patient analyzed
  In a particular trial:

- Pioglitazone arm = INR 780.62 (US$ 147.36)
- Placebo arm = INR 1232.50 (US $ 27.41)
                In India
  vs Pioglitazone arm in India: US$ 17.36

THANK YOU