Science World Publishing

Open Access Journal | Volume: 1.1

CLINICAL BIOSTATISTICS AND BIOMETRICS

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# Ramification of COVID-19 on Clinical Trials with Special Focus on Data Management and Possible Mitigation Strategies

Tanmay Dinesh Gawde | 1303, Sai Raj Heights, Sector-20, Plot no. 68, Roadpali, Navi Mumbai-410218

## Article Information

**Article Type:** Review
**Journal Type:** Open Access
**Volume:** 1 **Issue:** 1
**Manuscript ID:** CBB-1-101
**Publisher:** Science World Publishing

**Received Date:** 06 September 2020
**Accepted Date:** 12 September 2020
**Published Date:** 15 September 2020

***Corresponding author:**

**Tanmay Dinesh Gawde**

1303, Sai Raj Heights
Sector-20, Plot no. 68
Roadpali
Navi Mumbai
410218
E-mail: tanmaygawde311@gmail.com

**Citation:** Tanmay Dinesh Gawde, (2020) Ramification of COVID-19 on Clinical Trials with Special Focus on Data Management and Possible Mitigation Strategies. Clin Biostat Biometr. 1(1);1-5



## ABSTRACT

As we know how the current COVID-19 Pandemic situation is potentially affecting all over the globe. Like many other fields It influencing the clinical research areas as well. As we know the data generated from the clinical trials plays pivotal role in drug development process. The main source of information is investigator sites; however, due to current situation it is a strenuous task to collect and report data from investigator sites. It has increased potential risks over achieving primary or secondary objectives of the clinical trials. Considering these challenges, there is need to check for the alternatives, check for the feasibility of new technologies, new methods of data collections, think over the mitigation plans and look for the innovations. This is now become a new vision for many companies, institutes. This article will touch on few points on how clinical trials and data management system are impacted due to wake of COVID-19. We will try to throw some light on few mitigation strategies as well.

## KEYWORDS

Clinical Research, Clinical Data Management, COVID-19, Electronic Data Capture

## INTRODUCTION

Clinical Research is an important part in drug development process that evaluates the safety and effectiveness of medicines, devices & diagnostic products. Nature of Trials can be preventive, diagnostics or treatments. Clinical trials generate huge amount of data and to manage this data in effective manner clinical data management team plays a pivotal role. Paper forms were used initially for the data collection and now a days sites are using electronic devices, data capture tools to collect the information as a result of technology development.

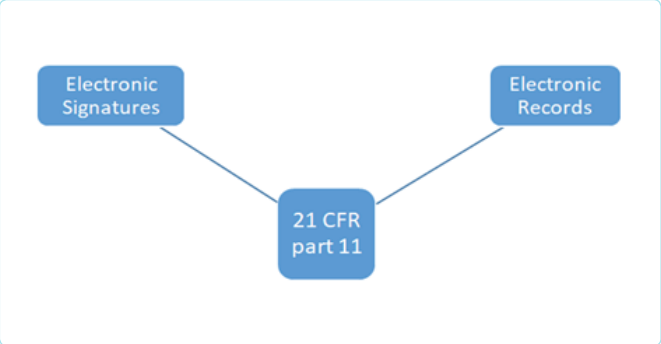
### What is Clinical data management?

Clinical data management is most important segment in clinical research, which helps in generation of reliable and statistically sound data with high quality. People working in this segment are designated as clinical data managers who are skilled persons involved in different activities, which take place in data management right from review of protocol till the data submissions to regulatory authorities. Systems used in data analysis should be regulatory compliant following the FDA guidelines to capture and maintain patient records in electronic systems.

***Following are controls and requirement defined in the guidelines*** **[1]**

- Limiting system access to authorized individuals
- Use of operational system checks
- Use of authority checks
- Determination that persons who develop, maintain, or use electronic systems have the education, training, and experience to perform their assigned tasks
- Establishment of and adherence to written policies that hold individuals accountable for actions initiated under their electronic signatures appropriate controls over systems documentation

FDA has provided guidance to industry on managing Electronic records and Electronic signature (FDA 21 CFR part 11, Aug 2003) since then reliability is increased over the years. To be compliant with FDA regulation pharmaceutical and biotechnology industries implementing these guidelines to be sure that it is been followed in each step in the process.




## Tools used in clinical data management:

Systems that are used in clinical data management are normally called as Clinical data management systems (CDMS) [2].

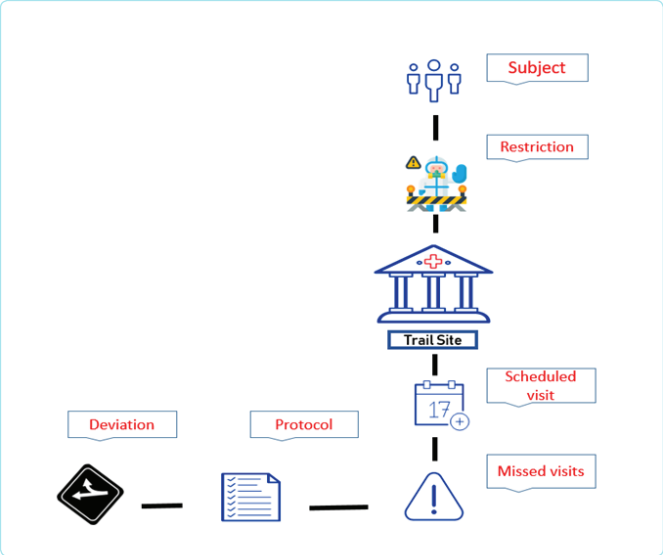
Nowadays data collection is being done with electronic data capture tools such as Medidata Rave [3], Oracle Clinical, clinical trials, In Form etc.

## Activities covered under Clinical data management

Since pharmaceutical industries have dependency on data collected electronically, there are standard guidelines for data management, which needs to be followed. Society for Clinical Data Management (SCDM) [4] published standard guidelines called as Good Clinical Data Management Practice (GCDMP) which is industry standard being applied in each of the activity that take place in Clinical data management.

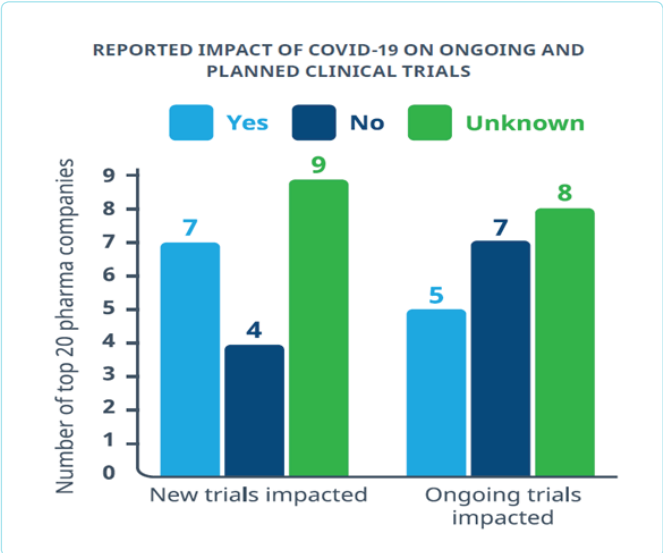
### *Challenges in achieving milestones due to pandemic situation*

1. **Travel Restrictions [5]:** Subjects are unable to reach sites because of the pandemic situation and lockdowns in many countries. In many areas people are not allowed to go outside where government has imposed a law and person who is not following law will be penalized, hence it become a difficult situation to all subjects who were enrolled into clinical trials to reach out to allocated sites for scheduled visits. It results in delayed or missed visits.
2. **Delay in patient enrollment [6]:** Due to travel restrictions and social distancing laws, patient enrollment is slowed down in new as well as ongoing trials.
3. **Halt for ongoing Study [7]:** When site staff or investigator is being a COVID positive then there is chance that site may be interrupted, which leads to incomplete eCRF and query is being unanswered for longer time.
4. **Protocol Deviation:** As study is not being conducted as per approved Protocol then protocol deviation to be filed. Which Increases work for site, investigator & Sponsor.

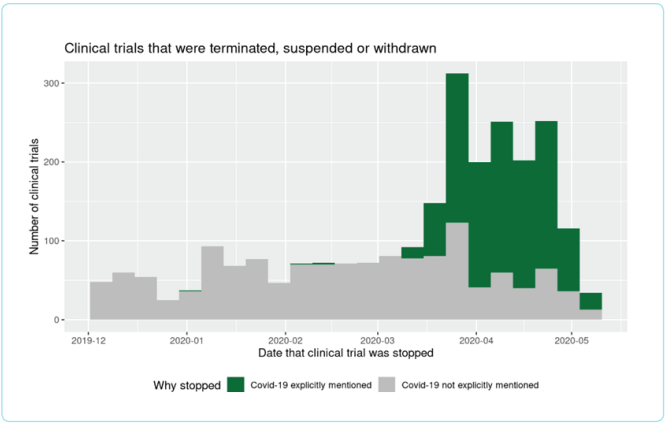



5. **Missing monitoring visit:** There is chance of missing monitoring visits from CRAs due to the current travel restrictions.
6. **Reliability on Local Lab:** Biological samples cannot be shipped to the central laboratories, analysis required to be performed locally. The result/reports need to be recorded appropriately and needs to be explained with detailed justification in clinical study report. In such cases, it is very important that the sponsor has given access to the normal ranges and certification information of any additional laboratory used in order to support the use and evaluation of results.
7. **Unavailability of Vendor:** Vendors such as Central Lab, IxRS, eCOA become unavailable due to facilities shut down or staff shortage.
8. **Regulatory Audits and Inspection [8]:** The impact of COVID-19 on global health authorities is continue to evolve. There is possibility of substantial delay in planned audits and inspections. It also has an impact on on-site GxP audits and vendor selections.

Below is the impact reported by global pharmaceutical organization [9], which shows that delay in ongoing activity and delay in startup activities for new trials. Considering this delay there is significant impact on Clinical data management milestone.

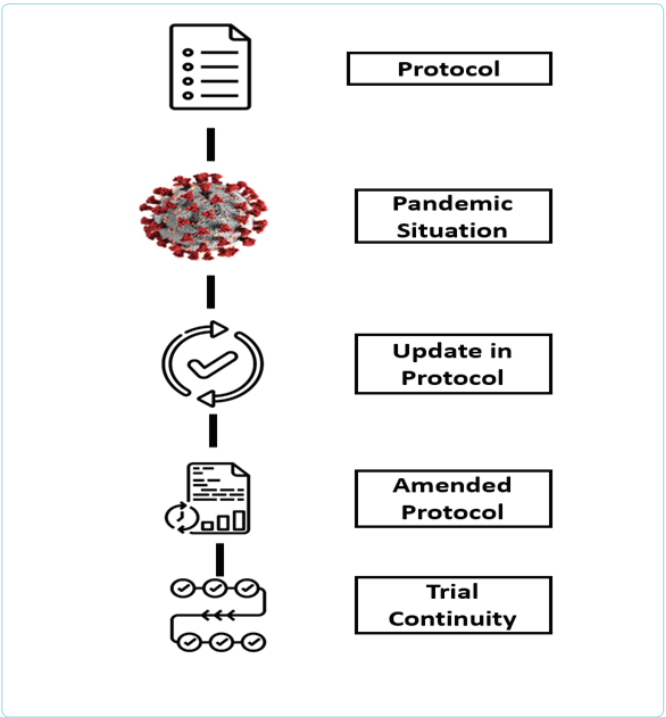



1. Global Medidata survey of over 1000 investigator site revealed that: 78% said COVID-19 has affected their ability to start new trials
2. Nearly 45% of respondent said they have switched study participants from in-clinic visit to virtual/telemedicine [10].
3. COVID-19 outbreak affected as many as 2,00,000 patients.
4. An analysis of studies based on clinicaltrial.gov [10] provided data that 2522 studies has been interrupted or postponed between 1 Dec and 5 May 2020 at least 1099 given reason as COVID-19.




## *Mitigation strategies*

1. **Amendment to protocol:** The trial Patient safety is paramount; Sponsor should analyze and modify study conduct accordingly. Compliance with the trial protocol should be ensured to such an extent that an ongoing benefit-risk assessment for the clinical trial and its participants is still possible. The impact of protocol changes on clinical data interpretability needs to be properly assessed by the sponsor and the overall evidence generation could be subsequently discussed within scientific advice with regulatory authorities [11]. A relevant guidance on the implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials by Biostatistics Working Party was published on 25 March 2020. Further to this sponsor will circulate this amended protocol to all work streams including Clinical data management and Data mangers will assess how updates are impacting on data reporting, will look for possible changes in CRF or if there is any need to create new forms, in parallel to this Data management team also need to think on how missed visits or delayed visit will be captured.



2. **In-Home Visits:** Traditional trials require Subject to visit Investigator sites; however, in Pandemic situation it is difficult for subject to reach out to site. Research-trained homecare nurses can conduct a number of procedures at patient's home, ranging from simple blood-draws and assessments to complex intravenous drug administrations. This is enabled by mobile centrifuge units, ECG units and other technologies including electronic-data-capture in patient's homes, which means clinical development teams can really focus on improving trial experience for the patient. Managing home care will require proper planning and execution.

**Below are some benefits [12] for using home visits:**

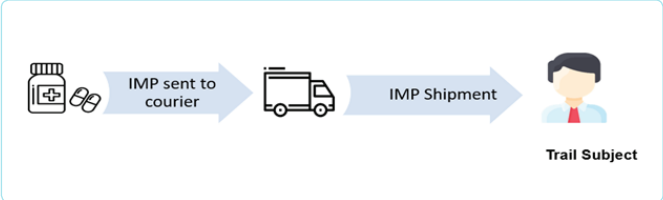
- ✓ Trial continuity during pandemic situation, no alteration
- ✓ Enhanced compliance to protocol
- ✓ Ensure protocol specified IMP (Investigational Medicinal product) delivery.
- ✓ Decrease inpatient's Burdon
- ✓ Increased retention
- ✓ Accelerated recruitments
- ✓ Subject as well as site satisfaction

So, this way In-home visits are giving us a way to maintain trial continuity during crisis. Hence adapting this method using technology will help study team in numerous ways.

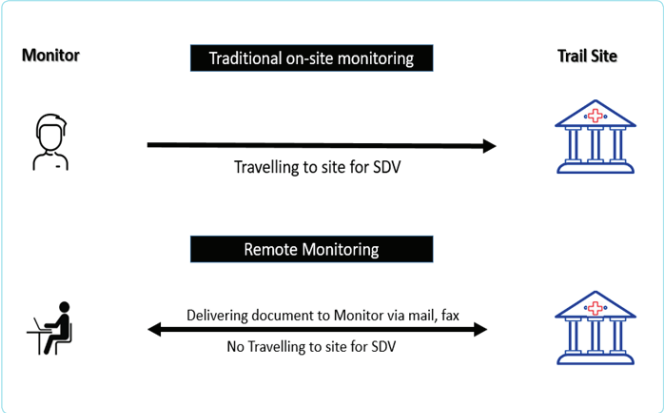
3. **IMP Delivery to subject's location:** Sponsor may have option to deliver IMP at subject's home since many subjects could not visit trial sites. Sponsor need to ensure that subject is able to do self-administration; appropriate trainings should be given if required. Logistic of IMP need to handle with extra care.

Below are few key points which should be consider while delivering IMP to Subject's home-

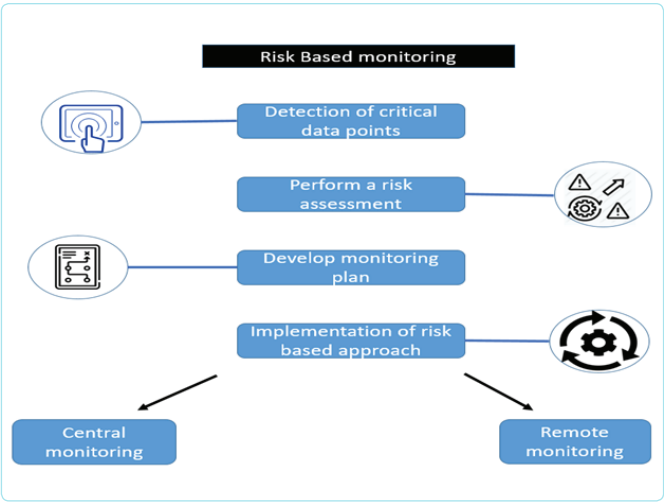
- Storage conditions or Temperature requirements related information should be properly shared with the subjects.
- Administration techniques or process should be discussed in detail.
- Medicine accountability needs to be monitored.




4. **Customized Metric Report:** Metrics always play a key role to summarizing data present in database which helps Data management team to focus on key data points which are critical in nature and need to be highlighted to relevant stakeholders. These reports will provide more, in-depth insight into pertinent information such as missed patient visits and site data backlogs that could result from COVID-19. Summarizing and Tracking Metrics at an increased frequency (weekly vs monthly) will assist Clinical Trial Team members to have more timely information to make proactive decisions.
5. **Metric Summary:** To deliver Metric summary to Clinical Trial team will increase decision-making process and transparency into clinical study. If there is need as to take some precautionary measures then it will be planned and implemented without any further delay. This will also help to achieve critical milestones.
6. **Review of data management & Statistical plan [13]:** If pandemic situation leads to changes/amendments in protocol and to reflect the same in Data management and statistical analysis plan is necessary as equivalent with consultation of FDA review division.
7. **Remote/Centralized monitoring:** Effective monitoring is required to ensure trial adherence to protocol as well as regulatory guidelines also to ensure protection of the rights, welfare, and safety of human subjects. FDA States that "If planned on-site monitoring visits are no longer possible, sponsors should consider optimizing use of central and remote monitoring programs to maintain oversight of clinical sites". There are multiple ways of performing ongoing monitoring of Clinical study and solely depend upon sponsor how they want to control and evaluate performance of trial. Since traditional on-site monitoring is not possible every time, hence there are other approaches available such as remote monitoring where monitor perform remote source data verification (rSDV) [14] this approach has benefits in terms of Quality, Cost and Speedy site interactions.




FDA also provided guidance to risk based [15] approach in monitoring of clinical studies. Risk based monitoring guidance are important in identifying critical data points/process, performing risk assessment and developing effective monitoring plan to mitigate the risk [16].




## DISCUSSION

Trial participant's Safety and wellbeing is at utmost priority, Sponsor should assess each circumstance, which will impact patient's safety and need to modify trials accordingly. Since trial participants are not able visit site for protocol scheduled visits, sponsor should think on alternative methods that may be included but not limited to one mentioned in this article. Changes in protocol not implemented before IRB/IEC Review or in some cases by FDA, sponsor should immediately notify IRB/IEC where urgent intervention is need because of COVID-19. Investigator must follow alternative process which may already mentioned in Protocol and should be well documented. There is possibility of subject may miss visits in such cases investigator should properly report the reason in data collection

tools so that while performing statistical analysis it will be helpful. Where trial can continue follow-up and monitoring activity are likely to be impacted by Investigator and site staff availability or due to social distancing norms, in this case sponsor should ensure that these as minimized. Protocol deviation are appropriately recorded and should be communicated to regulatory bodies.

## CONCLUSION

The COVID-19 pandemic is the biggest challenge the world has faced in the century. It is affecting every aspect of daily life and clinical trials are not exempt. The integrity and feasibility of ongoing studies is threatened as the outbreak continues to spread globally. Pandemic is creating a burdon on hospitals and health centers, which is highly disruptive to ongoing trials. By implementing mitigation strategies mentioned above will definitely salvage some of (if not all) study potential risk. This required continues review and monitoring to make sure that it is up to date, so it will be easy to establish highest standards and scientific integrity along with patient safety. Also following regulatory guidelines, which releases time to time will also help to fasten process for regulatory submissions.

## GLOSSARY FOR TERMS

| | | |
|---|---|---|
| EDC | - | Electronic Data capture |
| RDC | - | Remote Data capture |
| CDM | - | Clinical Data Management |
| FDA | - | Food and Drug Administration |
| CFR | - | Code of Federal Regulations |
| CDMS | - | Clinical Data Management Systems |
| SCDM | - | Society of Clinical Data Management |
| GCDMP | - | Good Clinical Data Management Practice |
| eCRF | - | Electronic Case Report Form |
| CRA | - | Clinical Research Associate |
| IxRS | - | Interactive Voice/Web Response System |
| eCOA | - | Electronic Clinical Outcome Assessment |
| GxP | - | Good Practice (X is variable = Clinical, Manufacturing, Documentation & Lab) |
| ECG | - | Electrocardiogram |
| IMP | - | Investigational Medicinal Product |
| SDV | - | Source Data Verification |
| IRB/IEC | - | Institutional Review Boards/ Independent Ethics Committee |

**Conflict of Interest:** There are no conflict of mentioned by author.

## BIBLIOGRAPHY

1. U.S. Department of Health and human service, Food and Drug Administration, Guidance for industry, Part 11, electronic records; Electronic signature – Scope and application.
2. Gazali, Sandeep Kaur, Inderbir singh. Artificial intelligence based clinical data management systems: A Review, Informatics in medicine unlocked. Science Direct. 2017;9:219-229.
3. Medidata Rave EDC, Medidata. Available from: https://www.medidata.com/wp-content/uploads/2019/05/Customer-Facing-Fact-Sheet-Rave-EDC-May-19-1.pdf
4. Good Clinical data management practice, Society of clinical data management, October 2013 edition.
5. https://scdm.org/covid19-and-clinical-data/
6. Laurie Halloran: 8 Significant risks COVID-19 poses to clinical trial- And how to mitigate. Clinical Leader. 2020;19.
7. Guidance on management of clinical trial during the COVID-19 (Coronavirus) Pandemic. European Medicines Agency. 2020; Version-3, Apr 24.
8. Laurie Halloran: Accessing the impact of COVID-19 on regulatory interaction, Inspection & Audits. Clinical Leader. 2020;19.
9. Navigating COVID-19 Impact: An initial assessment of the pandemic's effect on Australian healthcare, White paper series-part 1, IQVIA.inc. Available from: https://www.iqvia.com/-/media/iqvia/pdfs/library/white-papers/iqvia-anz-covid-19_white-paper.pdf
10. Benhamin Gregory Carlisle: Clinical trial stopped by COVID-19, May 7, 2020. Available from: https://covid19.bgcarlisle.com/published/full-report-2020-05-07.html
11. James Miessler: Pandemic is expediting protocol finalization in COVID-19 studies, Centre Watch Weekly, May 11, 2020.
12. Committee for Human Medicinal Products (CHMP): Points to consider on implications of Coronavirus disease 5 (COVID-19) on methodological aspects of ongoing clinical 6 trials, European Medicine Agency, Jun 26, 2020.
13. Graham Wylie: Home Clinical trial visit- A patient centric solution, Clinical Leader, Jan 26, 2020.
14. FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency, U.S. Food and Drug Administration, June 3, 2020.
15. Remote source data verification, Quanticate Inc. Available from: https://www.quanticate.com/remote-source-data-verification-rsdv-webinar-thankyou?submissionGuid=f75202ba-f772-4c7b-86c8-21867ade5362).
16. Guidance for industry, Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring, U.S. Food and Drug Administration, August 2013.