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COVID 19 and Clinical Trials: The Medidata Perspective

Release 2.0

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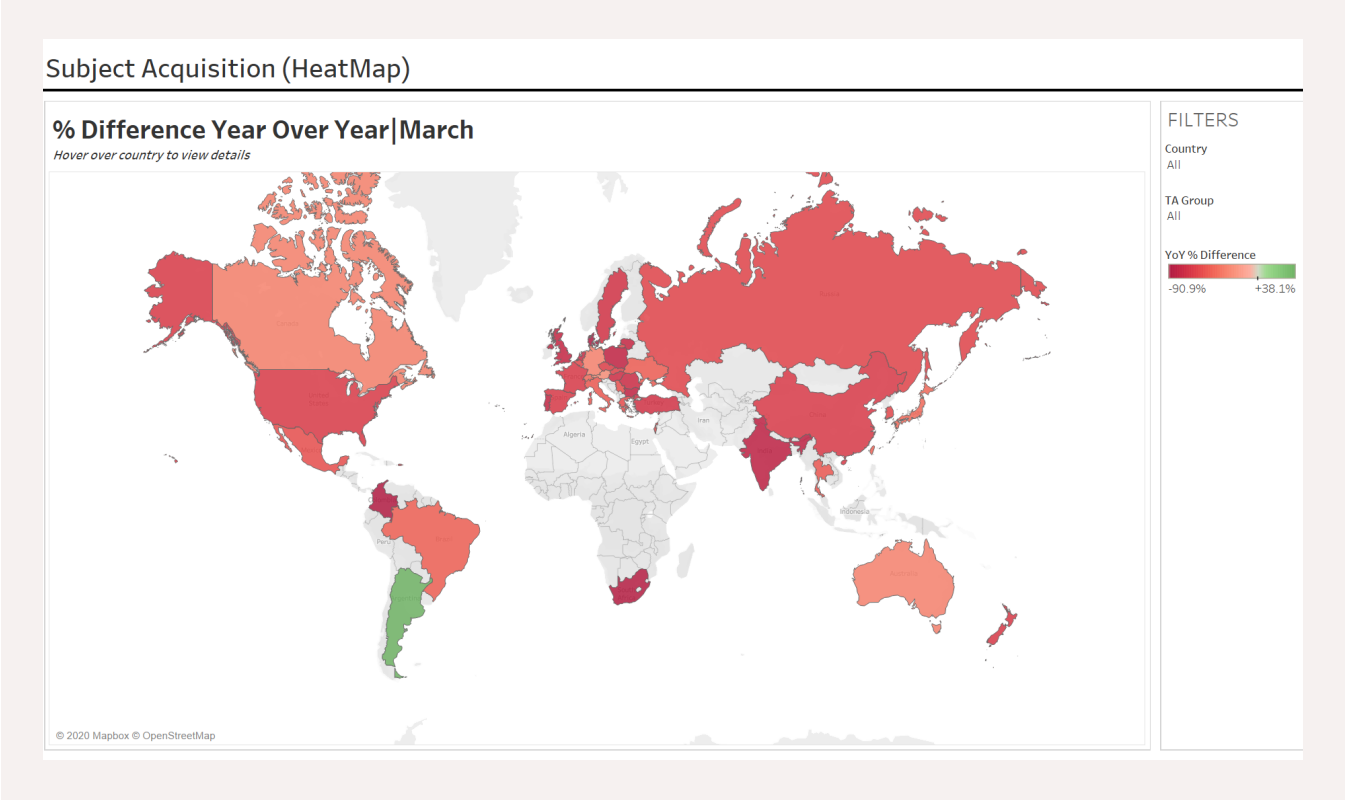
Introduction

As COVID-19 has spread, we have been monitoring its global impact on clinical trials. Our first data and insights impact report was released on March 23. Medidata's analysis of the change in new patients entering clinical trials for actively recruiting studies demonstrates the 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 March 23 analysis was performed on April 3, 2020, which now includes impact on trial enrollment by therapeutic area (TA) shown in Exhibit 1 below. The global data shows a 65% decrease in the average number of new patients entering trials per study-site YoY during March[1]. Most geographic regions have been heavily impacted. All of the countries analyzed experienced accelerated decreases in new patients entering trials YoY, except two. For example, during March there were enrollment decreases YoY for the US (67%), France (68%), Italy (52%), Germany (32%), Spain (68%), UK (80%), Japan (43%), India (84%), and South Korea (61%). The two countries that improved between February and March were Argentina and China. In China, we saw a 68% decrease in new patients entering trials YoY during March, but the silver lining was that March was 240% higher than February in terms of new patients added, which could be a leading indicator of China returning to normalcy.

Exhibit 1



[1] Analysis across 4,599 studies and 182,321 study-sites

		YoY Difference (%) Mar 2020 vs. Mar 2019
All Countries, All TAs	All	-65.1%
Country Breakdown	China	-67.5%
	United States	-66.7%
	Japan	-43.5%
	India	-83.9%
	South Korea	-61.1%
	France	-68.2%
	Italy	-52.3%
	Germany	-32.5%
	Spain	-68.1%
	United Kingdom	-80.1%
TA Breakdown	Respiratory	-33.7%
	ID	-46.8%
	Oncology	-48.4%
	Dermatology	-64.0%
	CNS	-68.5%
	Cardiovascular	-69.7%
	Endocrine	-80.5%

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 6, the European Medicines Agency (EMA), U.S. Food and Drug Administration (FDA), Medicines and Healthcare Products Regulatory Agency (MHRA), National Health Service (NHS), and Department of Health and Social Care (DHSC), Japan's Pharmaceuticals and Medical Devices Agency (PMDA), Health Canada, Singapore Health Sciences Authority (HSA), the Association of Clinical Research Organizations (ACRO) and multiple IRBs (an example here) have provided updated emergency guidance on trial conduct during the pandemic.

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. Note that while the FDA, MHRA, and HSA suggests remote SDV 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] have publicly announced that they are modifying their R&D plans - part of that modification is some form of temporary delay in site activation and/or patient enrollment in certain trials. 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.[4] These few but 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 three 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.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 SUPPLY AND QUALITY

Solutions:

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

Details on Medidata's Solutions

The following tables provide details around the Medidata's solutions available now to assist with your trial challenges. Since some aspects of the three 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	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 • Data tracked - measures of enrollment and data collection • Views at study, portfolio, geography level **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** • Develop views on likely volume of re-starts post-recovery by geography and indication • Develop recovery plan and scenarios for acceleration post-recovery across portfolio

Rave RBQM

CHALLENGE	SOLUTION
Regulatory risk assessment & documentation activities **Travel restrictions impacting ability of site staff and monitoring resources to perform oversight responsibilities to ensure subject safety and data quality**	To support regulatory oversight responsibilities Medidata offers 2 solutions within a Risk Based Quality Management (RBQM) framework. 1. The Medidata Risk Assessment Categorization Tool (RACT) supports risk assessment activities in the development and documentation of monitoring strategies by collecting critical to quality data and mitigation strategies 2. 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.

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 already 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 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 global COVID-19 studies with self-quarantined patients.	**Medidata and Dassault Systèmes** are working on an app design that can be used as a remote patient symptom tracker in France and the US. This app will function as a registry immediately (in an MVP version) and will allow hospital staff to remotely review symptoms and triage patients to the hospital only when medically necessary. In subsequent versions, we expect this to be a way to help find patients for trials and to consent them remotely before entering a site that may be performing a study or allowing patients to participate remotely.
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 Arms/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 Data (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.
Challenges 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.

CHALLENGE 3: MAINTAINING SUPPLY AND QUALITY

Rave RTSM

CHALLENGE	SOLUTION
Patients can't get to the site for dispensation but the site is open	Site 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, 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.

Summary

Medidata is working around the clock to identify enhanced and innovative ways to assist you in analyzing the impact of the pandemic on your trials and leveraging current and developing technologies to mitigate risk through increased use of virtual capabilities, advanced analytics for operations and oversight, managing supplies and innovations like synthetic control arms to reduce the number of patients needed for evidence creation, centralization of data oversight, and identification of alternatives in supply management.

While the virus and uncertainty continue unabated, what is certain is that we continue unrelentingly to live and deliver our shared imperative to bring safe and effective therapies to market. Medidata is here for our sponsors, partners and patients throughout this remarkable and challenging time. Our mission has never been more critical than it is right now — Conquering 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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