

## Original Research Article

# Influence of COVID-19 on cardiac clinical trials: an observational study from clinical trials registry India

S. Saradha<sup>1</sup>, Kamalam P. R.<sup>1\*</sup>, Arunkumar R.<sup>1</sup>, P. Indhra<sup>2</sup>

<sup>1</sup>Department of Pharmacology, <sup>2</sup>Department of Community Medicine, Chettinad Hospital and Research Institute, Chennai, Tamil Nadu, India

**Received:** 11 November 2022

**Revised:** 12 December 2022

**Accepted:** 11 January 2023

**\*Correspondence:**

Kamalam P. R.,

E-mail: [prkamalam14@gmail.com](mailto:prkamalam14@gmail.com)

**Copyright:** © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

### ABSTRACT

**Background:** Clinical trials on drugs for cardiac diseases becomes essential as coronary artery disease is the most common cause of death globally. This study observes if COVID-19 has influenced the number and pattern of cardiac trials conducted prior to and during COVID-19 from clinical trial registry of India web portal.

**Methods:** The CTRI website was searched for the key words “myocardial infarction”, “heart failure”, “cardiac arrhythmia”, “myocarditis” and “pulmonary embolism” and the trials registered were reviewed. Data was collected for every trial registered from 1st January 2019 to 16th April 2021.

**Results:** 156 Clinical trials were registered in the specified period. Of which 104 were on myocardial infarction, 24 on pulmonary embolism, 13 on cardiac arrhythmia, 9 on cardiac failure and 6 on myocarditis. Among the 156 trials, 98 were observational, 53 were interventional and 5 Post marketing surveillance type. 83% of the interventional studies were randomized controlled trials. Karnataka had the maximum number of trials registered 57, followed by Delhi 37 trials. 135 trials were done in India alone and 21 trials involved other countries as well. Among the interventions, 25 were drugs, 19 medical devices, 2 cardiac rehabilitations, 2 based on Yoga, 95 trials mentioned their intervention as NA and remaining 13 were adjuvant, standard treatment, physiotherapy, homeopathy and others.

**Conclusions:** It was observed that COVID-19 pandemic did not have an influence on the conduct and pattern of cardiac trials in India.

**Keywords:** Cardiac trials, Myocardial infarction, Heart disease, CTRI, COVID-19

### INTRODUCTION

Coronary artery disease is the most common cause of death globally as per the WHO: cause-specific mortality, estimates.<sup>1</sup> 16.59% deaths around the world are due to cardiac disease and is the first cause of death followed by stroke (10.16%) and chronic obstructive pulmonary disease (5.35%). India is experiencing a shift from communicable to non-communicable disease as the leading cause of death. The most prominent non-communicable disease is cardiac disease which accounts for 28.1% deaths in India.<sup>2</sup> Hence clinical trials on drugs for cardiac diseases becomes essential with the need for

newer drugs for effective management of cardiac diseases. These trials are registered in clinical trials registry India (CTRI).<sup>1</sup> This study is planned to observe if COVID-19 has influenced the number of trials, the pattern of trial and derive other information regarding the cardiac trials conducted prior to and during COVID-19 from CTRI web portal.

#### Objectives

Objectives of current study was to analyse the characteristics of clinical trials specific to Cardiac diseases

prior to and during COVID-19 from the web portal of CTRI.

**METHODS**

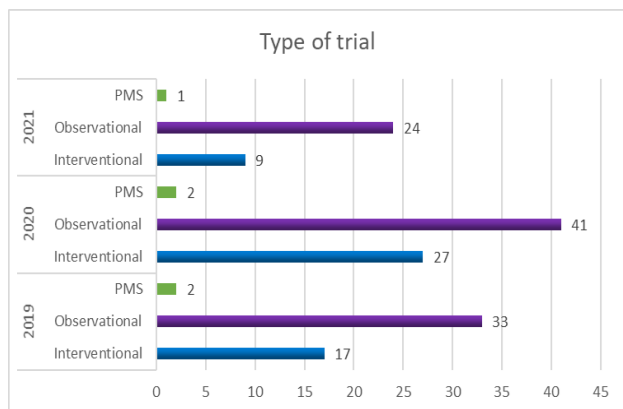
The CTRI web portal search was carried out with the key words “myocardial infarction”, “heart failure”, “cardiac arrhythmia”, “myocarditis” and “pulmonary embolism” and the trials registered were reviewed. Data was collected for the following categories for every trial registered from 1 January 2019 to 16 April 2021. Type of trial (interventional/observational), type of study (allopathic/other system of medicine), study design, funding nature, countries of recruitment, study sites, regulatory clearance, drugs under investigation, selection criteria for subjects, outcomes, sample size, phase of drug development, status of the study (ongoing/completed/not initiated) and publication details.

**Statistical analysis**

The data was tabulated in a Microsoft Excel Version 11 and frequency analysis was done. For mapping MS Paint Version 6.1 was used.

**RESULTS**

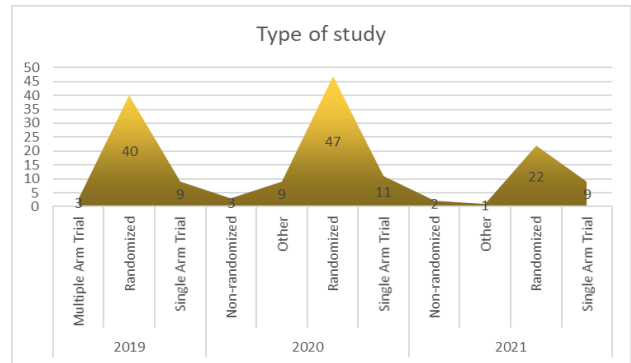
A total of 156 Clinical trials were registered in the specified period. Of the 156 studies, 104 were on Myocardial infarction, 24 on Pulmonary embolism, 13 on Cardiac arrhythmia, 9 on Cardiac failure and 6 on Myocarditis. Among the 156 trials, 98 were observational, 53 were interventional and 5 Post marketing surveillance type (Figure 1).



**Figure 1: Type of trial.**

Total 83% of the interventional studies were randomized controlled trials. 0.09% of the observational studies (9 out of 98) were cohort studies, 0.05% studies were cross sectional studies and the remaining studies follow various other designs. The interventional studies were categorized as Randomized, Parallel group, Placebo controlled trial, Active controlled trial and other types. The observational studies were categorized as cohort, cross sectional, case control studies and other types (Figure 2). The registration

of first trial selected was on 4 January 2019 and 156 trials were registered till 16 April 2021. 52 trials in 2019, 70 in 2020, 34 in 2021 till 16 April 2021.



**Figure 2: Type of study.**



**Figure 3: Study sites.**

**Study sites**

It was categorized into state wise distribution of studies registered in India. Among the states, Karnataka had the maximum number of trials registered 57, followed by Delhi 37 trials. States of Maharashtra, Tamil Nadu, Gujarat, Chhattisgarh had respectively 24, 23, 23, 22 trials. The other states and UT’s had trials ranging from 1 to 20. The states such as Jharkhand, Manipur, Mizoram, Nagaland, Tripura and union territories, Andaman and Nicobar, Ladakh, Lakshadweep, Dadra and Nagar Haweli did not have any trials registered (Figure 3). The Nature of funding was categorized as Government, Private, Self and Others. It was observed that Government had sponsored 70 trials, private institutions 59 trials and 27 trials were self-financed (Figure 4).

**Countries of recruitment**

This information was categorized as trials conducted in India alone and those trials involving other countries as

well.135 trials were done in India alone and 21 trials involved other countries. 15 studies on Myocardial infarction and 3 each on Cardiac arrhythmia and Pulmonary embolism were international trials involving countries other than India. The other countries were US, UK, Italy, Spain, Germany, Japan, Australia, etc.

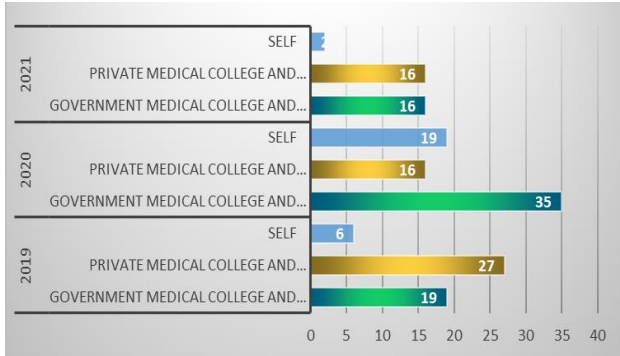


Figure 4: Nature of funding.

**Phase of drug development**

The categorization of phase of clinical studies included 7 categories such as Phase I, Phase II, Phase II/III, Phase III, Phase III/IV, Phase IV/Post marketing surveillance and not applicable (NA). Majority of the trials had specified the Phase of drug development as NA. Phase III being the second most common category (Figure 5).

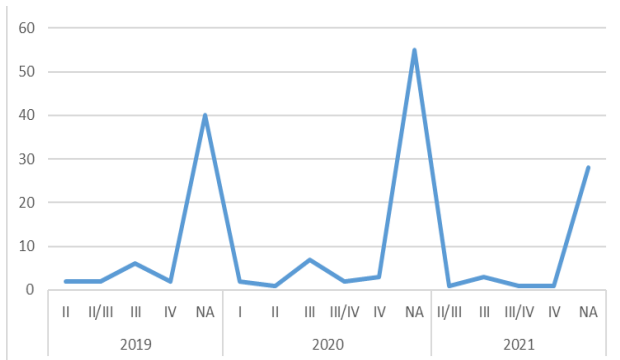


Figure 5: Phase of drug development.

**Regulatory clearance**

It was based on whether Drugs Controller General of India (DCGI's) approval was obtained or not applicable. It was observed that only 6 trials in 2019 and 2020 each and 1 trial in 2021 were DCGI approved.45 trials in 2019, 62 trials in 2020 and 33 trials in 2021 had mentioned that regulatory clearance is not applicable (Figure 6).

**Sample size**

The trials were categorized as sample size less than 500, 500-1000 and more than 1000. It was observed that 39 studies in 2019, 54 studies in 2020 and 22 studies in 2021

had sample size less than 500. 18 studies in total had sample size above 1000 and 21 studies had sample size between 500 and 1000 (Figure 7).

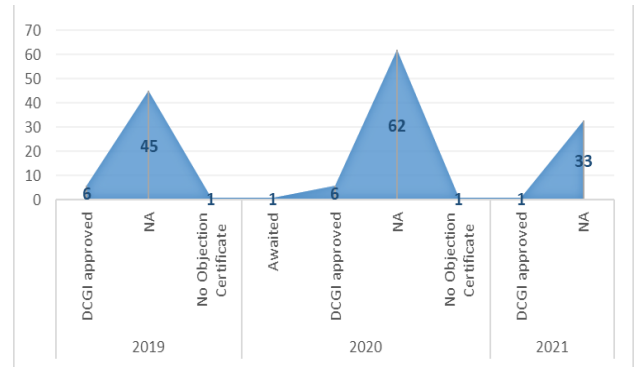


Figure 6: Regulatory clearance.

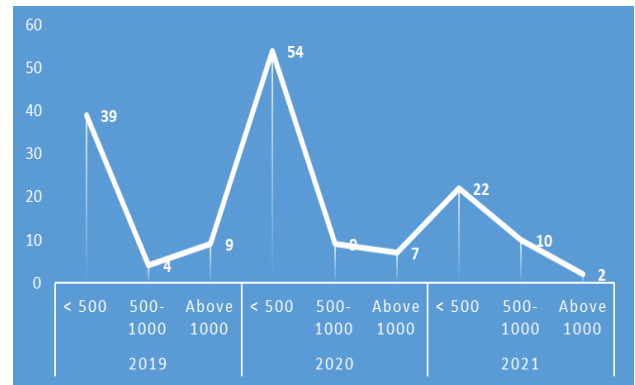


Figure 7: Sample size distribution.

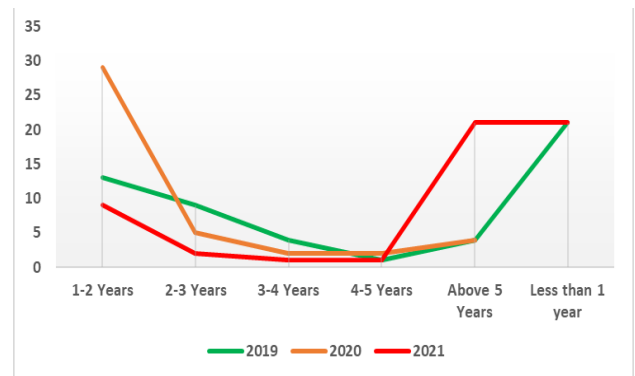


Figure 8: Trial duration.

**Trial duration**

The trial duration was segmented as less than 1 year, 1-2 years, 2-3 years, 3-4 years, 4-5 years and more than 5 years. It was observed that 30 trials in 2021, 14 trials in 2020 and 10 trials in 2019 were of the duration 1-2 years. Twenty studies in 2021 and 5 studies in 2019 and 2020 each were of the duration more than 5 years. Most other trials were of the duration between 2-4 years (Figure 8).

**Study status**

Out of the 156 trials, only 4 were completed and all were myocardial infarction studies. Other studies were either open to recruitment of subjects or not yet started recruitment.

**Publication details**

Two studies were published, the remaining not yet published or data on publication not available. Both these studies were on myocardial infarction.

**Test and control interventions**

The interventions were classified based on whether they were drugs, medical devices, cardiac rehabilitation, yoga, adjuvant, standard treatment of care, pharmaceutical care, surgical, physiotherapy, homeopathy, mesenchymal stem cells, not applicable or others. 25 were drugs, 19 medical devices, 2 cardiac rehabilitations, 2 based on Yoga, 95 trials mentioned their intervention as NA and remaining 13 were adjuvant, standard treatment, physiotherapy, homeopathy and others.

**Table 1: Interventions for myocardial infarction.**

Interventions studied for myocardial infarction				
Vitamin D	Tranexamic acid	Esmolol	Propofol	Ranolazine
Edoxaban	Semaglutide	Sirolimus-eluting coronary stent system	Arjuna Ksheerpaka	Percutaneous coronary intervention
Parasternal intercostal nerve block	Comprehensive Cardiac rehabilitation	Drug molecule: LNP023	Nagabala- Arjunadi Yoga	Structured Patient Education
Everolimus eluting cobalt chromium coronary stent system	Optical coherence tomography	Transradial access	Intravenous paracetamol with magnesium sulphate and dexamethasone	Intravenous paracetamol with tramadol
Angiogram - fractional flow reserve	Clopidogrel	Ticagrelor	Angiotensin Receptor Nephrolysin Inhibitor	Edoxaban
Silicone coated braided polyester suture	Bisoprolol	Tirzepatide	Post Stenting Dilatation	CHIP* – Percutaneous Intervention
Comprehensive nursing intervention program	Tenecteplase	Sonothrombolysis	Rivaroxaban	Atorvastatin

Complex high-risk and indicated revascularization using percutaneous coronary intervention (CHIP-PCI).

**Table 2: Interventions for pulmonary embolism and cardiac arrhythmia.**

Parameters				
Interventions studied for pulmonary embolism				
Edoxaban	Adjuvant Chemoradiotherapy	Foam Sclerotherapy	Radiofrequency Ablation	Enoxaparin
Pulmonary Endarterectomy	Apixaban	Tranexamic Acid	Mesenchymal Stem Cells	
Interventions studied for cardiac arrhythmia				
Double Loop catheter and HD Mapping Catheter	Biocalculus	Terlipressin and Norepinephrine	Servo-controlled Whole-Body Cooling	Early ambulation

**Methods of randomization**

The types of randomizations were computer generated randomization, stratified block randomization, coin toss, lottery, toss of dice, shuffling cards, permuted block randomization, adaptive randomization, random number table, stratified randomization, not-applicable and others.

**Concealment of treatment**

Sequentially numbered sealed opaque envelopes, coded identical containers, case record numbers and Centralized concealment were the methods of concealment.

## Study outcomes

The outcomes were based on the disease studied. The incidence of serious adverse effects like major bleeding, thrombo-embolic events like stroke, transient ischemic attacks and systemic embolism and myocardial infarction were the outcomes for pulmonary embolism. Changes in sequential organ failure assessment (SOFA) score, incidence of congestive cardiac failure, left ventricular dysfunction, cardiogenic shock and recurrent angina were few outcomes observed for Cardiac arrhythmia studies. Imaging outcome, clinical outcomes in terms of target vessel failure, cardiac death, ischaemia driven cardiac revascularization and improvement in left ventricular ejection fraction are some outcomes assessed for Myocardial infarction. Death due to cardiac event, symptomatic congestive cardiac failure, requirement of coronary intervention and development of an arrhythmia were few outcomes observed in Cardiac failure trials.

## PG dissertation

Among the 156 trials, 54 were studies conducted by Post graduates as dissertation and 102 were others.

## DISCUSSION

The COVID-19 pandemic has shifted resources from other non-COVID infectious, cardiovascular and lifestyle disease research to COVID-19. This article analyses the influence of COVID-19 on the registry and conduct of cardiac trials from Clinical Trial Registry India database. 156 clinical trials selected from CTRI web portal based on key words were analysed for various criteria year wise. It was observed that there wasn't a huge decline in cardiac trials during the pandemic as 2020 had 70 trials registered which was more than 52 in 2019.

During the pandemic, Government sponsored trials outnumbered private or self-funded trials. 35 trials were Govt sponsored in 2020 while 19 in 2019 and 16 in 2021. Among the states, Karnataka and Delhi had been the site with higher number of trials registered. 57 cardiac trials in Karnataka and 37 in Delhi. The pandemic didn't influence the type of trial and it was Observational studies that predominated the Interventional studies before and during the pandemic. 13% of the trials were International and remaining confined to India. The various interventions studied for different cardiac diseases are tabulated in (Table 1-2). Selvaraj et al analysed the characteristics of cardiovascular clinical trials before COVID-19 and COVID-19 trials with a Cardiovascular focus in United States as on May13, 2020, with data extracted from [clinicaltrials.gov](http://clinicaltrials.gov).<sup>3</sup> Among the pre-COVID-19 cardiovascular trials, the most common trial was on heart failure (29%) followed by electrophysiology (25%) and interventional cardiology (18%). Whereas in our study analysing Indian trial data, 67% trials focussed on myocardial infarction followed by pulmonary embolism (15%), cardiac arrhythmia (8%) and heart failure only 6%.

This shows the difference in trial pattern among the countries. The frequent trial sites in United States were New York, California and North Carolina and in India, Karnataka and Delhi were the popular trial sites. There aren't similar studies on Cardiac clinical trials in India. This study highlights the characteristics of Cardiac trials registered in Clinical Trial Registry of India from 1 January 2019 till 16 April 2021. Among the 156 cardiac trials registered, 104 were on Myocardial infarction, 24 on Pulmonary embolism, 13 cardiac arrhythmias, 9 heart failure and 6 on Myocarditis. 63% trials were Observational in nature, 34% Interventional and 3% Post marketing surveillance. 70% were Randomized controlled trials and the rest non randomized. Karnataka registered maximum number of trials, 57 and next Delhi 37 trials. 45% trials were Government sponsored and the rest by private institutions or self-funded. It was observed that the COVID-19 pandemic did not reduce the registry of cardiac trials and 2020 had more trials than 2019. Bhapkar et al have analysed the AYUSH studies for COVID-19 registered in CTRI from first February to 24 August 2020.<sup>4</sup> Among the 197 studies registered 191 were interventional. Government had sponsored more trials than private sectors similar to the current study. Maharashtra had the maximum trial sites for COVID-19 whereas Karnataka had the highest number of cardiac trials enrolled. This could have been due to the increase in number of COVID-19 infected cases in Maharashtra. Rao et al reviewed the COVID-19 clinical trials registered in CTRI till 5<sup>th</sup> June, 2020. A total of 122 trials were analysed and it was observed that 67 studies were on traditional medicine, 42 on modern medicine and 13 miscellaneous.<sup>5</sup> Most of the trials were either Phase 3 or Phase 2 similar to the current study. Among the traditional medicine trials, 45 were Ayurveda, 14 Homeopathy and 8 were on Yoga, Unani and Siddha. Out of the 42 Modern medicine trials, 28 were repurposed drugs. Abinaya et al reviewed the COVID-19 trials from CTRI till 14 July 2020. 293 trials were registered and 188 were Interventional and 105 Observational.<sup>6</sup> AYUSH based interventions constituted more than fifty percent. Delhi had 76 study sites, Maharashtra 73 and Karnataka 41. It is in accordance with our study were Karnataka and Delhi had maximum trial sites followed by Maharashtra. As per the [cardiologytrials.org](http://cardiologytrials.org) the following interventions have been tried in Acute coronary syndromes: ACE inhibitors, aldosterone antagonists, anti-platelet therapy, beta-blockers, effective diabetic-control with insulin, ezetimibe, glycoprotein IIb-IIIa inhibitors, heparinoids, hirudin and direct thrombin inhibitors, nitrates, percutaneous intervention, statins, thrombolysis and factor-Xa inhibitors. Ablation, anticoagulation, rate and rhythm control have been tried for atrial-fibrillation. ACE inhibitors, angiotensin receptor blockers, aldosterone antagonists, anticoagulation, beta-blockers, cardiac resynchronization therapy devices, IF-channel blockers, statins, surgery and ultrafiltration have been studied in heart-failure.<sup>7</sup> The clinical trial has been registered with a trial titled, "a double-blind, randomized, placebo-controlled phase 2 study to evaluate efficacy, safety, and

tolerability of olpasiran (AMG 890) in Subjects with elevated lipoprotein(a)” and the study has been completed on 8th November 2022. Olpasiran, a newer molecule under clinical trials is a small interfering RNA that has the ability to reduce the hepatic synthesis of Lipoprotein(a). The OCEAN(a)-DOSE trial states that 12th weekly administration of Olpasiran decreases the Lipoprotein(a) levels in patients with cardiovascular diseases associated with atherosclerosis.<sup>8</sup> The EARLY-AF trial suggests that earlier cryo-balloon ablation therapy sounds better than anti-arrhythmic drugs in reducing paroxysmal atrial fibrillation.<sup>9</sup> Still many more cardiac clinical trials are in the early stages and numerous drug molecules are in the pipeline to be used safely and efficaciously for the treatment of cardiac diseases.

### Limitations

The trials registered only till mid of April 2021 were analysed due to time constraints. Hypertension trials were preferentially excluded from analysis.

### CONCLUSION

Cardiac diseases are the commonest cause of mortality worldwide. Cardiac trials are essential to identify newer drugs and treatment modalities to cure cardiac diseases and prevent death. The current study analysed the data pertaining to Cardiac trials from the Clinical Trial Registry of India, web portal from January 2019 to April 2021. One hundred and fifty-six cardiac trials were registered in the specified period and the characteristics of the trials were analysed. It was observed that COVID-19 pandemic did not influence the conduct and pattern of cardiac trials in India.

### ACKNOWLEDGEMENTS

The authors are thankful to Chettinad Hospital and Research Institute and Chettinad Academy of Research and Education for the support rendered.

*Funding: No funding sources*

*Conflict of interest: None declared*

*Ethical approval: The study was approved by the Institutional Ethics Committee*

### REFERENCES

1. Clinical trials. Available at: <http://ctri.nic.in/Clinicaltrials/login>. Accessed on 20 November 2022.
2. Health. Available at: <http://www.healthissuessindia.com/2020/12/11/top-causes>. Accessed on 20 November 2022.
3. Selvaraj S, Greene SJ, Khatana SAM, Nathan AS, Solomon SD, Bhatt DL. The Landscape of Cardiovascular Clinical Trials in the United States Initiated Before and During COVID-19. *J Am Heart Assoc*. 2020;9(18):e018274.
4. Bhapkar V, Sawant T, Bhalerao S. A critical analysis of CTRI registered AYUSH studies for COVID- 19. *J Ayurveda Integr Med*. 2022;13(1):100370.
5. Rao MVV, Juneja A, Maulik M, Adhikari T, Sharma S, Gupta J, et al. Emerging trends from COVID-19 research registered in the Clinical Trials Registry-India. *Indian J Med Res*. 2021;153(2):26-63.
6. Abinaya E, Saradha S, Ilamathi KR, Ruckmani A, Arunkumar R. Description and Analysis of Characteristics of COVID-19 Clinical Trials Registered in the Clinical Trials Registry-India. *Biomed Pharmacol J*. 2021;14(1):23-9.
7. Cardiology trials. Available at: <https://www.cardiologytrials.org>. Accessed on 20 November 2022.
8. Government Clinical Trials. Available at: <https://clinicaltrials.gov>. Accessed on 20 November 2022.
9. Huynh, K. Cryoballoon ablation reduces AF progression. *Nat Rev Cardiol*. 2023;20(5):23-9.

**Cite this article as:** Saradha S, Kamalam PR, Arunkumar R, Indhra P. Influence of COVID-19 on cardiac clinical trials: an observational study from clinical trials registry India. *Int J Clin Trials* 2023;10(1):15-20.