Immunogenicity & Safety Study of Covid Vaccine in Children, India

Title: A pilot open label, randomized study to investigate the tolerability, acceptability and safety of IntegriMedical Needle Free Injection System in subjects receiving dose of COVID-19 Corbevax Vaccine.

CONFIDENTIALITY STATEMENT

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Principle Investigator:	Dr. Rajnish Nagarkar
Sponsor:	IntegriMedical
Sponsor Authorized signatory:	Scott McFarland
Date of study initiated:	12 Apr 2022
Date if study completed:	25 Apr 2022
Date of early study termination if any:	Not applicable
Date of Clinical study report:	05 June 2022
Name of investigational medical device:	IntegriMedical Needle Free Injection System
Name of COVID-19 vaccine:	Corbevax
Version:	1.0
Protocol identification:	NFIS.2022,02 Version 1.0
Name and affiliation of principle investigator:	Dr. Rajnish Nagarkar, Manavata Clinical Research Institute, Behind Shivang Auto Mumbai Naka, Nashik -422002, Maharashtra, India
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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
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
WHO	World Health Organization
LAR	Legally Acceptable Representative
NFIS	Needle Free Injection system

2. INDICATION STUDIED

Patient's tolerance to COVID-19 Corbevax vaccine when administered using the IntegriMedical Needle Free Injection System.

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/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 is very common and the oldest way to overcome the physical barrier. A 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 and instead 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 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.

6. STUDY OBJECTIVE AND ENDPOINTS

6.1. STUDY OBJECTIVE

To investigate the tolerability, acceptability, and safety of IntegriMedical Needle Free Injection System to demonstrate its performance.

6.2. STUDY ENDPOINTS

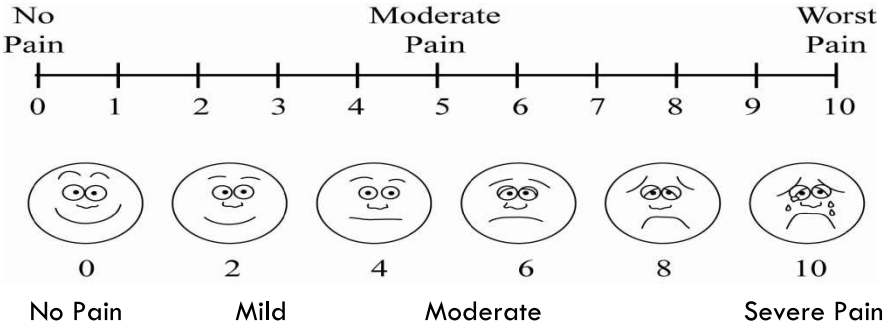
6.2.1. PRIMARY ENDPOINTS

Injection site monitoring including Redness, Swelling, Itching.

6.2.2. SECONDARY ENDPOINTS

Pain assessment using 10-mm VAS scores (0 mm = no pain at all; 10 mm = a lot of pain) immediately after each administration (before needle removal)

Visual Analogue Scale (VAS)



Correlation between Visual and verbal scale:

1-3 = mild pain; minimal impact on ADL's

4-6 = moderate pain; moderate impact on ADL's

7-10 = severe pain; major impact on ADL's

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 will be verified.
3. Pre-work activities shall be conducted 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. Vital signs (including heart rate, respiratory rate, SpO2, blood pressure, and body temperature) recording and clinical examination of body systems will be performed.
4. The study shall be commenced with the following activities.
   a. Covid 19 Vaccine dose will be administered using IntegriMedical NFIS device.
   b. VAS Score worksheet shall be given to the patient to indicate the pain assessment.
   c. Subject will be observed for 30 minutes after vaccination.
   d. Adverse reaction either volunteered by the subject or noticed by the doctor during the post vaccination observation period will be reported.
   e. A diary card will be issued to record local and systemic adverse reactions that are observed during the post vaccination observation period.
   f. The subject will be instructed to bring the diary card during subsequent visit.

7.1.2. VISIT 2 (DAY 3):

1. Vital signs (including heart rate, respiratory rate, SpO2, blood pressure, and body temperature) recording and clinical examination of body systems will be performed.
2. Adverse reaction either volunteered by the subject or noticed by the doctor during the post vaccination observation period will be reported.
3. Vaccination site monitoring will be conducted.

7.1.3. VISIT 3 (DAY 7):

1. Vital signs (including heart rate, respiratory rate, SpO2, blood pressure, and body temperature) recording and clinical examination of body systems will be performed.
2. Adverse reaction either volunteered by the subject or noticed by the doctor during the post vaccination observation period will be reported.
3. Vaccination site monitoring will be conducted.

7.1.4. VISIT 4 (DAY 11):

1. Telephonic follow up
2. Overall health status reported
3. Adverse Events (Local injection site)
    a. Pain
    b. Redness
    c. Swelling
    d. Itching
4. Adverse Events (Systemic)
    a. Fever
    b. Headache
    c. Tiredness
    d. Nausea
    e. Vomiting

7.2. INCLUSION/EXCLUSION CRITERIA

7.2.1. INCLUSION CRITERIA

1. Healthy subject of either gender 12 to 14 years of age group.
2. Must be eligible for 1st and 2nd of Corbevax vaccination as per Cowin registration.
3. Ability to provide consent.

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 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. Hypersensitivity reaction or any serious adverse event after any vaccination
8. Uncontrolled Co-morbidities.
9. History of drug / alcohol abuse.
10. Covid-19 sign and symptoms.
11. History of skin diseases or chronic eczema and any coagulation disease.

Table 1: SCHEDULE OF ASSESSMENTS

Sr. No	Assessment	Visit-1	Visit-2	Visit-3	Visit-4
1	Informed consent process	☒	☐	☐	☐
2	Eligibility criteria	☒	☐	☐	☐
3	Demographics (Age, Sex, Height, Weight and BMI)	☒	☐	☐	☐
4	Medical history	☒	☐	☐	☐
5	Clinical examination	☒	☒	☒	☐
6	Vital signs including SpO2 a	☒	☒	☒	☐
8	Vaccination (Corbevax vaccine)	☒	☐	☐	☐
9	Vaccination site Monitoring	☒	☒	☒	☐
10	Overall, Health status	☐	☐	☐	☒

7.3. TREATMENT

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

Intramuscular route.

7.3.1.3. ADMINISTRATION SCHEDULE

Subjects were randomized for receiving dose of COVID-19 vaccine, considering all Subjects will get Covid_19 vaccines by NFIS.

7.3.2. METHODOLOGY

This protocol describes tolerability, acceptability and safety of IntegriMedical Needle Free Injection System in subjects receiving dose of COVID-19 Corbevax vaccine.

7.3.3. ANALYSIS OF TOLERABILITY MEASUREMENTS-

Tolerability was determined using a VAS score respectively.

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.

7.3.5. 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.

8. SUBJECT DISPOSITION

8.1. STUDY SUBJECTS

Study subjects a total of 60 healthy volunteers providing consent and found eligible for participation in the study were enrolled.

All 60 volunteers successfully completed the study with Vaccination. Data generated on these 60 healthy volunteers who received both the intervention and control injections form the basis of this report.

8.2. DEMOGRAPHICS

Total 60 Subjects has been received Corbevax vaccine under the study. 48% of subjects are 13 years old while 21.7% are 12 years old and 30.0% are from 14 years old age group. 60% female and 40% male were administered with the vaccine through IntegriMedical Needle Free Injection System. (Presented in **Table *2***)

Table 2 . Demographic distribution of subjects.

Demographics		N (60)	%
Age	Mean	13.08	
	SD	0.72	
Age group	12 Years	13	21.7
	13 years	29	48.3
	14 years	18	30.0
Sex	Female	36	60
	Male	24	40
Weight(kg)	Mean	42.20	
	SD	6.64	
	Min	26.6	
	Max	59.9	
Height(cm)	Mean	147.44	
	SD	7.29	
	Min	130	
	Max	162	

8.3. PAST AND CURRENT MEDICAL HISTORY

None of the study subjects reported any past / current medical history

8.4. 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 (Pre vaccination).

Vital signs		Summary Statistics
Systolic Blood Pressure (mm Hg)	Mean	123.82
	SD	5.21
	Min	105
	Max	137
	Interpretation normal	**100%**
Diastolic Blood Pressure (mm Hg)	Mean	76.62
	SD	6.42
	Min	65
	Max	96
	Interpretation normal	**100%**
Body Temperature (°F)	Mean	97.69
	SD	0.76
	Min	95
	Max	99.4
	Interpretation normal	**100%**
Pulse Rate (bpm)	Mean	77.86
	SD	9.60
	Min	65
	Max	103
	Interpretation normal	**100%**
Respiratory Rate (bpm)	Mean	17.85
	SD	0.82
	Min	16
	Max	20
	Interpretation normal	**100%**

9. SAFETY EVALUATION (RESULTS AND DISCUSSION)

Vital signs including body temperature, heart rate, blood pressure, and respiratory rate were measured after administration of vaccine using IntegriMedical Needle Free Injection System post 30 min, at visit 2 and visit 3 to know the overall clinical status of subjects.

9.1. VITAL SIGNS (POST VACCINATION)

Table 4 below summarizes the data for vital sign at different time point after vaccination.

Table 4: Post Vaccination Vital Signs

Vital signs		After 30 min of vaccination	Follow up Visit2	Follow up Visit 3
Systolic Blood Pressure (mm Hg)	Mean	128.07	121.47	121.85
	SD	5.21	2.77	2.72
	Min	118	117	117
	Max	144	126	128
	Interpretation Normal	**100%**	**100%**	**100%**
Diastolic Blood Pressure (mm Hg)	Mean	80.95	80.35	77.6
	SD	4.95	4.07	3.82
	Min	72	72	72
	Max	88	89	85
	Interpretation Normal	**100%**	**100%**	**100%**
Body Temperature (ºF)	Mean	97.8	97.29	96.94
	SD	0.55	1.11	1.36
	Min	96.8	95	91
	Max	98.8	99.6	98.9
	Interpretation Normal	**100%**	**100%**	**100%**
Pulse Rate (bpm)	Mean	82.53	81.28	80.58
	SD	6.55	4.31	4.42
	Min	68	73	74
	Max	98	89	89
	Interpretation Normal	**100%**	**100%**	**100%**
Respiratory Rate (bpm)	Mean	17.7	18.0	18.6
	SD	0.76	1.15	1.03
	Min	17	16	17
	Max	20	20	20
	Interpretation Normal	**100%**	**100%**	**100%**

9.2. VAS PAIN ASSESSMENT SCORE (2 MIN POST INJECTION)

Pain score was assessed within 2 min following the IntegriMedical Needle Free Injection System.

(**Table *5***). The percentage of those who reported no pain post Needle Free Injection System was 46.7% while 26% felt mild pain with VAS score 1.00 and remaining 26.7% felt mild pain with VAS score 2.00 and 3.00.

Table 5: VAS pain score assessment following Needle free injections

	N	Percentage
00(No Pain)	28	46.7
1.00	16	26.7
2.00	12	20.0
3.00	4	6.7
Mean	0.87	
SD	0.96	
Min	0	
Max	3	

9.3. ACCEPTABILITY ASSESSMENTS

As per VAS Pain Assessment of 2 min post injections. The percentage of those who reported no pain post needle free injection was 46.7% while 53.3% felt mild pain (**Table *5***). Also, vaccination site Monitoring was done on visit-2(day-3) and visit-3(Day-7). For 93.3% subjects, injection site monitoring was observed normal. On Visit-4 / day-11 Telephonic visit for overall health status recorded that all the subjects were found normal. There was not any AE noted, and all subjects were stable.

9.4. ACCEPTABILITY CONCLUSIONS

IntegriMedical Needle free injection system was well accepted. None of the subjects receiving this injection complained of any moderate and severe pain, redness, swelling, itching at the injection site. More than 90% of the respondents indicated that the local reaction and pain was totally acceptable. As per verbally communicated by subjects during this subsequent visits NFIS injection had a significantly higher satisfaction percentage. A higher percentage (94%) responded that they did not feel anxious about receiving the IntegriMedical Needle Free Injection System.

10. References

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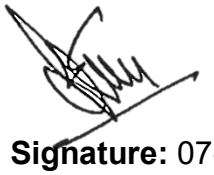
11. SIGNATURE PAGE

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:** 07-Jun-2022 **2) Name:** Mr. Roshan Patil Manavata Clinical Research Institute, Behind Shivang Auto, Mumbai Naka, Nashik, 422002.  **Date and Signature:** 07-Jun-2022
Biostatistician	**Name:** Mr. Dilesh Bagul  **Date and Signature:** 07-Jun-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.	
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Investigator	**Name:** Dr. Rajnish Nagarkar Manavata Clinical Research Institute, Behind Shivang Auto, Mumbai Naka, Nashik, 422002.  **Date and Signature:**