Immunogenicity & Safety Study of Covid Vaccine in Adults, India

Title: A pilot open label, randomized study to investigate the performance of the IntegriMedical Needle Free Injection System by assessment of Immunogenicity in subjects receiving booster dose of COVID-19 in comparison to subjects receiving booster dose of COVID-19 using a conventional hypodermic needle.

CONFIDENTIALITY STATEMENT

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Principle investigator:	Dr. Rajnish Nagarkar
Sponsor:	IntegriMedical
Sponsor Authorized Signatory:	Scott McFarland
Study initiated on:	26 Feb 2022
Date of early study termination if any:	Not Applicable
Study completed on:	20 Apr 2022
Version:	1.0
Name of investigational medical device:	IntegriMedical Needle Free Injection System
Name of COVID-19 booster dose used:	COVISHIELD
Protocol identification:	NFIS.2022, Version 1.0
Name of affiliation of principle investigator:	Dr. Rajnish Nagarkar, Manavata Clinical Research Institute, Behind Shivang Auto Mumbai Naka , Nashik -422002,Maharashtra, India
Date of clinical study report:	16th May 2022
Prepared by:	Manavata Clinical Research Centre, Nashik.

1. LIST OF ABBREVIATIONS OF TERMS

Abbreviations	Full Name
AE	Adverse Event
CRF	Case Report Form
CRO	CRO Contract Research Organization
ICF	ICF Informed Consent Form
ICH-GCP	International conference of Harmonization – Good Clinical Practice
ICMR	Indian Council of Medical Research Ethical Guidelines for Biomedical Research on Human Subjects
IEC	Institutional Ethics Committee
IMD	Investigational Medical Device
IRB	Institutional Review Board
MGRS	Multicentre Growth Reference Study
NFIS	IntegriMedical Needle Free Injection System
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
WHO	World Health Organization
LAR	Legally Acceptable Representative

2. INDICATION STUDIED

Patient immunogenic response to COVID-19 booster dose when administered using the IntegriMedical Needle Free Injection System compared with conventional hypodermic needle.

3. INVESTIGATOR AND STUDY ADMINISTRATIVE STRUCTURE

Principal Investigator:	Dr. Rajnish Nagarkar
Sponsor:	IntegriMedical
Clinical Laboratory:	Metropolis Lab
Clinical Study Site:	Manavata Clinical Research Institute, Behind Shivang Auto, Mumbai Naka, Nashik – 422002 Maharashtra, India

4. ETHICS

4.1. INSTITUTIONAL ETHICS COMMITTEE (IEC)

The protocol and consent form were reviewed and approved by the Institutional Ethics Committee of MCRI. The EC is registered with the CDSCO (Registration No.-ECR/500/Inst/MH/2013/RR-17) and accredited by Association for the Accreditation of Human Research Protection Program (AAHRPP). The Ethics Committee is accredited by National Accreditation Board for Hospitals and Health Care Providers (NABH) (Certificate No. EC-CT-2020-0146).

4.2. ETHICAL CONDUCT OF THE STUDY

This study was performed in compliance with ICH E6R2 “Guidance on Good Clinical Practice”, Indian Good Clinical Practices Guideline, National Ethical Guidelines for Biomedical and Health Research involving Human Participants, ICMR 2017, Declaration of Helsinki and relevant SOPs of Manavata Clinical Research Institute, Nashik, Maharashtra, India.

4.3. PATIENT INFORMATION AND CONSENT

The informed consent was obtained from the subject or LAR of the subject by the Principal Investigator. Subject / LAR provided written consent to participate in the study after having been informed about the nature and purpose of the study, participation/termination conditions, risks, burdens, and benefits of treatment. Personal data from subjects enrolled in this study were limited to those necessary to investigate the safety and tolerability of the investigational study device used in this study.

5. INTRODUCTION AND BACKGROUND INFORMATION

Drug delivery refers to the technology utilized to present the drug to the desired body site for drug release and absorption, or the subsequent transport of the active ingredients across the biological membranes to the site of action. A drug delivery system is a formulation or a device that enables the introduction of a therapeutic substance in the body and improves its efficacy and safety by controlling the rate, time, and place of release of drugs in the body.

Certain pharmaceuticals cannot be delivered orally due to susceptibility to enzymatic degradation and poor absorption due to their molecular size. Such pharmaceuticals are administered through the parenteral route by using hypodermic needle and a syringe. The use of hypodermic needles and syringes is very common and the oldest way to overcome the physical barrier, wherein, the solution of a drug is forced under piston stress straight into the bloodstream or tissue. This necessitates skin perforation using a needle, which is associated with trauma and pain. To overcome these drawbacks, other alternative methods have been investigated like jet injections, dermabrasion, thermal ablation, laser, tape stripping, etc. Reduction of the pain and time of injections may lead to improved patient satisfaction and compliance, as well as reduced anxiety in populations of patients who require frequent or ongoing injections to treat their medical conditions. A needle-free delivery system offers the potential to address such issues. They may enhance safety, improve dosing accuracy, and increase patient compliance, particularly in self administration settings. The needle free injection technology does not involve the use of needles for delivery of pharmaceutical, instead it is delivered via a high-pressure stream of liquid which penetrates the site of injection. The needle free injection technology has been reported to overcome some of the risks of needles including reduced risk of needle stick injury, eliminated risk of disease transmission from reused needles, reduce scar tissue at the injection site caused by needle damage to the tissue, easier self-administration, etc. The needle free injection works on different technologies including spring system, gas propelled system, etc. The newly designed IntegriMedical Needle Free Injection Systems have overcome most of the risks posed by needles by incorporating disposable cartridges to avoid infection, introducing adjustable parameters selected according to skin site properties and thickness as well as the desired depth level intended to deliver the medication. IntegriMedical® Needle Free Injection System (NFIS) is intended to deliver drugs and biologics through intramuscular, or subcutaneous sites. Typical doses range from 0.1 ml to 0.5 ml and are delivered to various injection depths. The energy for the device comes from the compressed spring. When the compressed spring is released, it propels the plunger forward delivering the medication at high speed thus penetrating the skin.

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. STUDY OBJECTIVES

6.1.1. PRIMARY OBJECTIVE

To investigate the performance of the IntegriMedical Needle Free Injection System in subjects receiving COVID-19 booster dose to demonstrate non-inferiority as compared to subjects receiving the same booster dose with a conventional hypodermic needle and syringe.

6.1.2. SECONDARY OBJECTIVES

To understand the tolerability of the IntegriMedical Needle Free Injection System in terms of pain and comfort and to demonstrate non-inferiority of the needle free injection as compared to subjects receiving the same booster dose using a conventional hypodermic needle.

6.2. ENDPOINTS

6.2.1. PRIMARY ENDPOINTS

Change in immunoglobulin levels (IgG, IgA, and IgM) at 2 weeks of receiving booster dose of COVID-19 vaccine in comparison to baseline.

6.2.2. SECONDARY ENDPOINTS

Pain assessment using 100-mm VAS scores (0 mm = no pain at all; 100 mm = a lot of pain) immediately after each administration (before needle removal).

7. INVESTIGATIONAL PLAN

7.1. OVERALL STUDY DESIGN

7.1.1. VISIT 1 – BEGINNING OF STUDY – DAY 0

1. A written informed consent will be given to the subject.
2. Eligibility criteria shall be verified.
3. Pre-work activities shall be conducted within 3 days prior to the commencement of the study. Following pre-work activities shall be performed after obtaining a written informed consent from the subject.
    a. Demographic parameters like age, sex, height and weight will be recorded.
    b. Medical history will be recorded.
    c. The vital signs (including heart rate, respiratory rate, SpO2, blood pressure, and body temperature) and clinical examination of body systems shall be performed and recorded.
    d. Urine pregnancy test will be performed for female participants of childbearing potential.

e. A blood sample will be collected to determine immunoglobulin (IgG, IgA and IgM) concentration before vaccination.

4. The study shall be commenced with the following activities.
   a. Vaccine booster dose will be administered using one of the administering methods. This will be denoted as DAY 0.
   b. VAS Score worksheet shall be given to the patient to indicate the pain assessment.
   c. The subject will be kept under observation for 30 mins after vaccination.
   d. Adverse reactions observed by the subject or the doctor during the post vaccination observation period will be recorded.
   e. A diary card will be issued to record local and systemic adverse reactions observed in the post vaccination observation period.
   f. The subject will be instructed to bring the diary at the next visit.

7.1.2. VISIT 2 – END OF STUDY – DAY 14 (TOLERANCE OF +3 DAYS)

1. Recording the vital signs (including heart rate, respiratory rate, SpO2, blood pressure, and body temperature) and clinical examination of body systems was performed.
2. Adverse reactions observed by the subject or the doctor during the post vaccination observation period were reported.
3. A blood sample was collected to determine immunoglobulin (IgG, IgA and IgM) concentration after vaccination.

7.2. INCLUSION / EXCLUSION CRITERIA

7.2.1. INCLUSION CRITERIA:

1. Healthy subject of either gender ≥ 18 years of age.
2. Subjects who have completed 2 doses of vaccines were eligible for booster dose of vaccination as per CoWIN registration.
3. Subjects who were able to provide consent.
4. Subjects willing to allow storage and use of biological samples for future research.

7.2.2. EXCLUSION CRITERIA:

1. Known SARS-CoV-2 positive (RTPCR).
2. History of contact with a confirmed active SARS-CoV-2 positive patient within 14 days.
3. Febrile illness (temperature ≥ 38°C or 100.4°F) or any acute illness or infection within 4 weeks of enrolment.
4. Subjects with confirmed immunosuppressive or immunodeficiency disorder; or subjects on any immunosuppressive or immunostimulant therapy.

5. Subjects who have administered blood, blood containing products or immunoglobulins within the last 3 months or planned administration during the study.
6. Any other vaccine administration within the last 30 days or planned to be administered during the study period.
7. Pregnant and lactating women.
8. Hypersensitivity reaction or any serious adverse event after any vaccination
9. Uncontrolled Co-morbidities.
10. History of drug / alcohol abuse.
11. Covid-19 sign and symptoms.
12. History of skin diseases or chronic eczema and any coagulation disease.

Table 1: SCHEDULE OF ASSESSMENTS

Sr. No.	Assessment	Visit – 1	Visit – 2
1	Informed consent process	☒	☐
2	Eligibility criteria	☒	☐
3	Demographics (Age, Sex, Height, Weight and BMI)	☒	☐
4	Medical history	☒	☐
5	Clinical examination	☒	☒
6	Vital signs	☒	☒
7	Vaccination (Booster Dose)	☒	☒
8	Immunogenicity (IgG, IgA and IgM)	☒	☒
9	VAS Pain Score Assessment	☒	☐

7.3. TREATMENT PLAN

7.3.1. TREATMENTS ADMINISTERED AND IDENTITY OF INVESTIGATIONAL PRODUCT(S)

7.3.1.1. INVESTIGATIONAL MEDICAL DEVICE:

IntegriMedical® Needle Free Injection System (NFIS).

7.3.1.2. MODE OF ADMINISTRATION:

The COVID-19 booster doses will be administered through the Intramuscular route for both methods of administration.

7.3.1.3. ADMINISTRATION SCHEDULE:

Subjects will be randomly selected to receive the booster dose of COVID-19 vaccine, from which 50% of population got Covid-19 vaccines by hypodermic needle while 50% of population by NFIS.

7.3.2. METHOD OF ASSIGNING SUBJECTS TO TREATMENT GROUPS

METHODOLOGY: In this study, subjects will be randomly assigned to receive a booster dose of COVID-19 vaccine by one of the following methods:

1. Group T1: Hypodermic Needle and Syringe
2. Group T2: IntegriMedical Needle Free Injection System

A target of 80 subjects (with a minimum of 60 subjects) will be assigned to Group T1 and another 80 subjects (with a minimum of 60 subjects) will be assigned to Group T2. The randomization schedule will be generated using SAS® software (Version: 9.4 or higher; SAS Institute Inc., USA).

7.3.3. ANALYSIS OF TOLERABILITY MEASUREMENTS:

Tolerability shall be determined using a VAS score methodology.

7.3.4. STATISTICAL ANALYSIS:

Statistical analysis was performed using the SPSS Version 25 and Stata 15 software. All available data was used in the analysis.

8. PROTOCOL DEVIATIONS:

There were no protocol deviations noted in the conduct of the study. All volunteers complied to the various trial related procedures and the study was conducted in compliance with the study protocol.

9. CLINICAL STUDY RESULTS:

9.1. STUDY SUBJECTS:

160 healthy volunteers provided consent and were found eligible for participation in the study. All 160 participants were enrolled. However, only 138 volunteers were successfully administered with the booster dose due to various reasons unrelated to the study. Data generated on these 138 healthy volunteers who received both the intervention and control injections was analysed and forms the basis of this report.

9.2. DEMOGRAPHICS:

A total of 138 subjects received the booster dose under the study. 71 participants received booster dose by method T1 (Hypodermic Needle and Syringe), and 67 participants received the booster dose by method T2 (NFIS). The demographics of the participants for each group is as shown in

Table 2.

Table 2: Demographic distribution of subjects.

Demographics		Group T1		Group T2 (NFIS)	
		N (71)	%	N* (67)	%
Age	Mean (Years)	56.34		52.66	
	Range (Years)	24 - 87		20 - 85	
Sex	Female	38	53.5	36	53.7
	Male	33	46.5	31	46.3
Weight	Mean (Kg)	66.2		65.0	
	Range (Kg)	36.6 – 89		40.4 – 91	
Height	Mean (cm)	155.8		155.1	
	Min (cm)	143		132	
	Max (cm)	182		184	
BMI	Below 18.5	2	3.0	3	4.5
	18.5-24.9	18	26.9	21	31.3
	25.0-29.9	30	44.8	20	29.9
	Above 30.0	17	25.4	23	34.3

**Height and weight was not captured for 2 subjects. Hence, they were excluded from all analyses.*

9.3. PAST AND CURRENT MEDICAL HISTORY:

None of the study subjects reported any past / current medical history (Appendix B).

9.4. VITAL SIGNS:

Vital signs of the study subjects at screening are summarized in **Table 3**. The study subjects had 'normal' body temperature, heart rate, respiratory rate, and blood pressure at the time of screening.

Table 3: Subject characteristics at baseline - Vital signs.

Vital signs		Group T1	Group T2 (NFIS)
Systolic Blood Pressure (mm Hg)	Mean	125.25	124.61
	SD	3.72	5.32
	Min	118	105
	Max	132	137
	Interpretation Normal	**100%**	**100%**
Diastolic Blood Pressure (mm Hg)	Mean	75.92	76.94
	SD	6.07	6.58
	Min	67	65
	Max	89	96
	Interpretation Normal	**100%**	**100%**
Body Temperature (ºF)	Mean	97.6	97.5
	SD	0.8	0.9
	Min	95	94
	Max	99.1	99.4
	Interpretation Normal	**100%**	**100%**
Pulse Rate (bpm)	Mean	77.7	78
	SD	7.7	8.5
	Min	65	66
	Max	89	103
	Interpretation Normal	**100%**	**100%**
Respiratory Rate (bpm)	Mean	17.85	17.87
	SD	0.87	1.09
	Min	16	16
	Max	20	20
	Interpretation Normal	**100%**	**100%**

9.5. IMMUNOLOGY DATA AND ANALYSIS

For Hypodermic Needle and IntegriMedical Needle Free Injection System, pre and after dose Mean value of concentration of IgG, IgA and IgM is given in ***Table 4***.

Table 4: Summary statistics of concentration of IgG, IgA, and IgM

Immunological Parameters		**Group T1 (N=71)**			**Group T2 (NFIS) (N=67)**		
		Pre Dose	**Post Dose**	**P-value (paired t-test)**	**Pre Dose**	**Post Dose**	**P-value (paired t-test)**
IgG concen.	Mean	1083.32	1296.77	0.000	1107.93	1306.75	0.000
	STDEV	174.86	198.32		211.61	197.35	
IgA concen.	Mean	193.24	304.08	0.000	188.88	282.95	0.000
	STDEV	64.32	66.74		63.11	77.02	
IgM concen.	Mean	119.80	197.01	0.000	124.24	189.37	0.000
	STDEV	50.32	55.42		57.10	49.24	

Change in immunoglobulin levels ($p<0.05$, paired t-test) of IgG, IgA, and IgM concentration, before and after vaccination was found to be increased in both groups.

Distribution of immunoglobulin levels shown in Box plot (Shown in Error! Reference source not found.**, Graph 2, Graph 3**)

Interpretation of Box plot (Error! Reference source not found.**, Graph 2, Graph 3**) Box plots are used to show overall patterns of response for a group. They provide a useful way to visualise the range and other characteristics of responses for a large group. The middle “box” represents the middle 50% of the group. The range of concentration value from lower to upper quartile is referred to as the inter-quartile range. The middle 50% of population fall within the inter-quartile range.

The minimum is the far-left hand side of the graph, at the tip of the left whisker. Q1 is represented by the far-left hand side of the box, The median is represented by the vertical bar. The maximum is the end of the “whiskers”. Small circles or Filled circles are used for known outliers.

In Error! Reference source not found., IgG pre vaccination concentration was found to have a similar distribution for T1 and T2 group as median (middle of “box”) has

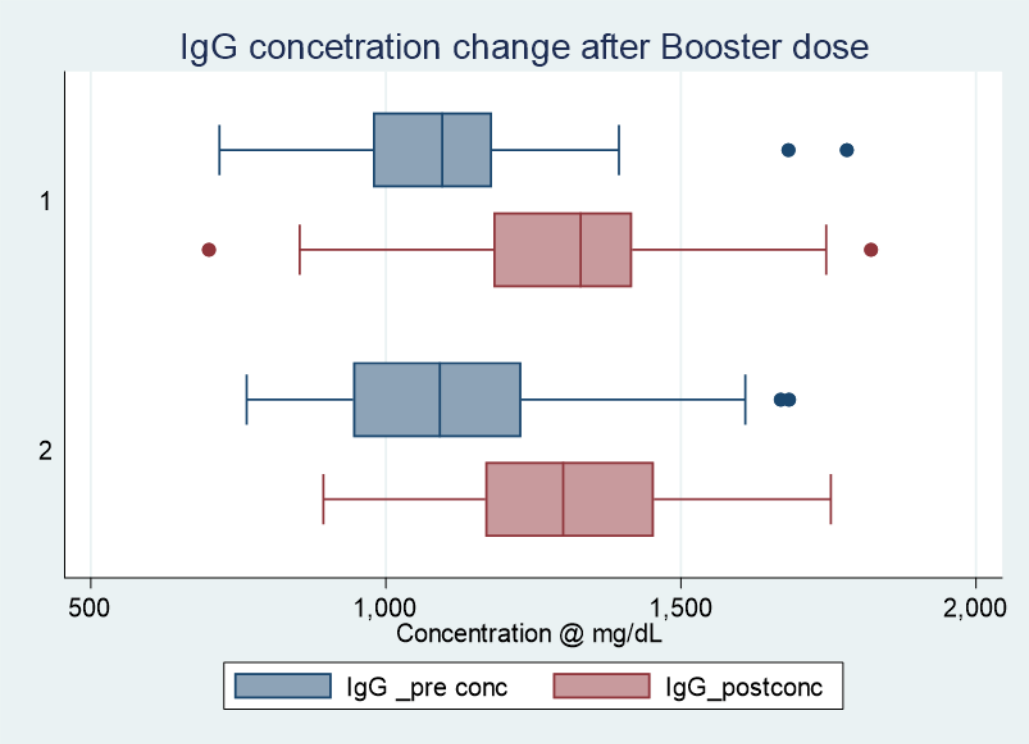
fall concentration around 1100mg/dl and 900 mg/dl for q1(left hand side of the box) and 1250mg/dl for q2(right hand side of the box), however post IgG concentration has been increased from pre concentration as median fall around 1300 mg/dl.

Similarly, IgA and IgM concentration level has been increased from pre to post vaccination for both groups.

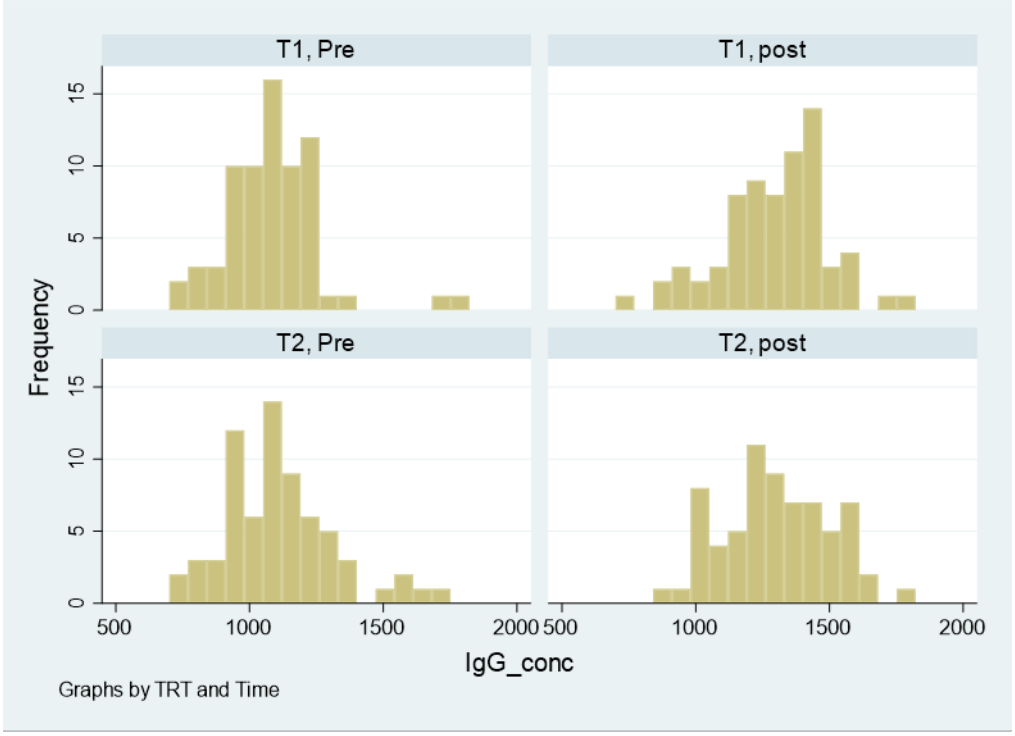
It is also observed that in T2 group (needle less vaccination) some of the cases achieved increased concentration level of IgG, IgA and IgM after vaccination as compared to T1 group. (Shown in Graph 1 A, Graph 2 A, Graph 3 A)

*Overall, the Immunoglobulin levels were at par or better than the hypodermic needle.

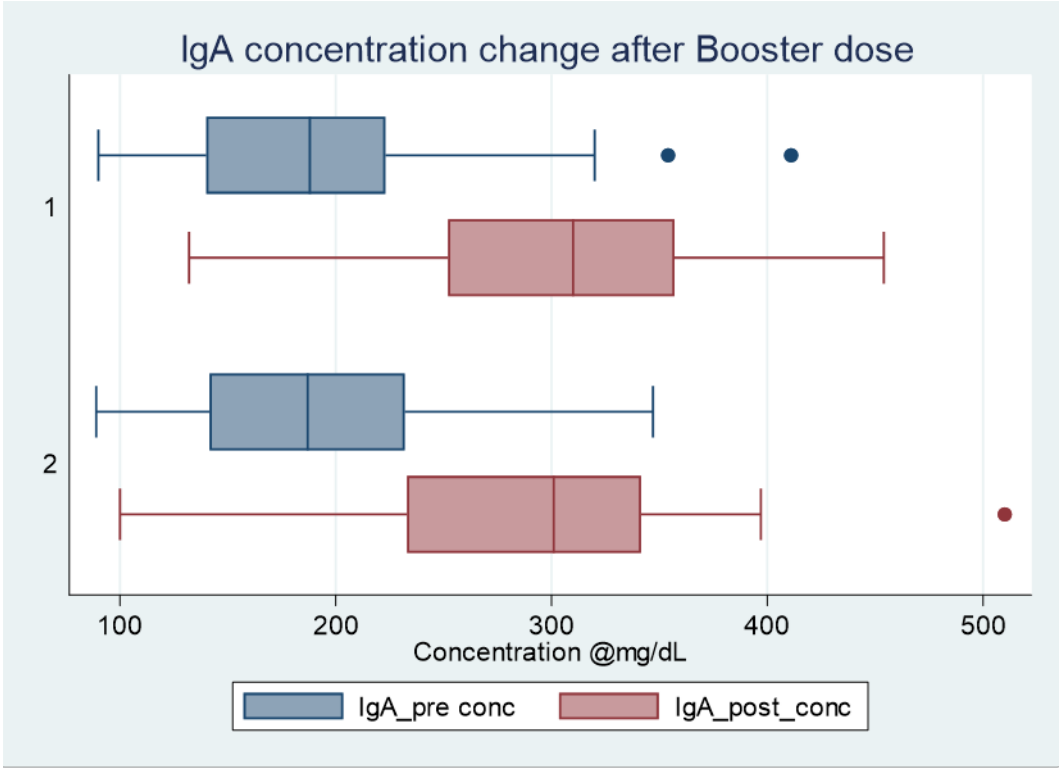
Graph 1



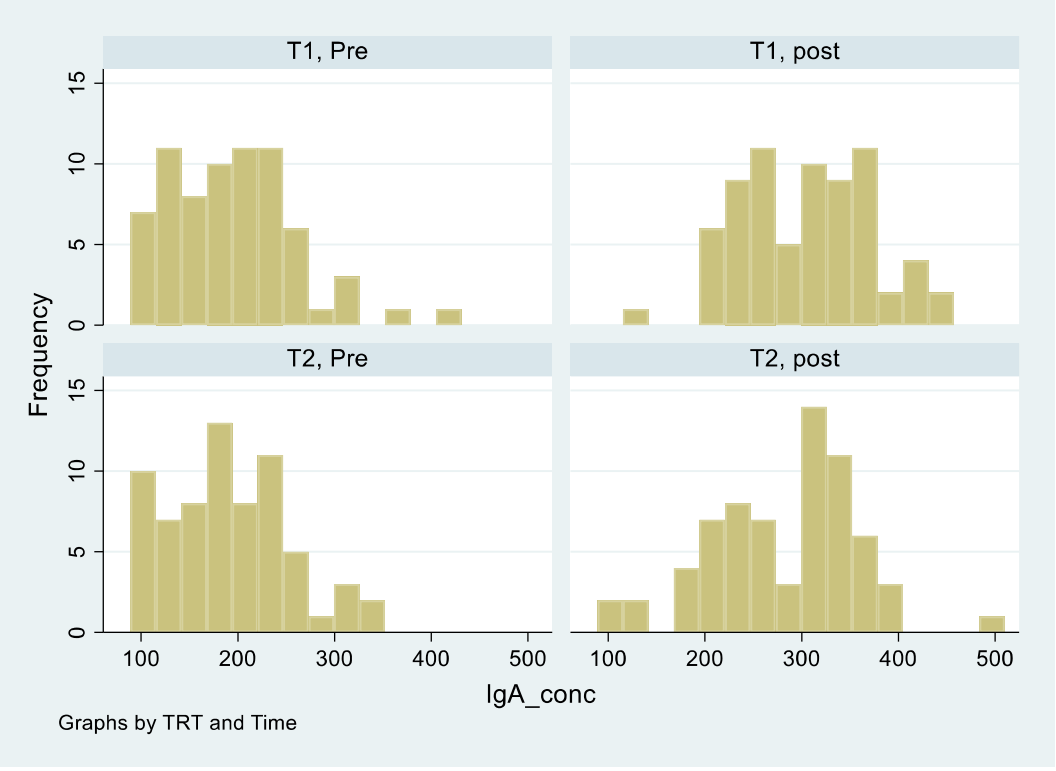
Graph 1 A : <u>Frequency distribution of IgG pre and post concentration of both groups:</u>



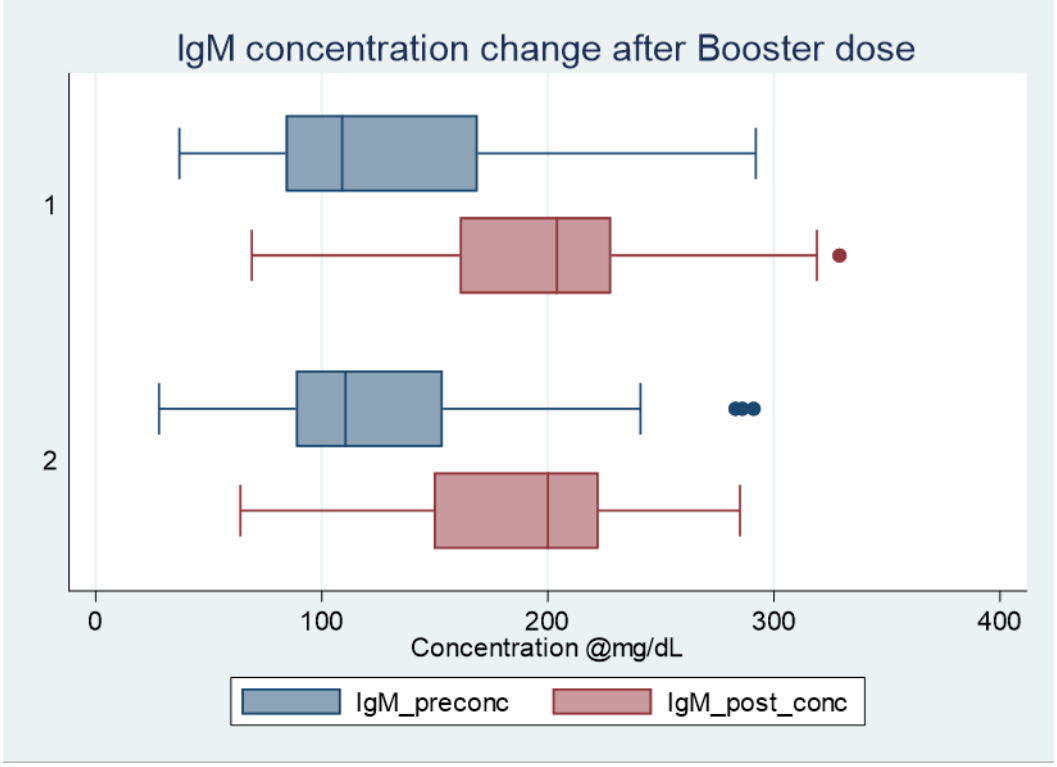
Graph 2



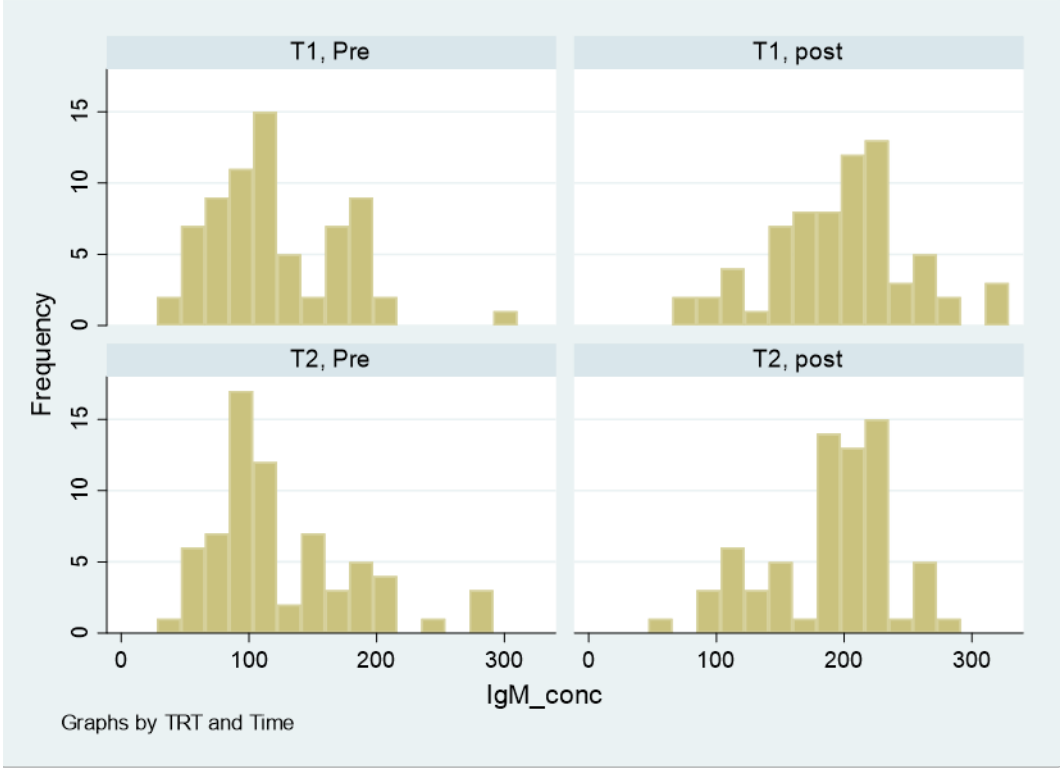
***Graph 2 A*: Frequency distribution of IgA pre and post concentration of both groups:**



Graph 3



***Graph 3 A*: Frequency distribution of IgM pre and post concentration of both groups:**



9.6. STATISTICAL INFERENCE FOR SIGNIFICANCE OF CHANGE:

To evaluate statistical significance in change found between Immunoglobin level after 2 weeks of booster dose. Mixed model has been fitted for immunoglobin level (concentration of IgG, IgA, and IgM) with respect to time (pre dose and post dose) and study population (T1 Vs T2). It was found that there was significant difference($P<0.05$) between pre dose and post dose concentration level of Immunoglobins IgG, IgA and IgM. IgG mean concentration of post dose was greater than 0.1754 units to pre dose concertation. IgA mean post dose concentration was found to be greater than 0.4561 units to pre dose concentration and IgM post dose concentration was greater than 0.5099 unit to mean pre dose concentration. The results show that for IgG concentration mean of T2 is 0.0124 unit greater than T1, and for IgM concentration mean of T2 is 0.0018 unit greater than to T1. Although Concentration of IgG, IgA and IgM are not significantly different for T1 and T2 group ($p>0.05$) (given in Table 5). Hence, it could be concluded that Increased change in immunoglobin level after 2 weeks of booster dose has been found similar for subjects dosed with Hypodermic Needle and IntegriMedical Needle Free Injection System.

Table 5: Model Estimation to show comparison of Change in Concentration of IgG, IgA, and IgM with respect to Dosing Method and baseline (Pre) concentration value.

Parameters compared	IgG concentration		IgA concentration		IgM concentration	
	Estimate	p-value	Estimate	p-value	Estimate	p-value
Dosing method T1 vs Dosing method T2	0.01248	0.528	-0.0525	0.159	0.0018	0.968
Time pre vs post	0.1754	0.000	0.4561	0.000	0.5099	0.000

10. SAFETY EVALUATION (RESULTS AND DISCUSSION):

Vital signs including body temperature, heart rate, blood pressure, and respiratory rate were measured after administration of needle free injection and needle injection post 30 min.

Table 6 below summarizes the data for both these groups at two time points defined.

Mean vital sign parameters after 30 mins of injecting with IntegriMedical Needle Free Injection System were not statistically (P >0.05) different from similar measurements taken after injecting with needle injection, except for systolic blood pressure that is because of pain due to injection with needle while no pain in needle less injection.

10.1. VITAL SIGNS (POST VACCINATION -After 30 min of Vaccination)

Table 6:

Demographics		Group T1	Group T2 (NFIS)
Systolic Blood Pressure (mm Hg)	Mean	129.83	128.18
	SD	2.76	3.72
	Min	122	118
	Max	138	136
Diastolic Blood Pressure (mm Hg)	Mean	81.07	80.07
	SD	4.5	4.88
	Min	72	72
	Max	90	88
Body Temperature (oF)	Mean	97.58	97.86
	SD	0.67	0.58
	Min	95	96.8
	Max	98.7	99
Pulse Rate (bpm)	Mean	80.81	81.19
	SD	6.10	5.92

	Min	68	70
	Max	90	98
Respiratory Rate (bpm)	Mean	17.77	17.71
	SD	0.68	0.92
	Min	17	16
	Max	20	20

10.2. VAS Pain Assessment Score (2 min post injections):

Pain score was assessed within 2 min following the Needle free injection and needle injection (**Table 7**). The percentage of those who reported no pain post needle free injection (86%) was significantly higher as compared with needle injection group (P <0.01). Mean pain score for the Needle free injection was 0.16 and for needle injection was found to be 2.6. The lower pain score measured post Needle free injection as compared with needle injection was statistically significant (P <0.01; t test for comparison of 2 means). Hence, tolerability of needle free injection was determined through the VAS Pain Assessment score.

Table 7: VAS pain score assessment following Needle Injection and Needle free injections.

	Group T1 (N=71)	**Group T2 (NFIS) (N=67)**	**P-value**
0.00 (No pain)	0(0%)	59(86.76%)	0.000
1.00	5(7.14%)	8(11.76%)	
2.00	23(32.85%)	0(0%)	
3.00	37(52.85%)	1(1.4%)	
4.00	5(7.14%)	0(0%)	
Mean	2.6	0.16	
SD	0.73	0,47	
Min	1	0	
Max	4	3	

11. References

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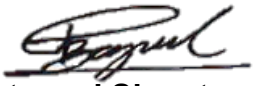
12. Signature Page:

Clinical Study Report Prepared By:	
I have prepared and read this report and confirm that to the best of my knowledge it accurately describes the conduct and result of the study.	
Medical Writer	**1) Name:** Dr. Shrikant Suryavanshi Manavata Clinical Research Institute, Behind Shivang Auto, Mumbai Naka, Nashik, 422002.  **Date and Signature: 18-May-2022** **2) Name:** Mr. Roshan Patil Manavata Clinical Research Institute, Behind Shivang Auto, Mumbai Naka, Nashik, 422002.  **Date and Signature**: **18-May-2022**
Biostatistician	**Name:** Mr. Dilesh Bagul  **Date and Signature**: **18-May-2022**
Clinical Study Report Approved By:	
I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and result of the study.	
Sponsor Representative	**Name:** Scott McFarland **Address:** INTEGRIMEDICAL LLC 805 N,4th AVENUE, UNIT 903, PHOENIX. ARIZONA 85003 **Date and Signature:**