COVID 19 and Clinical Trials: The Medidata Perspective

Release 3.0

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Introduction

As COVID-19 has spread and, in some Asian countries, begun to recede, we have been monitoring the global impact of the virus on clinical trials. Our first data and insights impact report was released on March 23 with subsequent updates on April 3rd and April 17th. Medidata's analysis of the change in new patients entering clinical trials for actively recruiting studies demonstrates the growing significance of the pandemic's impact on cities, regions, and countries with increasingly tighter laws and guidelines restricting movement by anyone outside of the home.[1]

An update to the April 3 analysis was performed on April 17, 2020 and the results for the first two weeks of April are shown next to the March results (See Exhibit 1), The global data now shows an 75% decrease in the average number of new patients entering trials per study-site YoY for the first two weeks of April compared to the same time frame last year.[1] This compares to a 65% decrease we saw in the month of March. The data clearly indicate that the impact of the pandemic on patient enrollment in most countries continues to grow. Only China, South Korea and Italy sawa decrease in impact.

Exhibit 1

		YoY Difference (%) Mar 2020 vs. Mar 2019	YoY Difference (%) Apr 2020 vs. Apr 2019
All Countries, All TAs	All	-65.%	-75%
Asia	China	-68%	-39%
	India	-84%	-96%
	Japan	-44%	-57%
	South Korea	-61%	-44%
Europe	France	-68%	-80%
	Germany	-33%	-76%
	Italy	-53%	-37%
	Spain	-68%	-81%
	United Kingdom	-80%	-98%
North America	United States	-66%	-80%
Therapeutic Area	Cardiovascular	-69%	-95%
	CNS	-68%	-73%
	Dermatology	-64%	-90%
	Endocrine	-81%	-89%
	ID/Anti-Infectives	-47%	-62%
	Oncology	-48%	-51%
	Respiratory	-34%	-78%

*Monthly data from 2019 normalized to corresponding two weeks in 2020

[1] Analysis across 4,600 studies and 182,227 study-sites

Additionally, we are launching with this release a new metric tracking **visits-per-study-subject** in on-going studies (See Exhibit 2). Both globally and in the US specifically, there has been a 17% decrease in visits per subject between Oct 2019 and March 2020. China has seen a steeper decline with a 30% decrease between Oct 2019 and February 2020 but similar to patient enrollment China saw 22% improvement in visits per subject between February and March 2020. We will continue to update and refine this new metric in upcoming releases.

Exhibit 2
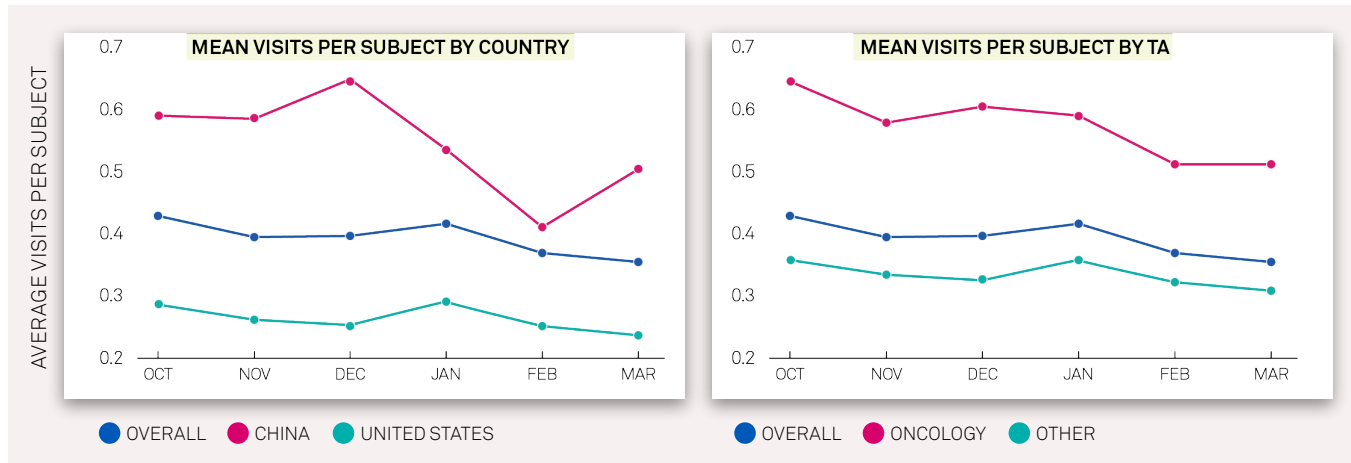
Understanding what is happening on the ground is critical to define a path forward. We will continue to publish updated analyses twice a month on overall industry trends throughout this pandemic and beyond.

Regulatory Response

As of April 16, multiple authorities including the European Medicines Agency (EMA), U.S. Food and Drug Administration (FDA),UK Medicines and Healthcare Products Regulatory Agency (MHRA), Germany (BfArM), France (ansm), Netherlands (ccmo), Ireland (HPRA), Switzerland (swissmedic), Japan (PMDA), South Korea (MFDS), Health Canada, Australia (DoH), and Singapore (HSA), have provided updated emergency guidance on trial conduct during the pandemic. In addition, multiple stakeholder organizations including the Association of Clinical Research Organizations (ACRO) and multiple IRBs (an example here) have issued guidance documents as well. What's clear is that regulations and guidance differ from country-to-country.

Due to the recent disruptions and challenges posed by COVID-19, there has been an increase in activity promoting the use of technology in clinical trials. Additionally, the regulators and stakeholder groups are expressing pragmatism and flexibility in terms of mitigating when possible. Common topics include triggers for protocol amendments and deviation processes, risk assessment expectations, continuing or halting a trial, continued subject participation, informed consent -including eConsent (FDA), and remote monitoring (see 16 April FAQ update). Note that while the US FDA, UK MHRA, Australia DoH, Health Canada, and Singapore HSA suggest remote source data verification is possible, the EMA discourages it.

For more detailed information on the global regulatory responses to the impact of COVID-19 on clinical studies, visit Medidata's blog here.

Impact to Medidata Customers, Patients and Trials

Real-time and detailed reporting and analytics are critical for sponsors and CROs to assess the day-to-day impact of the pandemic on a trial at the patient, site and country level and so they can quickly implement changes to mitigate the risk of trial failure.

Rapid and safe implementation of protocol amendments is vital to address both site closures and the fact that trial participants no longer receive or have access to the investigational product. Inaccessible sites mean that alternative, remote approaches to drug supply, monitoring study conduct, compliance, patient safety and data quality are needed. The more trials can be safely "virtualized," the more likely they will be able to successfully proceed.

As of April 3rd, several large pharma (Pfizer, Bristol Myers Squibb and Eli Lilly)[2] and smaller Biotech companies (Moderna Therapeutics[3] , Iveric Bio[4] , Aslan[5] , Provention Bio[6] and Addex[7]) have publicly announced that they are modifying their R&D plans. Typical modifications in certain trials are some form of temporary delay in site activation and/or patient enrollment. The impact of COVID-19 on trial success is already an issue, as evidenced by Aveo Pharmaceuticals Inc. citing COVID-19 as a reason for the study failure of ficlatuzumab in acute myeloid leukemia.[8] These growing examples of trial delays or stoppage by biopharma to mitigate the cost and impact of the pandemic dramatically highlight the need for rapid, innovative solutions to help trials successfully start, continue and finish.

Medidata Solutions to Assist Sponsors/Partners, Patients and Trials

Medidata has solutions that can be immediately leveraged by our customers to both better understand the impact of the pandemic on their trials, and to mitigate the challenges of patients unable to visit sites for their drugs and protocol-directed clinical and patient-reported data capture.

There are **four** main categories of challenges facing clinical trials. The following is a high level summary of these challenges and the solutions that Medidata is prepared and ready to provide:

CHALLENGE 1: UNDERSTANDING THE EVOLVING SITUATION

Solutions:
- Study/sponsor level metrics and dashboards to understand impact on enrollment, patient visits, data collection, query response rates, and additional metrics to help diagnose risk areas
- Industry-wide dashboards and analysis to understand trends globally and areas of greater or lesser disruption

[2] https://www.fiercebiotech.com/biotech/covid-19-prompts-pfizer-to-stop-enrollment-most-studies. Accessed April 4, 2020

[3] https://www.fiercebiotech.com/biotech/covid-19-causes-moderna-to-pause-a-clutch-clinical-trials. Accessed April 4, 2020.

[4] https://www.fiercebiotech.com/biotech/iveric-bio-latest-to-be-hit-by-covid-19-as-it-delays-a-key-trial. Accessed April 19, 2020

[5] https://www.fiercebiotech.com/biotech/covid-19-outbreak-prompts-provention-to-pause-diabetes-trial. Accessed April 19, 2020

[+]otech/aslan-s-dupixent-rival-test-put-hold-amid-covid-19-but-delays-shouldn-t-hit-readout. Accessed April 19, 2020

[6] https://www.fiercebiotech.com/biotech/covid-19-outbreak-prompts-provention-to-pause-diabetes-trial. Accessed April 19, 2020

[7] https://www.fiercebiotech.com/biotech/swiss-bio-addex-halts-parkinson-s-test-as-trial-delays-tick-up-covid-19-disruption. Accessed April 19, 2020

[8] https://www.reuters.com/article/brief-aveo-oncology-and-biodesix-to-disc/brief-aveo-oncology-and-biodesix-to-discontinue-cyfi-2-study-of-ficlatuzumab-idUSFWN2BK1LR. Accessed April 4, 2020

CHALLENGE 2: RECONSIDERING TRIAL DESIGN TO ENABLE DATA CAPTURE

Solutions:

- Shift to more virtualization – reduce patient visits; minimize site burden
- Shift site mix to lower-impacted countries / regions
- Consider Synthetic Controls to reduce patient enrollment needs

CHALLENGE 3: MAINTAINING QUALITY AND SUPPLY

Solutions:

- Centralize data oversight and monitoring activities, bringing identification of patient anomalies earlier in the process and away from onsite identification
- Closely monitor patient volume and drug supply to minimize supply disruptions

CHALLENGE 4: ACCELERATING STUDY START UP

Solutions:

- Sponsors focused on developing vaccines against, and treatments for COVID, must safely and effectively accelerate study start up times through faster investigator budgeting, so cures and treatments can get to market faster

Details on Medidata's Solutions

The following tables provide details about the Medidata's solutions available now to assist with your trial challenges. Since some aspects of the four challenges are not mutually exclusive, some solutions may be applicable to more than one challenge.

CHALLENGE 1: UNDERSTANDING THE EVOLVING SITUATION

Acorn AI Intelligent Trials

CHALLENGE	SOLUTION
Understanding the country/site/ disease area impact across the industry, and developing risk mitigation and recovery plans	**COVID-19 Trial Impact Analytics***: Data and analytics to develop industry tracking, forecasting and deep dives for priority studies to support client's COVID-19 impact assessment, risk mitigation and recovery decisions. **Situation Tracking** • Deploy standard reports to track impact of COVID-19 for Client and industry • Data tracked - measures of enrollment and data collection • Views at study, portfolio, geography leve **Impact Forecasting** • Overlay trends in COVID-19 testing and infection rates with impact on trials to understand leading indicators of slowdown • Identify markers of recovery at a country and region level **Recovery Planning** • Recovery planning / scenarios for acceleration across portfolio
***New Medidata Solution**	• Deep dive in priority studies

CHALLENGE 2: RECONSIDERING TRIAL DESIGN TO ENABLE DATA CAPTURE

Rave eCOA

CHALLENGE	SOLUTION
Provide ways for missed or risked visit forms to be remotely filled out by patients on existing studies.	Medidata's eCOA solution can be used to convert site-based data forms to remote data forms. If study modifications are made to accommodate this approach, patients can download the patient cloud app from the app store and provide urgent data forms as needed for missed visits. Any Rave EDC study using eCOA can have additional data forms pulled into the eCOA app and made available to patients. Any Rave EDC studies not using eCOA can add eCOA to the project and immediately begin converting forms to remote-enabled forms.

Rave eConsent

CHALLENGE	SOLUTION
Providing remote eConsent on trials that are underway or are starting up.	Currently, our iPad based consent is not set up for BYOD with a patient device. However, remote consent is possible through the use of the legacy Engage (Rave Virtual Trials/Patient Portal) platform and can be supported as a standalone activity. Some integration with Rave EDC is possible, although different usernames and passwords are used for the legacy Engage platform. The primary use case for this technology would be ongoing studies where a remote consent is required to keep the study up and running. In this case, a special instance of the Engage technology could be launched allowing patients to remotely log in and provide consent.

Rave Patient Portal / Rave Virtual Trials

CHALLENGE	SOLUTION
Prepare for COVID-19 studies with self-quarantined patients globally.* *New Medidata Solution	Medidata and 3DS are launching a COVID-19 Screening app as part of Medidata's Patient Portal that can be used as a remote patient symptom tracker in France and the US. This app will function as a registry (in an MVP version) and will allow hospital staff to remotely review symptoms and triage patients to the hospital only when medically necessary. Subsequent versions will enable patients to find trials and to consent remotely before entering a site that may be performing a study.
Provide rescue and/or new study designs that enable virtualization of visits and data capture.	In ongoing studies and/or new study designs, the Rave Patient Portal can be used to virtualize more aspects of the study design. New generation versions of the portal will be released later this year but our existing technology is used today on ongoing virtual trials managing thousands of patients and is a fully functional and validated system for clinical research. In many cases, this version can be modified for a study that needs to accommodate remote consent, remote randomization, remote data capture, reporting and site access. Because this app is web-based, it is also easily available for all patients on all types of platforms and does not require a mobile device or device distribution..

Acorn AI Synthetic Control Database / Trial Design

CHALLENGE	SOLUTION
Improving understanding of safety in experimental treatments (e.g., chloroquine) that are now under review for cross-indication use.	Support research by providing aggregated data, e.g., Synthetic Control Database (SCD) to support understanding of expected and unexpected AEs for products being studied for COVID-19. These drugs are already marketed with a mature safety profile, but an SCD might improve the analyses above what published literature can provide. In addition, historical trial data can be compared against real-world data from claims or EMRs to provide confidence and validation in trial design, better understand inclusivity of patients populations to better reflect real world clinical practice, and potentially decrease sample size requirements for event-driven trials.
Closing out on-going studies given barriers completing visits.	Leveraging historical clinical trial data to augment or replace control arms of trials that are in danger of high dropout or unfulfilled enrollment due to COVID-19; reduce scientific uncertainty to advance to the next phase, reduce patient enrollment burden or increase statistical power.

Rave Imaging Critical*

CHALLENGE	SOLUTION
As a result of global restrictions, most sponsors are unable to monitor their active studies on site, and may not be able to manage critical document management activities. Some sponsors have turned to FTP, Box, Webex and Email to manage these critical documents. Without the ability to securely manage these documents, patient safety and data integrity are at risk and studies may not progress. **Regulatory guidance allows for sponsors to find ways to perform critical document management and SDR remotely in certain regions, excluding EMEA.** ***New Medidata Solution**	Medidata has tailored its Rave Imaging workflow to enable certain clients to rapidly and remotely deploy a method to assist monitors in their critical document management workflows and Source Document Review (SDR). **Rave Imaging Critical** is a streamlined and quick-to-implement solution (2 weeks go-live) that helps fill the gap when studies have critical timelines and no secure option to collect, manage, review and verify critical study documents. **Rave Imaging Critical:** • Acquires documents, via secure browser-based uploads, routes and manages document workflows to support source document review and verification • Is a 21 CFR Part 11 compliant system that includes the ability to de-identify and redact Personally Identifiable Information (PII) and Protected Health Information (PHI) • Mitigates risk due to site monitoring and patient visit disruption for some studies with no secure option to manage critical documents

CHALLENGE 3: MAINTAINING QUALITY AND SUPPLY

Rave RBQM

CHALLENGE	SOLUTION
Restrictions of access to sites by staff and patients may affect the investigators' ability to maintain medical oversight. This may impact, among other key processes, completion of trial assessments, completion of trial visits, and the provision of Investigational Medicinal Products (IMPs). ***New Medidata Solution**	To assess the potential impact of such challenges sponsors should conduct a risk assessment to evaluate potential risks and define appropriate risk control mechanisms. To support industry in establishing risk management practices, Medidata is offering a free Risk Assessment Template* to support in the development and documentation of monitoring strategies by collecting critical to quality data and mitigation strategies. The Risk Assessment Template can be accessed [here]().
Travel restrictions are impacting the ability of site staff and monitoring resources to perform oversight responsibilities to ensure subject safety and data quality. ***New Medidata Solution**	**Rave CSA Critical*** (Centralized Statistical Analytics) is a customized solution to support sponsor oversight responsibilities by incorporating next-generation analytical tools and algorithms into a quickly implemented solution (<2 weeks go-live) providing: • Real-time data availability for proactive early data oversight • Focused Key Risk Indicators (KRI) on areas of greatest risk • Remote management of site processes to mitigate risk • Detection of data patterns and anomalies • Automated insights into subject safety, data integrity, and site performance • Mitigation of risk due to site monitoring and patient visit disruption These allow for increased efficiency in data review and centralization of review activities and risk/issue detection - a critical capability that can maintain and support sponsor oversight responsibilities and allow earlier access to data and enhance key decisions making capabilities.

Rave EDC and Rave RTSM

CHALLENGE	SOLUTION
Patients can't get to the site for dispensation but the site is open.	Sites can process dispensation through Rave EDC as a visit and send the drug to the subject via a courier. Rave EDC could be updated to store the courier tracking number (collected as text data). Adding a new field would require a migration in Rave EDC.
Patients can't get to the site for dispensation - sites are open but do not have supply for dispensation.	There are several options to have drug sent to the patient from the depot or a central pharmacy. In Rave RTSM (randomization and trial supply management), the subject has to exist at the site where the drug supply is located. There are several options we are executing to manage transferring subjects and creating dummy shipments to allow a shipment to be sent to the patient's home from a location other than the site. We're able to work with study teams to help set up the best option based on the study design and logistic considerations.

CHALLENGE	SOLUTION
Sites are closed and patients need a dispensation.	Some of the methods above can also be used to allow a direct to patient shipment when the site is closed. Alternately, subjects may be transferred to sites that are open. We have a "How-to" procedure ready to share with you.
Subjects are able to have an onsite visit but future visits are questionable.	Multiple dispensing visits can be made in Rave EDC at the same time, providing additional IMP for the subject. If this will become standard, DND dates should be updated so that the drug does not expire over the longer time period between dispensations. Our Services team can provide specific steps that can be utilized to ensure off-cycle/unscheduled visits can be conducted without issue.
Supply chain concerns make sites want to have more buffer stock on hand or less (depending on if the concern is availability of drug or availability of shipments).	Update supply plans - here is basic learning information for supply plan settings.The supply plan can be instantly adjusted to ensure that the site is stocked with additional drug, such as calculating drug needed for additional visits. Depending on the individual study design, these methods can be combined to address any challenges faced by the study.

CHALLENGE 4: ACCELERATING STUDY START-UP

Rave Grants Manager COVID IIS*

CHALLENGE	SOLUTION
Budgeting for the investigator-initiated studies (IIS) is different from a normal trial. IIS trail budgets are typically built as small cost buckets, with the Sites (not the Sponsor) indicating what the costs are and what they want the Sponsor to pay. This approach causes delays in getting approval with the Sponsor as a more granular activity level budget is needed. The Sponsor will also need reliable data to verify if the costs are fair.	Medidata has developed a COVID19 vaccination study budgeting solution, **Rave Grants Manager COVID IIS**, to help investigator- initiated studies develop detailed trial budgets for patient, procedure and site costs. Leveraging Medidata's deep fair market value data and our clinical trial budgeting expertise, Sponsors can streamline the budget build process for their sites.
With COVID-19 investigator-initiated studies, there are budget negotiation delays due to the gap between the Site's and Sponsor's individual cost benchmarks. Disparate data sources for clinical procedure activities and other direct costs at the investigator and site-level can undermine decision-making. There is a need for an independent industry benchmark.	**Rave Grants Manager COVID IIS** enables Sponsors to negotiate investigator-initiated studies quickly using a single, reliable fair market value data source as well as a complexity analyzer. The complexity analyzer calculates benchmarks with industry averages, along with a site's work effort required by the procedures, visits and protocol. This helps sponsors determine fair site payments based on relative study complexity..

CHALLENGE

Compliance and auditing risks. Lack of internal COVID-19 related data to establish FMV to ensure Sponsors are not overpaying or underpaying sites.

* New Medidata Solution

SOLUTION

Medidata's deep fair market value data provides auditable defensible rates. An audit trail of negotiation activity is retained for reference and compliance with fair market value regulations.

Summary

Medidata's commitment to supporting the life sciences community is unwavering. We will continue to monitor the impact of the virus on clinical studies, and provide updated information as available. We are working hand-in-glove with our sponsors and partners to identify issues caused by the pandemic and to find innovative ways to support you with solutions, technology and advanced analytics. From operations to oversight, from supply management to synthetic control arms, from virtualization to centralization of data oversight, we are committed to helping you continue your clinical research.

In this environment of uncertainty and anxiety, what is certain is Medidata's commitment to our mission, we exist to Conquer Diseases together.

About Medidata

Medidata is leading the digital transformation of life sciences, creating hope for millions of patients. Medidata helps generate the evidence and insights to help pharmaceutical, biotech, medical device and diagnostics companies, and academic researchers accelerate value, minimize risk, and optimize outcomes. More than one million registered users across 1,400 customers and partners access the world's most-used platform for clinical development, commercial, and real-world data. Medidata, a Dassault Systèmes company (Euronext Paris: #13065, DSY.PA), is headquartered in New York City and has offices around the world to meet the needs of its customers. Discover more at **www.medidata.com** and follow us **@medidata**, The Operating System for Life Sciences™.

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