WEEKLY EPIDEMIOLOGICAL REPORT

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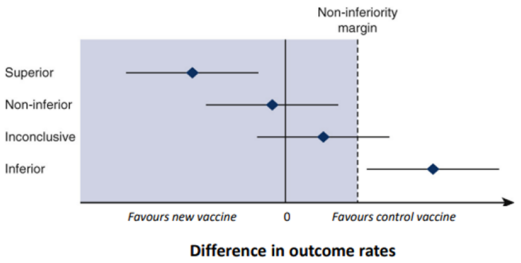
Non-inferiority Studies

In evaluating medical treatments, placebo-controlled trials are often considered the gold standard. These trials involve comparing a treatment group receiving the experimental treatment with a control group receiving a placebo (an inactive substance) where researchers can account for the placebo effect. However, conducting placebo-controlled trials is ethically justified only in certain situations. For example, when there is no existing standard treatment available, when the effectiveness of the standard treatment is not proven, when delaying treatment does not pose risks to participants, or when escape clues are included to ensure participants can seek alternative options if needed.

Nevertheless, there are situations where conducting a placebo-controlled trial may be ethically problematic. This is particularly true when there already exists a proven effective treatment for the condition under investigation. In such situations, it would be considered unethical to deny participants the known effective treatment by using a placebo control. Instead, active-controlled trials, where the experimental treatment is directly compared to existing effective treatment, are more appropriate.

Non-inferiority studies are a type of clinical research designed to demonstrate that a new treatment/intervention, is not inferior to an existing standard treatment/intervention. These studies are typically conducted in situations where it may not be feasible or ethical to conduct a placebo-controlled trial or when the goal is to establish the non-inferiority of a new treatment.

Suppose we have a new vaccine (estimated vaccine efficacy of 85%) that we want to assess, and we believe it should be at least as effective as the current vaccine. While providing that it is equally efficacious is not feasible, we are willing to consider it "non-inferior to the existing vaccine if we can demonstrate that its efficacy is no more than 5% lower. To evaluate this, we will conduct a "head-to-head" study comparing the new Covid-19 vaccine with the Pfizer-BioNTech Covid-19 vaccine.



A sponsor of an experimental treatment may decide to conduct a non-inferiority trial even when they believe the active control's efficacy cannot be surpassed for several reasons as follows.

- Safety advantages: the new treatment may offer safety advantages over active control. For example, it may have fewer side effects, lower toxicity, or reduced risk of adverse events.
- Resistance prevention: in the case of anti-infective products, the new treatment may have the advantage of not producing resistant bacteria.
- Risk reduction: In certain cases, the new treatment may result in less risk to patients compared to the active control. For example, a respiratory distress product for premature infants that is synthetic and does not rely on animal-derived components may reduce the risk of allergic reactions or transmission of zoonotic infections.
- Improved delivery or convenience: The new treatment may offer improvements in delivery methods, making it more convenient to use for patients. For instance, an asthma treatment inhaler that does not contain chlorofluorocarbons (CFCs) may be considered more environmentally friendly.
- Simplified regimen and adherence promotion: In the case of chronic illness like HIV, the new treatment may have a simpler regimen that promotes better adherence to the prescribed therapy.
- Cost consideration and market access:

Contents

While not directly related to the treatment's efficacy, costs, marketing, and potential profits can also play a role in the decision to conduct the non-inferiority trial. The new treatment may be less expensive to produce, which can lead to cost savings for both patients and healthcare systems.

So, the objective of a non-inferiority study is to determine whether a new treatment is at least as effective as the standard treatment within a pre-specified margin of non-inferiority. The non-inferiority margin is a pre-defined limit that is considered clinically acceptable for the difference in effectiveness between the new and standard treatment.

Non-inferiority trials are often challenging to conduct using clinical disease as the primary endpoint because they typically require larger sample sizes compared to placebo-controlled trials evaluating efficacy. The reason for this is that non-inferiority trials aim to establish that the new treatment is not substantially worse than the existing treatment, which requires demonstrating a smaller margin of difference.

Non-inferiority trials in assessing Immunogenicity.

Non-inferiority trials are more commonly based on comparisons of immunogenicity, particularly in the field of vaccines. Immunogenicity refers to the ability of a vaccine or treatment to induce an immune response in the body. By measuring immunogenicity, researchers can assess the ability of the new treatment to generate a similar immune response in the body as the existing treatment.

However, it's important to note that the relationship between immunogenicity and protection against the disease may not always be clear. While a robust immune response is generally associated with protection, it doesn't guarantee clinical effectiveness in preventing or treating the disease. Therefore, the use of immunogenicity as a surrogate endpoint in non-inferiority trials may require additional evidence or validation to establish its correlation with clinical outcomes.

Statistical Analysis of Assessing Non-inferiority

Let's say,
T = 'Test' = the value of the efficacy variable for the new (experimental) treatment.
C = 'Control' = the value of the efficacy variable for the Active control treatment.
M= Inferiority Margin
Further, say we have a trial where higher values of this efficacy variable are desirable.
The standard null and alternative hypotheses for proving non-inferiority are,
Null hypothesis (H0): C − T ≥ M (C is superior to T)
Alternative hypothesis (H1): C – T< M (T is not inferior to C)
In non-inferiority trials, the objective is to demonstrate that a new experimental treatment, denoted T, is not inferior to an active control treatment denoted C by more than a predetermined non-inferiority margin (M). The non-inferiority margin represents the maximum acceptable difference between T and C, beyond which T would be considered inferior to C.
The null hypothesis in a non-inferiority trial states that the active control treatment (C) is superior to the experimental treatment (T) by at least the non-inferiority margin (M). In other words, it assumes as the true treatment effect of C is greater than or equal to M compared to T. The alternative hypothesis, on the other hand, suggests that the active control treatment (C) may be marginally superior to the experimental treatment (T), but by no more than the inferiority margin (M).
To establish the non-inferiority, the null hypothesis must be rejected. If a statistical analysis of the trial data provides sufficient evidence to reject the null hypothesis, it implies that T is not inferior to C by more than the pre-determined non-inferiority margin.

It is important to note that non-inferiority trials have specific design considerations and statistical analyses. The sample size calculation is crucial to ensure adequate power to detect a difference within the predetermined non-inferiority margin (M). The choice of M is a critical decision that should be based on clinical and regulatory considerations, considering what would be considered a clinically meaningful difference.

Sample size calculation for Inferiority trial

The sample size required in each group is,
$2(z_1 + z_2)\ 2p(1-p)/\delta\ 2$
Where: p = seroconversion rate with the existing vaccine (as a proportion)
δ = maximum difference in seroconversion rates for the new vaccine to be considered "non-inferior"
z_1 = 1.64 (for significance at P<0.05) = this time based on a one-sided test
=2.05 (for significance at P<0.01)
Z_2= 0.84 for 80% Power
=1.28 for 90% Power
= 1.64 for 95% Power
Let's consider a scenario where we have an existing vaccine that shows a seroconversion rate of 85%. We are developing a new vaccine and are confident that it will perform at least as well as the existing vaccine. To demonstrate this with a reasonable level of certainty (e.g., 80% statistical power), we want the upper bound on the difference in seroconversion rates between the two vaccines to be below 5% (this 5% is known as the "non-inferiority margin").
To conduct such trials, we would need 627 participants in each arm, making a total of 1254 participants. However, if we are willing to use a larger non-inferiority margin of 10% instead 5%, the sample size required in each arm reduces to 156.
Calculators for non-inferiority trials are available on the web – e.g., https://www.sealedenvelope.com/power/binary-noninferior/
Conclusion
In summary, it is important to emphasize the need for a rigorous and thoughtful approach when planning and conducting non-inferiority trials. The importance of acknowledging uncertainties, determining the margin in advance, evaluating previous trial conditions, and avoiding false claims need to be considered. These considerations contribute to the reliability and validity of noninferiority trials, ensuring that accurate conclusions are drawn regarding the effectiveness of new treatments compared to established ones.

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Table 1: Selected notifiable diseases reported by Medical Officers of Health 22nd– 28th July 2023 (30th Week)

RDHS	Dengue Fever		Dysentery		Encephalit		Enteric		Food Poison-		Leptospirosis		Typhus		Viral		Human		Chickenpox		Meningitis		Leishmania-		WRCD	
	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	T*	C**
Colombo	312	10338	0	8	0	10	0	1	0	7	2	206	0	0	0	3	0	0	6	186	1	29	0	5	**30**	**100**
Gampaha	256	10602	0	15	0	13	0	3	0	3	9	362	0	7	0	11	0	0	5	180	2	54	1	30	**4%**	**100**
Kalutara	95	3491	0	14	0	2	0	0	0	6	20	555	0	1	0	5	0	1	14	308	0	64	0	1	**23**	**100**
Kandy	253	4424	0	27	0	0	1	8	0	15	6	189	1	42	0	3	0	1	2	169	0	18	1	23	**87**	**100**
Matale	35	1029	0	2	1	3	0	1	0	10	0	115	0	12	0	3	0	0	3	36	0	4	4	205	**26**	**100**
NuwaraEliya	9	173	4	94	0	3	0	3	1	42	3	82	1	50	0	4	0	0	6	93	1	9	0	1	**62**	**100**
Galle	87	1751	1	35	0	12	0	5	0	21	31	625	0	33	0	1	0	1	6	225	0	15	1	3	**37**	**100**
Hambantota	23	1132	1	8	0	3	0	1	0	8	11	227	1	55	0	8	0	0	4	104	0	16	14	410	**27**	**100**
Matara	41	1298	0	19	0	8	0	1	0	12	15	399	3	26	2	5	0	2	10	185	0	16	7	122	**55**	**100**
Jaffna	36	1764	2	57	0	2	0	9	0	17	0	9	4	487	0	2	0	1	3	129	1	10	0	2	**64**	**93**
Kilinochchi	5	83	0	7	0	0	1	1	0	16	1	8	0	7	0	0	0	0	0	13	1	2	0	0	**22**	**100**
Mannar	3	77	0	6	0	0	0	1	0	0	0	30	0	5	0	0	0	0	1	2	1	8	0	0	**41**	**100**
Vavuniya	5	123	0	5	0	1	0	0	2	2	1	29	0	8	0	1	0	0	0	19	1	11	0	10	**13**	**100**
Mullaitivu	1	107	1	11	0	0	0	3	0	12	0	29	0	5	0	1	0	0	0	12	0	0	0	6	**23**	**100**
Batticaloa	26	2035	5	150	0	7	0	5	0	18	2	71	0	1	0	5	0	1	1	54	0	25	0	1	**60**	**100**
Ampara	4	193	0	5	0	1	0	1	51	52	2	106	1	2	0	1	0	0	1	56	2	38	0	5	**5%**	**100**
Trincomalee	18	1948	1	17	0	1	0	0	1	65	1	55	0	15	1	1	0	0	1	42	0	22	0	1	**27**	**100**
Kurunegala	57	2286	0	31	0	8	0	0	0	6	2	245	0	9	0	9	0	2	7	343	10	116	15	332	**25**	**100**
Puttalam	33	2740	0	9	1	3	0	1	0	1	3	45	0	8	0	1	0	0	0	81	4	44	1	17	**23**	**100**
Anuradhapur	12	606	0	8	0	0	0	1	0	2	2	228	0	29	0	3	0	0	7	170	3	38	19	358	**25**	**99**
Polonnaruwa	3	465	0	12	0	5	0	0	0	10	1	137	0	5	0	12	0	0	4	60	1	16	1	260	**36**	**97**
Badulla	30	800	0	26	0	5	0	0	2	34	7	237	2	37	2	70	0	0	2	117	1	33	0	28	**66**	**100**
Monaragala	12	447	0	15	0	6	0	0	0	0	3	410	0	32	3	20	0	1	1	51	0	49	4	123	**26**	**100**
Ratnapura	53	1592	0	32	0	13	0	2	1	16	29	831	1	22	1	14	0	2	8	127	0	111	1	125	**35**	**100**
Kegalle	71	2216	2	19	0	2	0	2	0	11	17	489	2	28	0	4	0	0	9	284	3	49	0	27	**31**	**100**
Kalmune	20	1596	1	51	0	10	0	0	0	0	1	37	0	1	0	0	0	0	5	55	2	27	0	0	**43**	**100**
SRILANKA	**1500**	**53316**	**18**	**683**	**2**	**118**	**2**	**49**	**58**	**386**	**16**	**5756**	**16**	**927**	**9**	**187**	**0**	**12**	**10**	**3101**	**34**	**824**	**69**	**2095**	**38**	**99**

Source: Weekly Returns of Communicable Diseases (esurvillance.epid.gov.lk). T=Timeliness refers to returns received on or before 28th July, 2023 Total number of reporting units 358 Number of reporting units data provided for the current week: 356 **C****-Completeness *

A = Cases reported during the current week. B = Cumulative cases for the year.

Table 2: Vaccine-Preventable Diseases & AFP

22nd– 28th July 2023 (30th Week)

Disease	No. of Cases by Province									Number of cases during current week in 2023	Number of cases during same week in 2022	Total number of cases to date in 2023	Total number of cases to date in 2022	Difference between the number of cases to date in 2023 & 2022
	W	C	S	N	E	NW	NC	U	Sab					
AFP*	00	03	00	01	00	00	00	00	00	04	01	54	45	20 %
Diphtheria	00	00	00	00	00	00	00	00	00	00	00	00	00	0 %
Mumps	01	01	00	01	00	01	00	00	00	04	01	131	44	197.7 %
Measles	16	00	00	13	00	00	01	02	04	36	00	124	14	785.7 %
Rubella	00	00	00	00	00	00	00	00	00	00	00	01	00	0 %
CRS**	00	00	00	00	00	00	00	00	00	00	00	00	00	0 %
Tetanus	00	00	00	00	00	00	00	00	00	00	00	06	05	20 %
Neonatal Tetanus	00	00	00	00	00	00	00	00	00	00	00	00	00	0 %
Japanese Encephalitis	00	00	00	00	00	00	00	00	00	00	00	02	07	- 71.4 %
Whooping Cough	00	00	00	00	00	00	00	00	00	00	00	05	01	400 %
Tuberculosis	68	00	34	11	23	18	04	13	10	181	142	5430	3396	59.8 %

Key to Table 1 & 2

Provinces: **W**: Western, **C**: Central, **S**: Southern, **N**: North, **E**: East, **NC**: North Central, **NW**: North Western, **U**: Uva, **Sab**: Sabaragamuwa.

RDHS Divisions: **CB**: Colombo, **GM**: Gampaha, **KL**: Kalutara, **KD**: Kandy, **ML**: Matale, **NE**: Nuwara Eliya, **GL**: Galle, **HB**: Hambantota, **MT**: Matara, **JF**: Jaffna, **KN**: Killinochchi, **MN**: Mannar, **VA**: Vavuniya, **MU**: Mullaitivu, **BT**: Batticaloa, **AM**: Ampara, **TR**: Trincomalee, **KM**: Kalmunai, **KR**: Kurunegala, **PU**: Puttalam, **AP**: Anuradhapura, **PO**: Polonnaruwa, **BD**: Badulla, **MO**: Moneragala, **RP**: Ratnapura, **KG**: Kegalle.

Data Sources:

Weekly Return of Communicable Diseases: Diphtheria, Measles, Tetanus, Neonatal Tetanus, Whooping Cough, Chickenpox, Meningitis, Mumps., Rubella, CRS,

Special Surveillance: AFP* (Acute Flaccid Paralysis), Japanese Encephalitis

CRS =**Congenital Rubella Syndrome

NA = Not Available

Seek medical advice if you get a fever after exposure to muddy water or soil.

It could be Leptospirosis.

Comments and contributions for publication in the WER Sri Lanka are welcome. However, the editor reserves the right to accept or reject items for publication. All correspondence should be mailed to The Editor, WER Sri Lanka, Epidemiological Unit, P.O. Box 1567, Colombo or sent by E-mail to **chepid@sltnet.lk. Prior approval should be obtained from the Epidemiology Unit before publishing data in this publication**

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