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The Need for Flexible Pregnancy Safety Studies
An Example in COVID-19 Vaccines

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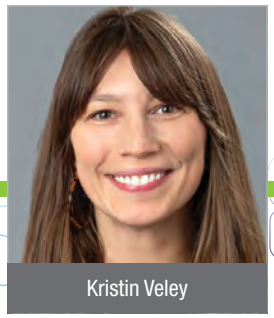
Introduction

The exclusion of pregnant and lactating women from pre-approval clinical trials, for COVID-19 vaccines and other products, results in a lack of safety and efficacy information for this population and necessitates post-approval research. Flexible, observational safety studies of pregnant and lactating women, and of their infants, are imperative to ascertain the impact of product exposure and assess the risk of adverse pregnancy, fetal, and infant outcomes. These studies complement pre-approval clinical trial data and add to the body of evidence regarding product safety and effectiveness.

COVID-19 vaccines present a current and salient example of the need for flexible pregnancy safety study design, allowing us to demonstrate the importance of these studies, propose solutions to commonly encountered challenges, and highlight the best practices and benefits associated with various study designs. To meet the need for post-approval research on the safety of COVID-19 vaccines in pregnant and lactating women, several types of real-world study designs can be implemented—all of which meet regulatory standards and supplement existing vaccine surveillance systems.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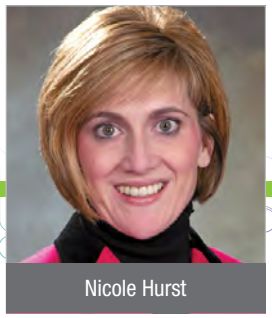
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Current Regulations for Pregnancy Safety Studies in the US and EU

Before we review pregnancy study options, let's survey the current regulatory landscape related to pregnancy safety studies, both in the United States (US) and in the European Union (EU).

The US: Food and Drug Administration (FDA) Requirements

The draft guidance released by the FDA in May 2019[1] increased the rigor of pregnancy safety studies considerably. Now, for products expected to have sufficient pregnancy exposures, the FDA may require sponsors to conduct *both*:

- A prospective, registry-based observational exposure cohort study comparing the maternal, fetal, and infant outcomes of women exposed to the product during pregnancy to an unexposed control population. Adverse outcomes will be assessed throughout pregnancy. Adverse infant outcomes will be assessed through at least the first year of life, AND
- A retrospective cohort study using claims or electronic health records (EHRs) data, or a case control study to assess adverse pregnancy outcomes in women exposed to the product during pregnancy compared to an unexposed control population.

For products expected to have rare pregnancy exposures, the FDA requires that sponsors conduct:

- A worldwide descriptive study, or a global surveillance program, that collects prospective and retrospective data in women exposed to the product during pregnancy to assess the risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through at least the first year of life, and the study will collect information for a minimum of 10 years.

The EU: European Medicines Agency (EMA) Requirements

Risk Management Plans (RMPs)

In the EU, every authorized product requires a risk management plan (RMP). RMPs should reflect the measures considered necessary to identify, characterize, and minimize a medicinal product's important risks. For products with anticipated use in women who are or who may become pregnant, the RMP should also include current understanding of safety in pregnancy and/or breastfeeding, along with the likelihood of use of the medicine in women of child-bearing potential, or who are pregnant or breastfeeding.

Adverse Pregnancy Outcomes Assessed by the FDA

Primary Outcome

- Major congenital malformations (MCM)

Potential Secondary Outcomes

- Pregnancy complications: pre-eclampsia and eclampsia
- Minor congenital malformations
- Spontaneous abortions
- Stillbirth
- Elective termination
- Preterm birth
- Small for gestational age
- Postnatal growth deficiency
- Infant developmental delay
- Any other known or suspected adverse outcomes

Post-Authorization Safety Studies (PASS)

Additional pharmacovigilance activities in the form of PASS should be used if/when:

- The use of a product cannot be discontinued due to the disease being treated, when a disorder arises during pregnancy that necessitates treatment, or when changes in treatment during pregnancy are associated with risks for the pregnant woman and/or fetus.
- A potential risk to the child has been suggested by non-clinical data, a signal, or based on the chemical or pharmacological properties of the medicine.
- The medicine is used to treat conditions that commonly occur in women of child-bearing potential.
- Measuring compliance with risk minimization measures (RMM) regarding pregnancy or breastfeeding.

The EU's current good pharmacovigilance practices (GVP) guidelines for pregnancy studies recommend the following:

- Disease-specific rather than product-specific registries
- Use of existing registries and databases
- Hybrid/ambispective, multi-country study designs
- Prospective enrollment
- Comprehensive inclusion criteria (minimal exclusion criteria)
- Long-term infant follow-up to assess developmental outcomes
- Standardized data collection
- Inclusion of study information in mandated educational materials

The EU currently recommends pregnancy studies to record the following pregnancy outcomes:

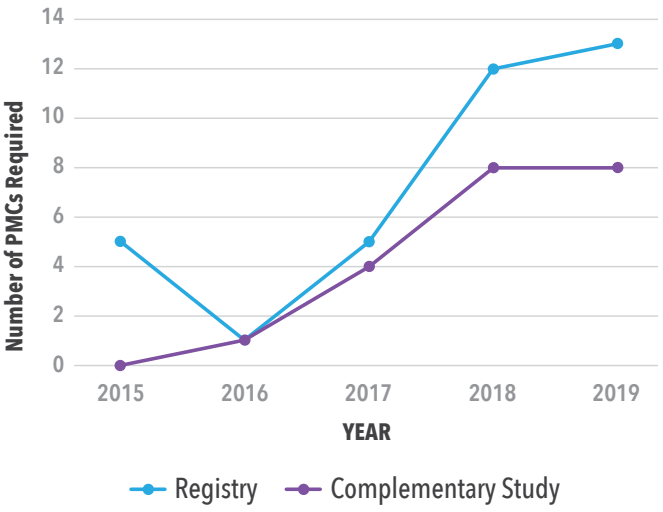
- Malformation/anomalies diagnosed in utero, at birth, or at follow-up
- Ectopic pregnancy, molar pregnancy, spontaneous abortion, elective termination, late fetal death, stillbirth, or live birth
- Infant growth, development, illnesses, and hospitalizations

Pregnancy Safety Studies Are on the Rise

There is an encouraging upward trend in the number of pregnancy safety studies conducted in both the US and the EU.

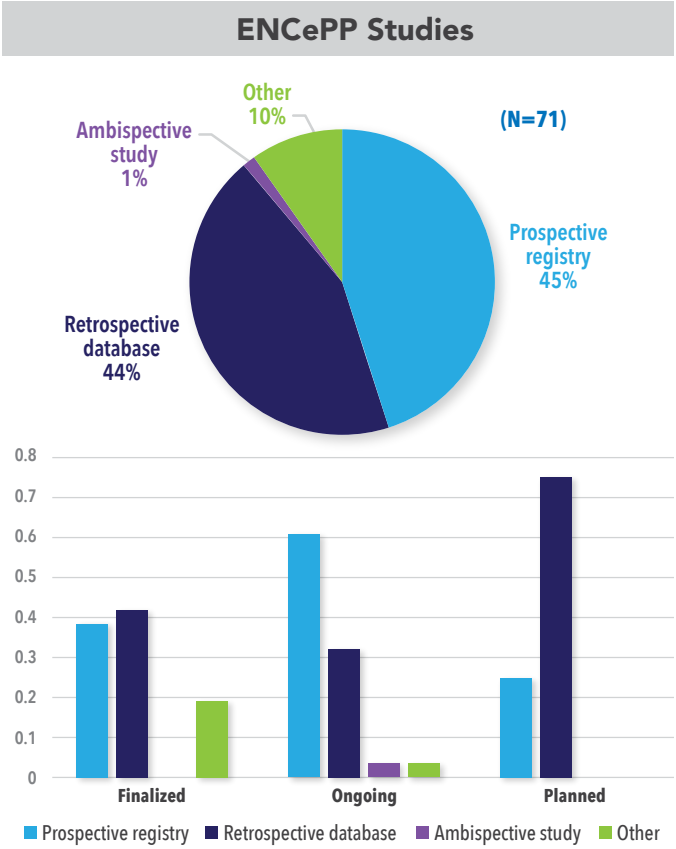
A search of the FDA listing of post-marketing commitments (PMCs)[2] revealed a significant increase, from 2015 to 2019, in the number of pregnancy safety requirements mandated by the Center for Drug Evaluation and Research (CDER) for New Drug Applications (NDA) and Biologics License Applications (BLA). This trend applied for both pregnancy registries and complementary studies (e.g., retrospective database studies) (See Figure 1). By 2019, more than 25 percent of approvals required a pregnancy registry, and nearly 20 percent required a complementary study. Complementary studies were always paired with registry studies unless an existing registry (for example, for the class of medications or disease) was already in progress. Pregnancy post-marketing commitments varied by therapeutic area, with products treating autoimmune disorders being most likely to need a pregnancy safety study and oncology and infectious disease products being least likely.

Figure 1. Frequency of Pregnancy Registry PMCs by Year



A search of the ENCePP (European Network of Centers for Pharmacoepidemiology and Pharmacovigilance) database produced 71 studies that were conducted among pregnant women and assessed the risk of adverse pregnancy and infant outcomes. Of these, about 10 percent were classified as "other," as they were case-controlled studies, meta-analyses, or systematic reviews. There was one ambispective study, and the rest were fairly evenly split between prospective and retrospective studies. When stratified by study status—finalized, ongoing, or planned—we noticed a large uptick in the number of retrospective studies in the planning phase (See Figure 2).

Figure 2. ENCePP Pregnancy Study Types



We anticipate that these positive trends observed in FDA and ENCePP data will continue, and that we will see an increasing number of pregnancy safety studies implemented to assess product safety in pregnant and/or breastfeeding women.

COVID-19 Vaccines and the Need for Flexible Pregnancy Safety Studies

The recently approved COVID-19 vaccines present a timely and compelling opportunity to design flexible pregnancy safety studies. Evidence has accumulated from a variety of sources indicating that pregnant women are at higher risk of severe COVID-19 infection compared to non-pregnant adults.

A study published in the *American Journal of Obstetrics and Gynecology* in January of 2021[3] found that pregnant women are in fact at higher risk of severe disease and mortality compared to non-pregnant adults. This multi-center retrospective cohort study in Washington state compared case fatality rates between pregnant women and similarly aged, non-pregnant adults; maternal and neonatal outcomes were also compared by trimester of infection and disease severity at the time of delivery. The study found that hospitalization and case fatality rates were significantly higher in pregnant women, and that pregnant women with severe COVID-19 infections were at higher risk of pre-term delivery than women who recovered or had mild infections.

The Centers for Disease Control (CDC) and other institutions have published similar findings related to COVID-19 and pregnancy. Based on the accumulation of data, the American College of Obstetricians and Gynecologists (ACOG) recommends that COVID-19 vaccines should be available and administered to pregnant women who wish to be vaccinated, that pregnant women should be free to make their own decision regarding vaccination, and that women should not be denied a vaccine due to their pregnancy status alone.[4]

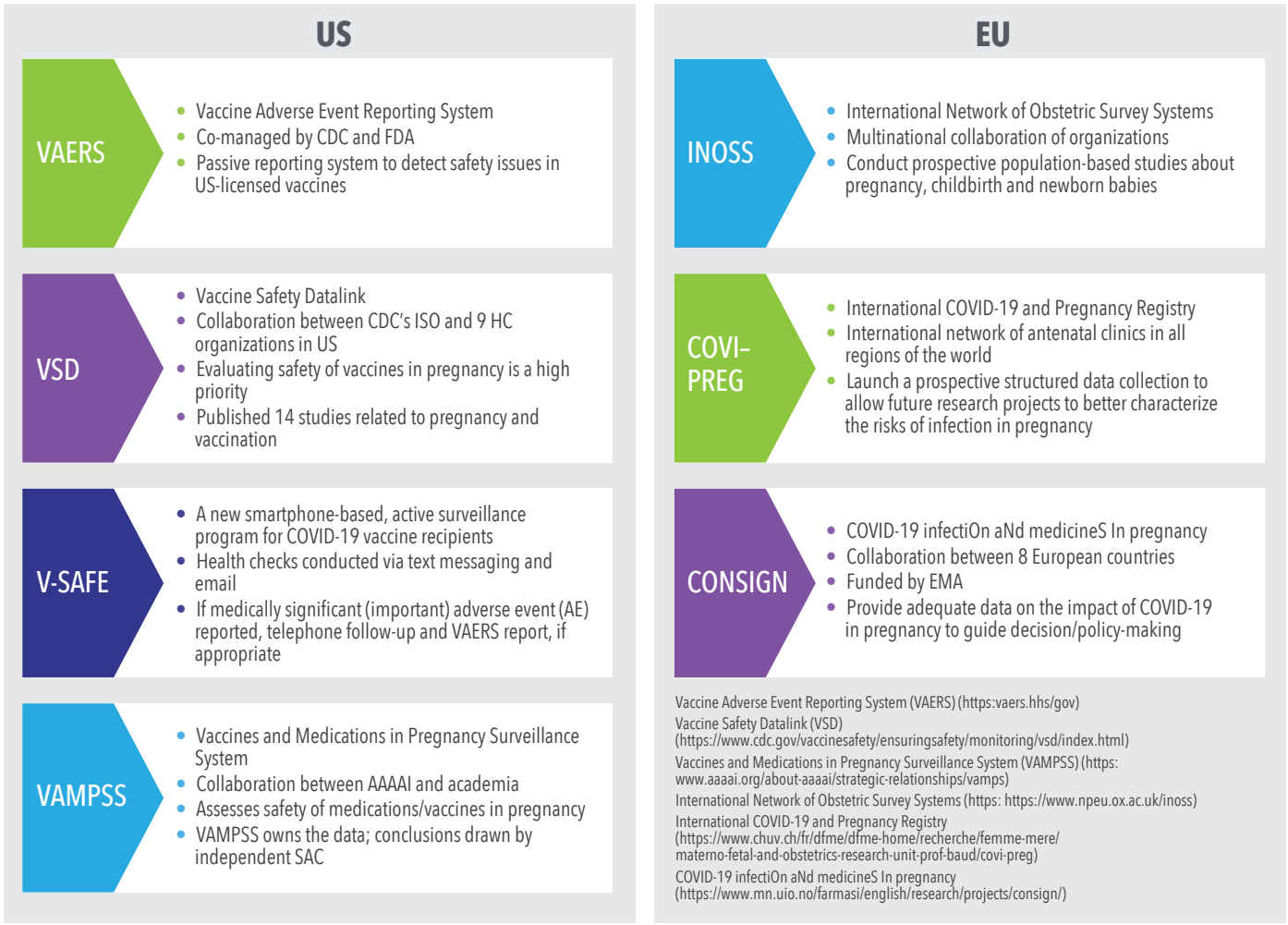
ACOG Recommendations for COVID-19 Vaccination in Pregnant Women[4]

1. COVID-19 vaccines should be available and administered to pregnant women who wish to be vaccinated.
2. Documentation of a discussion is not required.
3. Pregnancy testing prior to vaccination is not required.
4. Pregnant women can receive a vaccine in any setting.
5. Precautions should be discussed if there was a previous allergic reaction to vaccines or polysorbate.
6. If anaphylaxis occurs, the same management is recommended.
7. If a fever occurs, administer acetaminophen.
8. Encourage participation in V-SAFE after vaccination.

Safety Surveillance Systems for COVID-19 Vaccines in Pregnant Women

The CDC and the EMA have both identified pregnant women as a population of interest relative to COVID-19 vaccinations, and have issued plans and recommendations

Figure 3. Existing Surveillance Systems for Monitoring COVID-19 Vaccine Safety in Pregnancy



for further research in this population. Both the US and the EU plan to utilize existing safety surveillance systems to monitor COVID-19 vaccine safety in pregnant women In the US, the CDC plans to leverage Vaccine Adverse Event Reporting System (VAERS), Vaccine Safety Datalink (VSD), and V-SAFE; in the EU, the EMA encourages collaboration with COVID-19 infectiOn aNd medicineS In preGNancy (CONSIGN), International COVID-19 and Pregnancy Registry (COVI-PREG), and the International Network of Obstetric Survey Systems (INOSS).

Some of these systems existed prior to COVID-19, including VAERS, VSD, Vaccines and Medications in Pregnancy Surveillance System (VAMPSS), and INOSS, while others are COVID-19-specific. V-SAFE is a new, smartphone-based active surveillance program in the US that conducts health checks of vaccine recipients via text message or email. If an important adverse event is reported, a telephone follow-up and a report are completed if appropriate. COVI-PREG and CONSIGN are also COVID-19-specific initiatives. Figure 3 outlines the existing surveillance systems that can be leveraged to monitor COVID-19 vaccine safety in pregnancy.

Approved COVID-19 Vaccines and Planned Pregnancy Safety Studies

In the US, three COVID-19 vaccines are currently approved under the FDA's Emergency Use Authorization: those manufactured by Pfizer-BioNTech, Moderna, and Johnson & Johnson (Janssen). The FDA approval letters for these vaccines indicate that all three have identical post-marketing requirements related to pregnancy. They must conduct observational studies to evaluate the safety of their vaccines in several populations of interest, including pregnant women, and the FDA further specified that these studies should be conducted in large-scale databases with active comparator groups.

In the EU, four vaccines are currently authorized for use. In addition to the three COVID-19 vaccines approved in the US, the AstraZeneca vaccine is authorized in the EU. Routine safety monitoring for these vaccines includes adverse event reporting via EudraVigilance, which is the system operated by the EMA for tracking suspected product side effects. The EMA also releases monthly safety updates on each authorized vaccine. The RMP for each vaccine includes several studies that either specifically or potentially evaluate pregnancy safety. Several prospective pregnancy registries are planned, and studies using secondary data sources are ongoing or planned for each vaccine.

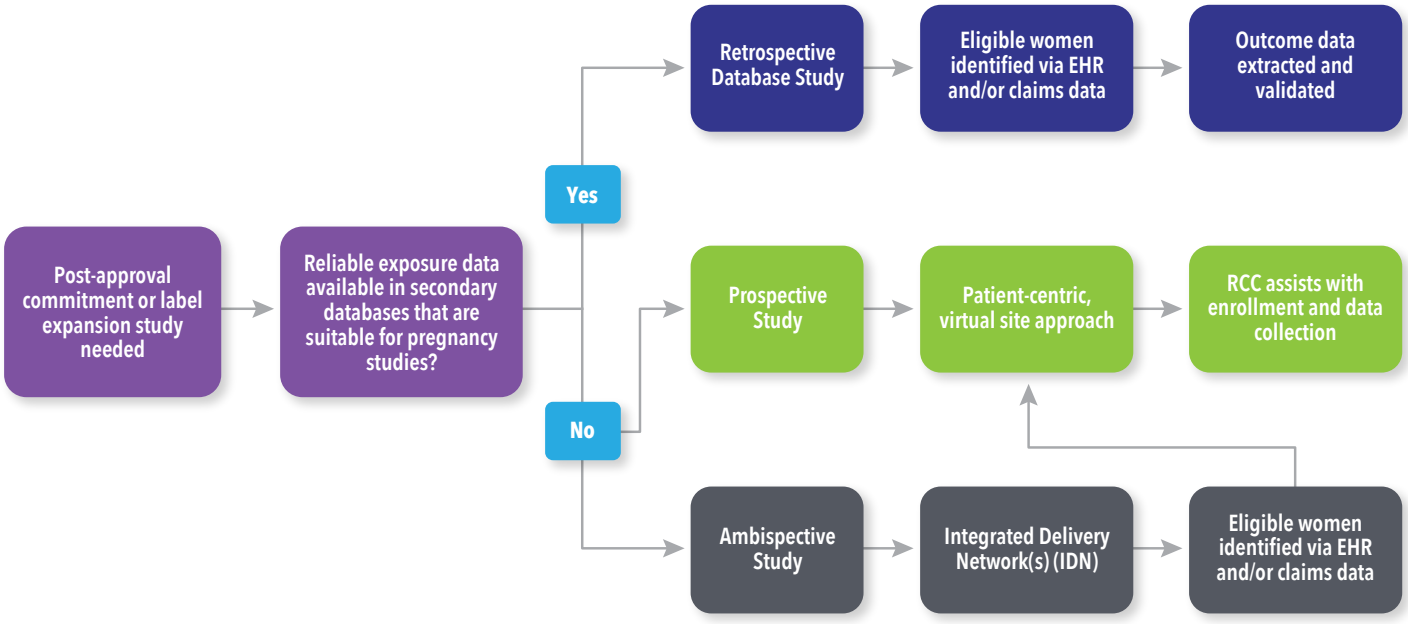
A Closer Look at Flexible Pregnancy Study Designs

A flexible approach to pregnancy study design encourages participation and facilitates data collection, resulting in greater sample sizes and a more thorough assessment of safety. We'll consider the common challenges presented by prospective, retrospective, and ambispective pregnancy study designs, and offer practical solutions. There are multiple factors to consider when selecting a study design (See Figure 4).

Prospective Pregnancy Registry Design

Eligible women typically enroll in a prospective registry after they become aware of their pregnancy, and they provide consent and medical releases for their healthcare providers (HCPs) to submit data to the registry. Only data routinely

Figure 4. Pregnancy Study Design Decision Tree



RCC: Registry Coordinating Center

documented in the patient's chart as part of usual care are collected. Data are typically collected at enrollment, at the end of the second trimester, and at or immediately after the pregnancy outcome. For live-born infants, data collection is continued post delivery, typically at four and twelve months. The pregnant woman herself is typically responsible for answering some initial eligibility questions and providing basic demographic data at enrollment. The majority of the data are collected from the healthcare providers involved in her care, or in the care of her infant, minimizing the burden on the patient.

One of the greatest challenges with prospective studies is recruiting eligible patients. A patient-centric, virtual site approach enables pregnant women to enroll in a prospective registry regardless of their proximity to a study site. Creation of a targeted and customized awareness plan for each registry assists in reaching HCPs and patients in a variety of settings. To encourage enrollment, it is helpful to create a registry website, and to place links to the website on other prominent websites, such as the FDA's listing of pregnancy registries and sponsor- and product-specific websites.

There are some notable recruitment challenges that are specific to COVID-19 vaccines. Because COVID-19 vaccines are not currently explicitly indicated in pregnancy, there may be a barrier to recruitment. It will be important to use a multi-pronged recruitment strategy to leverage existing data sources to bolster recruitment, and to monitor COVID-19 cases and vaccines in real time. It may also prove challenging to confirm exposure data, due to the variety of settings in which vaccines are offered, and perhaps also the lack of patient awareness of the brand of vaccine that was received. A potential solution may be photo documentation of vaccine records to confirm exposure, or confirmation of exposure through either the patient's HCP or the vaccine administrator.

Retrospective Pregnancy Registry Design

Retrospective study designs utilize secondary data, which are collected in the usual course of medical care and accessed through de-identified databases that represent large populations of patients. The data are historical and analyses are typically iterative, in which interim analyses are repeated until the set of final analyses. Subsequent analyses can include women who newly qualify for the study based on drug exposure, as well as additional follow-up data on infants. Twelve-month infant follow-up is typically required because not all congenital malformations—which are the standard primary outcome of interest—are diagnosed at birth. The baseline period is used to characterize patients based on demographic and clinical characteristics, as well as healthcare resource utilization, and the pregnancy period is estimated based on gestational age information within diagnosis codes recorded during the pregnancy.

Retrospective Pregnancy Registry Design: Database Considerations

- Pregnant women are identified from claims or EHR database
- When using claims, typically use a closed claims system database for complete view of all covered services
- Must be able to link mother to child in database
- Even in databases where a linkage is available, not all mothers can be linked to their infants
- In the absence of a validated algorithm to identify outcomes, must be able to directly validate outcomes via charts
- Sample size must be considered, but use of newly-approved drugs is expected to be low at initiation of study

There are several challenges unique to retrospective study designs. It can be difficult to select an appropriate comparator, given that comparators may differ by therapeutic area and other approved medications for that indication. Appropriate comparators may include "healthy" controls and women taking medications off-label for that indication. Low sample sizes are a common concern, particularly when a medication, treatment, or vaccine is new. Sample sizes might be increased by adding databases or extending the study period when necessary. While the date of conception or date of last menstrual period is not captured in claims data, the start of pregnancy can be estimated using validated algorithms that use the gestational age information recorded in diagnosis codes during the pregnancy period.

Ambispective Pregnancy Registry Design

An ambispective registry design implements some of the features of both retrospective and prospective registries. The term hybrid is sometimes used to describe this design, but ambispective is more accurate. Ambispective studies use data from large integrated delivery networks (IDNs). Patients are identified via EHRs, which can be supplemented with prospective data collection if needed. The greatest benefit is that data can be captured from multiple sources without having to go directly to that source or site. Because patients who are insured by the IDN are typically incentivized to visit IDN-owned facilities, there is typically reliable identification of care across various healthcare settings.

Ambispective registries can mitigate many of the challenges associated with retrospective and prospective study designs. For example, potentially eligible patients can be identified directly from the EHR data to mitigate recruitment challenges, and data that are not available or poorly captured in the EHRs may be collected directly from patients.

Additional Pregnancy Safety Studies

Lactation Studies

In lactation studies, the objective is to evaluate whether there is a breastmilk transfer of the product from the mother to the infant, to calculate the estimated infant dose, and also to evaluate the safety of the breastfed infants.

Placental Transfer Studies

In placental transfer studies, the objective is to evaluate whether there is a placental transfer of the product from the mother to the infant.

Pharmacokinetic Studies

In pharmacokinetic (PK) studies, the objective is to evaluate whether the physiological changes that occur during pregnancy impact the PK profile of a product.

Other Observational Studies

Other types of observational studies can be conducted for a variety of reasons (e.g., to expand the label or to inform future research).

Regardless of the type of pregnancy safety study, it is critical to design flexible models that encourage patient enrollment. Solutions may include hybrid models with both in-person and remote enrollment, as well as flexible recruitment methods that utilize advertising, social media, and advocacy groups. Streamlined data collection relieves the burden on the patient and the HCP. For example, home health nurses can be used in lactation and/or placental transfer studies, allowing data collection to occur without the patient ever leaving home and without undue burden at the healthcare facility. Patient reimbursement can also increase enrollment and retention.

Conclusion

Flexible study designs are imperative for assessing product safety during pregnancy. While prospective and retrospective study designs may be sufficient, ambispective designs optimize the benefits of each, while avoiding many of the challenges. Multiple sources of data and multiple perspectives are complementary, and together provide a more holistic view of the pregnant woman and her infant(s)—and the journey through pregnancy, delivery, and beyond. For each new product that comes to market, including COVID-19 vaccines, regulators must decide whether further post-marketing research will be required to assess product safety in pregnancy, and the studies that are designed to meet this objective must be tailored to the characteristics of the product and the patients who are using it. ■

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Emergency Use Authorization and Antigen Diagnostic Tests for COVID-19

Challenges and Future Trends

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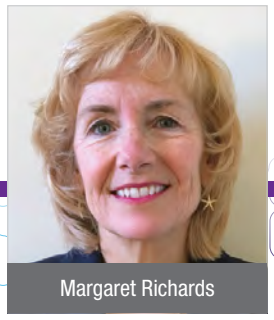
In Vitro Diagnostic EUAs for COVID-19

Since the US Department of Health and Human Services Secretary declared COVID-19 a public health emergency on February 4, 2020, the US Food and Drug Administration (FDA) has issued numerous Emergency Use Authorizations (EUAs) for in vitro diagnostic devices (IVDs) to detect various targets of current or past COVID-19 infection.

An EUA is one of several tools the FDA has used to quickly make certain medical products available during the COVID-19 pandemic. In emergencies, the FDA can issue an EUA to provide access to medical products that may be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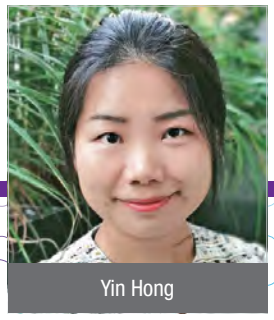
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Table 1. In Vitro Diagnostic (IVD) EUAs[2]

Type of IVD	Number of Authorized Tests as of April 27, 2021	Purpose
Molecular Diagnostic Test	241	Detection of SARS-CoV-2 nucleic acid for current infection; sample collection devices for molecular testing
Molecular Laboratory Developed Test	32	Detection of SARS-CoV-2 nucleic acid for current infection
Antigen Diagnostic Test	23	Detection of SARS-CoV-2 antigen for current infection
Serology Test	76	Detection of SARS-CoV-2 antibodies for past infection
Tests for Management of COVID-19 Patients	3	Detection of biomarkers for patients diagnosed with COVID-19
TOTAL	**375**	

used when there are no adequate, approved, or available options.[1] The EUA process is different than an FDA approval or clearance. Under an EUA, the FDA makes a product available to the public based on the best available evidence, without waiting for all the evidence that would be needed for full approval.[1] EUAs remain in effect until the emergency declaration ends.

The amount of EUA activity for IVDs in the past year is stunning, as shown in Table 1.

The greatest number of IVD EUAs are associated with molecular diagnostic tests (n=241). We chose to take a closer look at antigen diagnostic tests, however, because they hold the most public health promise in terms of speed, ease of administration, reasonable sensitivity and specificity, and cost.

Antigen Diagnostic Tests

Antigen diagnostic tests identify the SARS-CoV-2 nucleocapsid protein antigen. Currently, the molecular diagnostic test using real-time reverse transcriptase-polymerase chain reaction (RT-PCR) remains the "gold standard" for the diagnosis of COVID-19 due to its high sensitivity and specificity to detect viral RNA.[3] However, RT-PCRs often require longer turnaround times and must be processed by trained laboratory staff with higher associated costs for the test kit and equipment.[4] Antigen diagnostic tests, which require minimal training and equipment, have faster processing times and lower costs. Table 2 compares the antigen diagnostic test to the standard RT-PCR.

A total of 23 antigen diagnostic tests have been authorized by the FDA as of April 27, 2021 (See Table 3). Samples from nasopharyngeal or nasal swabs can be collected and

Table 2. Antigen Diagnostic Test vs. Standard RT-PCR[5,6]

Characteristic	Antigen Diagnostic Tests	Standard RT-PCR Tests
Wait Time	~ 15 minutes processing	~ 2–6 hours processing, 2–4 days if samples need to be shipped
Cost	Low ($5–$10 per test)	High (test kit up to $200 plus shipping, lab equipment, staff, etc.)
Staff Required	Healthcare provider or self–/other–collected	Healthcare provider and highly trained laboratory staff
Sample Types	NP or NS if collected by healthcare provider; NS if home use	NP preferred, but NS, saliva, and other tissue samples are, or will become, available
Sensitivity and Specificity	High specificity; sensitivity drops with medium or low viral load	High sensitivity and specificity

NP: nasopharyngeal swab; NS: nasal swab

Table 3. List of EUAs for Antigen Diagnostic Tests as of April 27, 2021[2]

Intended Use	Number of Antigen Test EUAs	Sample Type	Reading Method	Days Since Symptom Onset	Total Samples Tested	% Positivity (test positive proportion)	PPA	NPA
Lab Use (H/M) Prescription	5	NP NS	Instrument read	0–5, 0-7, or 0–14 days	72–141	22.7%–69.8%	80%–97.7%	100%
POC Use Prescription with or without serial screening	12	NP NS	Instrument read; Visual read	0–5, 0-7, or 0–12 days or without symptoms	92–460	13.7%–42.4%	84%–97.6%	96.6%–100%
Home Use Prescription	2	NS	Visual read	0–6 or 0–7 days	52–161	28.6%–46.2%	84.8%–91.7%	99.1%–100%
Home Use OTC screening or serial screening	4	NS	Instrument read; Visual read	With or without symptoms	52–350	18.7%–46.2%	83.5%–95%	99.2%–100%

PPA: Positive Percent Agreement; NPA: Negative Percent Agreement; NP: nasopharyngeal swab; NS: nasal swab; Lab: Laboratories certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), 42 U.S.C. §263a, that meet requirements to perform moderate (M), high (H), or waived (W) complexity tests; POC (Point of Care): Patient care settings operating under a CLIA Certificate of Waiver; OTC: Over the Counter

processed by healthcare providers for point-of-care (POC) use or self-/other-administration in home use. Some antigen tests require a prescription and symptoms, whereas others are made available over-the-counter (OTC) with symptoms optional. Some tests are for adults only whereas others can be used for ages two and older.

EUA for Antigen Diagnostic Test

For antigen diagnostic test developers requesting an EUA, the FDA recommends several validation studies to determine the test's clinical and analytical performance. The FDA website has two templates, one for an antigen diagnostic test for laboratory and POC use and one for home use,[2] that include some of the validation studies needed for analytical performance (See Figure 1). For clinical performance, a usability study is recommended for the POC claim to demonstrate that healthcare providers can perform the test from the instructions given in the test kit. This is also recommended for home use to demonstrate that an individual can perform the test accurately, either self-collected or other-collected, depending on the intended use.

Clinical evaluation is done to compare the performance of the antigen test versus a comparator RT-PCR test authorized by the FDA.[7] Performance is assessed as Positive Percent Agreement (PPA) and Negative Percent Agreement (NPA), percentages that are similar in concept to sensitivity and specificity, respectively. As there is no current reference standard available, PPA and NPA are used instead of sensitivity and specificity because the latter assume a reference standard.

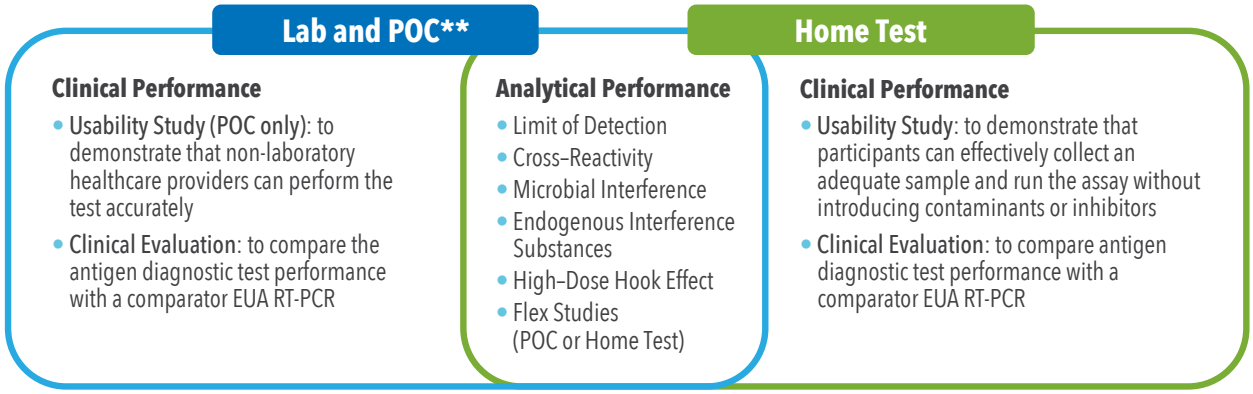
A PPA of ≥ 80% is required for laboratory-based POC and home use tests that are prescription only. For OTC home use, a PPA ≥ 90% and an NPA ≥ 99% are required for both asymptomatic and symptomatic individuals.

Challenges

In general, antigen tests have high specificity (NPA), but relatively moderate sensitivity (PPA) compared to an RT-PCR (See Table 2). The sensitivity of antigen tests drops in samples with RT-PCR cycle threshold (Ct) values > 30, which are samples with medium to low viral loads.[8] A Ct value is the cycle of amplification at which the fluorescence crosses the threshold to become positive and viral load and Ct threshold values are inversely correlated. Simply put, the higher the viral load the lower the Ct value and vice versa. Although more data are required, higher viral load is thought to be related to higher transmissibility[9] and risk of intubation and mortality.[10] An antigen test may identify individuals with higher viral load who are most likely to infect others. Viral loads correlate well with date of diagnosis and/or symptom onset; they are the highest within 1-5 days of infection and decline thereafter.[9]

Interestingly and importantly, viral load does *not* seem to correlate with any one COVID-19 symptom or symptom constellation. Those who are asymptomatic but have a positive test can nonetheless have a high viral load (and transmit disease), which is one of the characteristics of COVID-19 that has made it difficult to manage. As the pandemic begins to wane globally, rapid antigen tests on both symptomatic and asymptomatic persons for screening purposes could be particularly useful.

Figure 1. Validation Studies Recommended for Antigen Diagnostic EUAs*



* This list covers the main validation studies recommended in the EUA templates and some studies may not be applicable in certain conditions. For a complete list of validation studies, please refer to the FDA website.[2]

** Laboratories certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), 42 U.S.C. §263a, that meet requirements to perform high or moderate complexity tests; Patient care settings operating under a CLIA Certificate of Waiver.

Future Trends

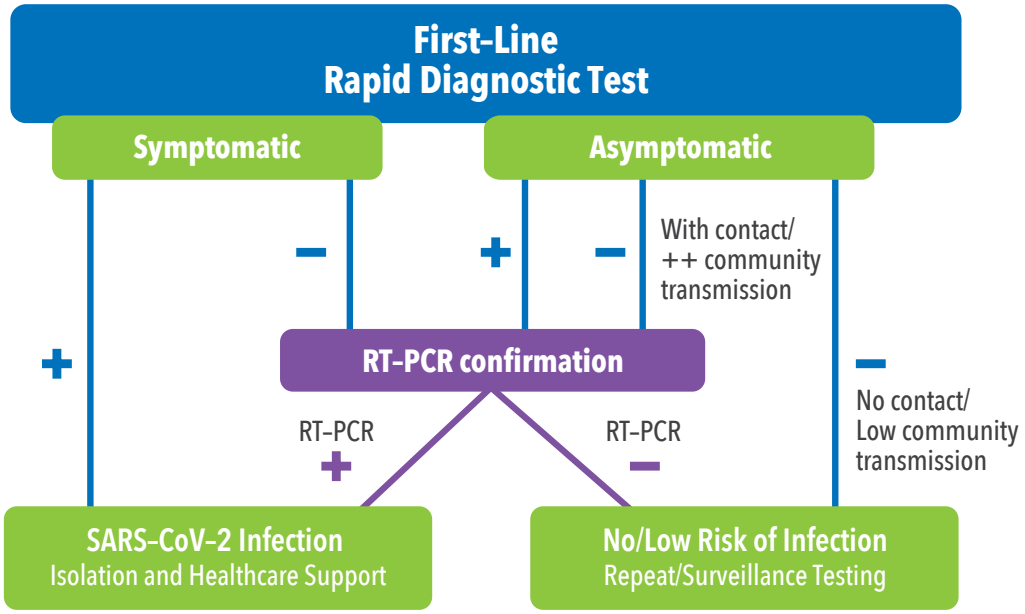
Although an antigen diagnostic test is not as sensitive as an RT-PCR, it can be very useful from a public health perspective. Situations of public health import include:

- Persons with limited access to a standard RT-PCR
- Individuals not meeting RT-PCR testing criteria
- Home-use/screening (when COVID-19 exposure is suspected or known, especially with underlying conditions or susceptibility)
- Community settings such as universities or workspaces where large numbers of people gather regularly and need to be tested often

One study has shown that frequent mass testing using rapid tests as part of a screening program might be more cost-effective than a standard testing approach.[11] To date, only four rapid antigen tests and two rapid molecular tests have received an EUA for OTC use (symptomatic and asymptomatic individuals, screening, or serial screening). Various testing algorithms have been proposed by health authorities using rapid tests as first-line screening under certain conditions and, depending on the screening result, branching out into different decisions involving RT-PCR test confirmation, isolation, surveillance testing, etc.

Figure 2 shows one test flow. Other test flows have been devised by regulatory and health authority agencies around the globe.

Figure 2. COVID-19 Diagnostic Test Flow Chart[6,12,13]



The beauty of a rapid diagnostic first-line test is the ability to scale mass testing with low cost and rapid response. An approach that involves RT-PCR testing first-line is potentially expensive and can cause delays. The fact that these rapid tests have moderate sensitivity and high specificity is an advantage. There are few false positives (due to high specificity) and more false negatives (due to moderate sensitivity), but the latter are assumed to be associated with a lower viral load and thus a less contagious individual. If a false negative rapid test individual is allowed to move about his/her sphere, the chances are that his or her viral load is no longer a threat.

Conclusion

The COVID-19 pandemic has stimulated innovation in COVID-19 IVD assays, treatments, and vaccines, and that progress has brought confusion, disappointment, rapidity, ingenuity, and elegance. There is no doubt that diagnosis, treatment, and prevention will all play key roles in managing the current and any future pandemics. Hopefully, the lessons learned from COVID-19 diagnostic product development will translate to other IVD diagnostics, infectious or otherwise. ■

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Enhancing Clinical Trial Diversity in the Era of Decentralized Trials

The Value of Patient Insights

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Introduction

Decentralized trials provide new opportunities to achieve more diverse geographic and socioeconomic patient participation in clinical trials.[1] Proactively assessing study design and recruitment approaches to improve access and diversity has become an essential aspect of decentralized trials.[2]

In the past year, recruitment for COVID-19 clinical trials faced unprecedented challenges.[3] There was a need to fast-track trials for testing treatments for people at high-risk for disease complications. COVID-19 treatment trials that favored a decentralized approach, however, were faced with additional challenges. Potential participants lacked a familiarity and understanding of the clinical trial testing and drug development processes, which exacerbated these challenges.

Early engagement with potential study participants at the start of clinical trials presents an opportunity to explore patients' expectations, experiences, and perspectives;

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examine recruitment approaches and materials used to support recruitment; and explore what resonates with target subgroups.[4] This article will discuss a case study which gathered patient insights using qualitative methods to provide a more in-depth and nuanced understanding beyond the restrictions of traditional survey methods.[5]

Finding the Right Avenues for Recruitment

Pathways for obtaining a COVID-19 test were similar across age groups and ethnicities in the United Kingdom and United States (US). Overall, most participants (86%) reported getting tested only after developing symptoms. A small subset, 26% of US Spanish speakers, reported getting tested before developing symptoms, mainly due to known exposure or job requirements.

Participants said they found COVID-19 testing sites via local public health websites or from friends and family. A large proportion (43%-58%) consulted a healthcare professional to identify a testing site location or testing site appointment

Case Study Overview

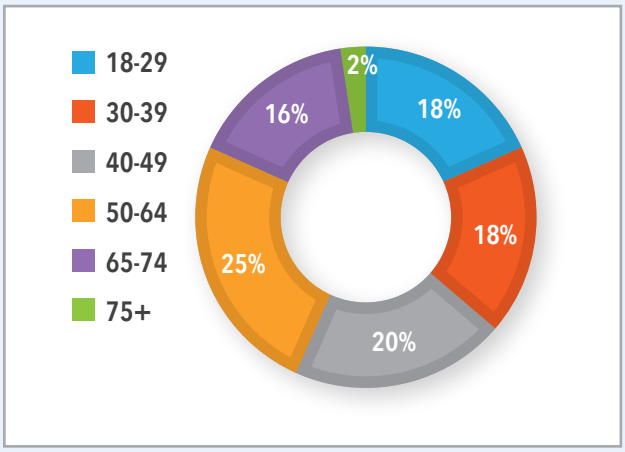
Population: A sample of 100 adults who tested positive for COVID-19 from April 2020 to October 2020, experienced symptoms, and sought medical consultation or treatment. The sample included specific age and race/ethnicity targets. Adults considered high risk for COVID-19 progression (≥55 years of age and/or with a comorbid condition) made up about 50% of the sample.

Challenge: To address recruitment challenges related to COVID-19 treatment trials aimed at reducing symptom duration or disease progression.

Approach: Focus groups and interviews. Ahead of the interview, a structured questionnaire asked participants to characterize their experience with the disease (symptoms, duration, severity), treatment information, medical consultation, and any expectations and/or experience participating in a clinical trial. A semi-structured interview guide was used to support the qualitative research; trial outreach materials were also discussed.

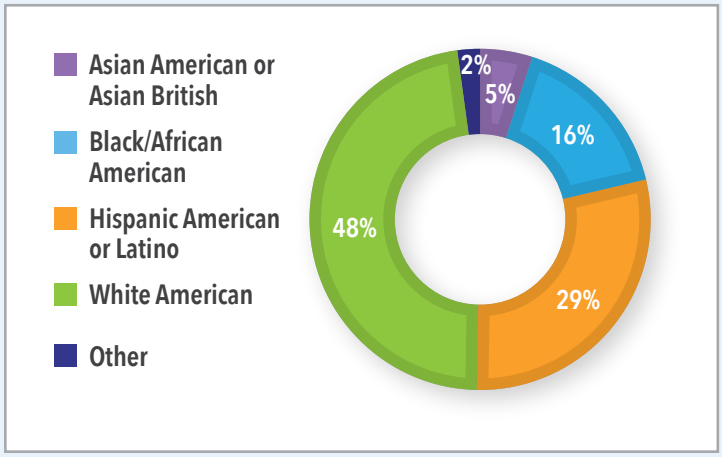
Key Findings: Most of the participants were female (64%), from the United States (89%) or the United Kingdom (11%), at high-risk for progression of COVID-19 (55%), with diverse ages and ethnicities (See Figures 1 and 2). Symptoms ranged from mild to moderate, with fatigue, muscle aches, headache, and fever resolving after two weeks. Several individuals in the high-risk group reported severe symptoms and complications that required hospitalization. The groups discussed the need to understand a COVID-19 patients' journey from testing to diagnosis and treatment, the path to wellness, and the potential touchpoints and opportunities for recruitment. Ensuring the right stakeholder to support recruitment, especially one that potential study participants could trust, would be important, as was the patient's motivation to test for COVID-19, the timing of the test, and touchpoints with healthcare professionals and testing centers.

Figure 1. Focus Group Participants by Age



> "It wasn't like I had it and it was over, you start feeling good after a week - and then bam, it hits you again. That happens for about 2-3 weeks: you feel great, and then all a sudden I couldn't do anything."
>
> *– US029, high-risk group, Age 50-64, male, White American*

Figure 2. Focus Group Participants by Race/Ethnic Groups



system. The high-risk participants were more likely to seek medical consultation before testing positive for COVID-19 compared to those with a lower risk. Everyone agreed that their medical doctor, healthcare team, or other highly regarded public health or medical authority, such as a local hospital, the Centers for Disease Control and Prevention, etc., would be a trusted source for information about COVID-19 treatment trials.

Some participants said receiving information about COVID-19 treatment trials at a testing site might not be ideal since people waiting for a COVID-19 test may be apprehensive and unreceptive to trial advertisements or flyers. Several pointed out that since they knew where to go to get tested, they could have been made aware of treatment trials if they had been advertised in the same way. They also noted that people who seek testing before they develop symptoms (i.e., in the case of known exposure) may be more receptive to learning about treatment trial opportunities. The high-risk group also thought people in a similar demographic may be easier to target since they receive regular medical care and are likely aware of the potential risk for long-term symptoms and/or complications. The recommended touchpoints for recruitment to COVID-19 treatment clinical trials were healthcare providers, COVID-19 testing sites, local public health websites, and contact tracers.

> "When someone is positive and sick, the timing does not allow to find out about a treatment trial and enroll. It would be important to get the word out before people get sick."
>
> – *US-038, **Low-risk group, Age 50-64, female, White American***

Drivers for Participation in Clinical Trials

Overall, 38% of all study participants indicated they would be willing to participate in a COVID-19 treatment trial while 43% said they were not sure. In the high-risk group, 35% said they would be willing to participate and 47% said they were not sure. Only 18% of both groups said they would not participate in a trial (See Figure 3).

Most Asian American and Asian British participants said they would consider participating in COVID-19 treatment trials. White American, White British, Black/African Americans and Hispanic Americans/Latinos were less sure (See Figure 4).

> "Since I had symptoms for 1-2 days, I would only participate if I had more symptoms, knowing there is a potential benefit to participating."
>
> – *US-026, **High-risk group, Age 50-64, male, Hispanic American or Latino***

Figure 3. Participants Who Would Consider Participating in a COVID-19 Treatment Trial by Risk Group

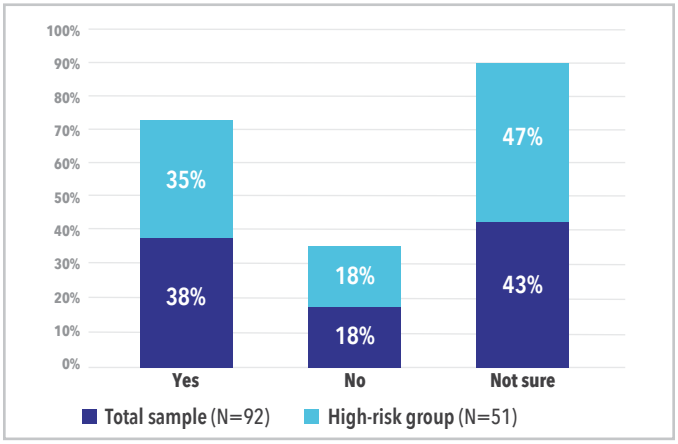


Figure 4. Participants Who Would Consider Participating in COVID-19 Treatment Trials by Race/Ethnicity

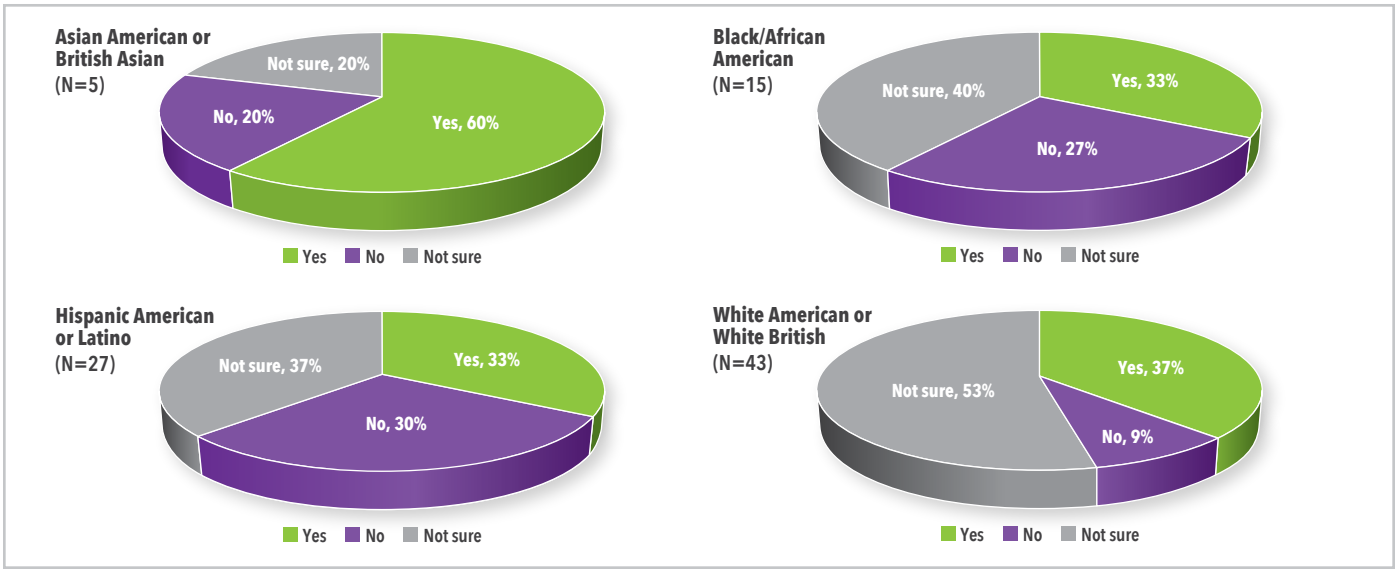
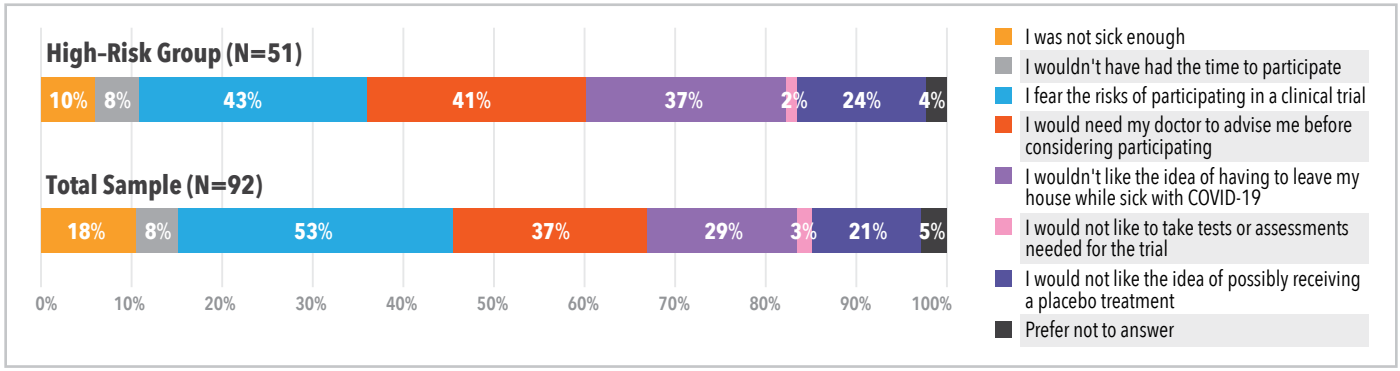


Figure 5. Barriers for COVID-19 Clinical Trial Participation by Risk Group



> "Time would be an obstacle for me. I would be motivated if it didn't take a lot of time."
>
> – *SP03, Low-risk group, Age 65-74, female, Hispanic American or Latino*

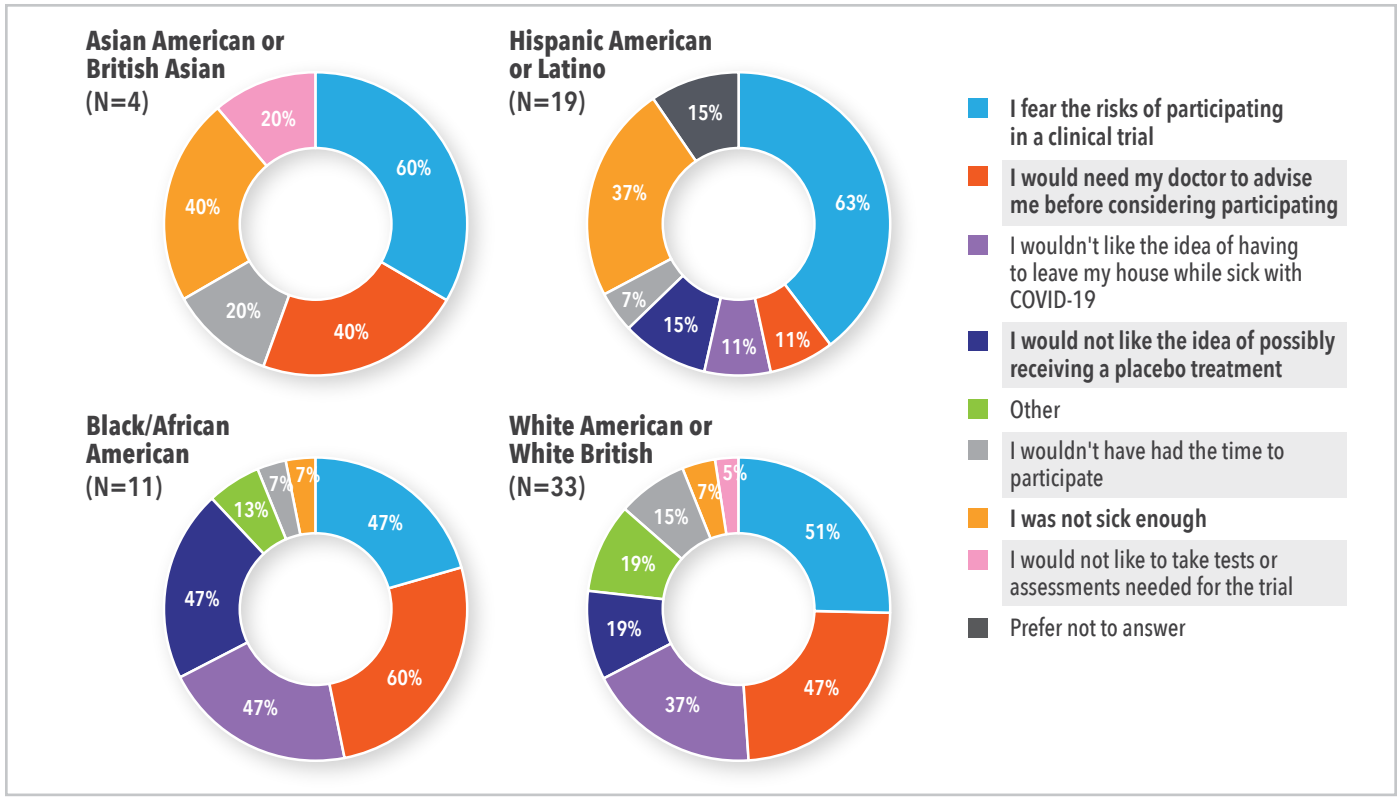
Addressing Barriers to Participation in COVID-19 Treatment Trials

When asked why they were hesitant or did not want to participate in a clinical treatment trial, many participants said they were afraid of an unknown treatment and unsure whether the risk of complications was greater than the risk of a new treatment. Ideally, they wanted a doctor to advise them whether to participate. In the high-risk group, participants said they would be worried about leaving their house while sick with COVID-19 to fulfill clinical trial requirements (See Figure 5).

Similar barriers were discussed across race/ethnicity groups. The top four barriers were fear of the risks of participation, not thinking they were sick enough, wanting a doctor to advise them, and not wanting to leave the house while sick with COVID-19 (See Figure 6).

> "I have diabetes. I would participate if I knew side effects would be minimal, and if someone can advise me. I like that you can participate in the trial at home."
>
> – *SP024, High-risk group, Age 40-49, female, Hispanic American or Latino*

Figure 6. Barriers for COVID-19 Clinical Trial Participation by Race/Ethnicity



> "It [feels like] kind of the right thing to do, but I'd need to be pretty majorly reassured [on what will need to do]."
>
> – *UK05, **Low-risk group, Age 40-49, male, White British***

Considerations for Enhancing Diversity of Clinical Trial Sample

Overall, participants noted that they would like more information before deciding whether to participate in a treatment trial. Across race/ethnicity groups, what information participants wanted to know before participating in a treatment trial varied (See Table 1). African Americans, Hispanic Americans, and White Americans wanted to understand the risks of the treatment being tested, as well as who was sponsoring or was responsible for the treatment trial. For Asian Americans and Hispanic Americans, knowing where the trial would take place was most important.

> "I would be motivated to participate if I can help someone else and keep them from going through what I did."
>
> – *US068, **High-risk group, Age 75+, female, Black/African American***

Participants had many opinions about the COVID-19 clinical trial study flyer used to advertise recruitment and made suggestions for what other information should be included on the flyer or made available on a recruitment website. Practical information about what the trial entails also factored into the decision-making process:

- Is this an existing medication or a new medication?
- What procedures are involved?
- Will there be a medical professional available if I have questions?
- How will I be monitored?
- How long will the trial last and what responsibilities do I have as a participant?
- Can treatment and/or assessment be done at home?
- Who is the study sponsor?
- What are the potential benefits and risks of participating?
- Are study participants compensated? If travel is required, will travel expenses be reimbursed?

Name recognition is also important, as is trust in the company running the trial. Trial recruitment materials should consider using inclusive pictures or graphics depicting broad age, gender, and ethnicity ranges. The slogan for the study should also be a broad message that draws people in, and should have an option for a website, text/SMS, or QR code for people to access more information or have options to speak to a healthcare professional directly. Many talked about the value of focused messaging to appeal to humanity's altruistic nature and desire to help others during the pandemic.

Lessons Learned from Early Engagements

Through early engagement efforts using in-depth qualitative focus groups and interviews it is possible to understand a patient's experience, the touchpoints patients might have with the healthcare system, the potential barriers and motivators for clinical trial participation, and messaging that could enhance recruitment.

Table 1. Top 3 Things Potential Participants Want to Know About COVID-19 Treatment Trials: Information to Include in Recruitment Materials

	Asian American Asian British	Black/African American	Hispanic American or Latino	White American White British
1	Where the visits would take place	Type of treatment tested	Risks of treatment tested	Risks of treatment tested
2	Duration of trial	Risks of treatment tested	Where the visits would take place	Type of treatment tested
3	Payment for participation	Who is responsible for the trial	Who is responsible for the trial	Who is responsible for the trial

In the case study presented, a diverse group of patients with previous experience with COVID-19 explored ways to enhance diversity in clinical trials. They discussed patient-preferred touchpoints where they receive information about treatment trials, trusted sources for receiving information, and preferred clinical trial messaging. This patient engagement effort resulted in informing recruitment strategies and ensured that outreach materials for the COVID-19 clinical treatment trials contained inclusive messaging, appealing images, and accessible information. ■

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A New Framework for Modeling Disease-Modifying Treatment Strategies for Parkinson's Disease

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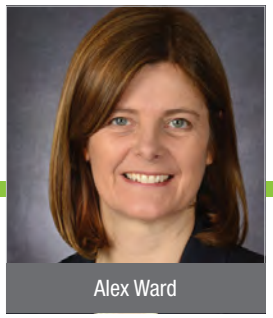
Introduction

Parkinson's disease (PD) is a progressive disease that leads to both motor and non-motor symptoms. There is currently no disease-modifying therapy (DMT) available for the treatment of patients with PD, but new therapies are being studied and entering clinical trials.[1] Most of these clinical trials will use the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) subscales as primary outcomes, and plan to study patients recently diagnosed with PD.

Many health economic models have assessed the cost-effectiveness of existing treatments for PD. According to the findings of a systematic literature review, most published models used a Markov cohort approach, where the Hoehn and Yahr scale was commonly used to define and model transitions between health states. As the models identified did not consider MDS-UPDRS, a need was identified for a de novo model to support the assessment of the health economics of DMTs administered soon after diagnosis. The de novo model was built upon the MDS-UPDRS scales to align with the clinical trial designs.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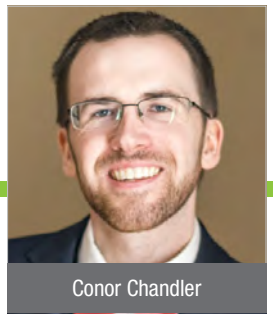
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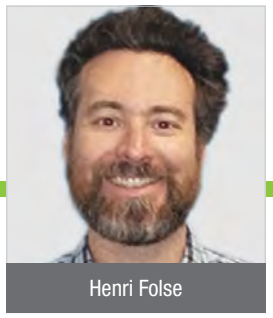
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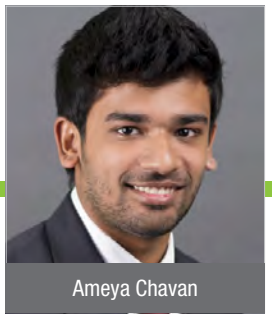

Ameya Chavan

This article describes a new model framework developed to simulate PD progression from diagnosis, capturing both motor and non-motor symptoms, the impact on health outcomes, and the associated costs. This simulation framework can be used to predict the long-term clinical outcomes of new treatments, such as DMTs, in addition to the current standard of care, and can be leveraged to conduct cost-effectiveness analyses and clinical trial simulations.[2,3]

In this article we first outline the model's structure, data sources, and validation, and then discuss the potential applications for this disease simulator to inform internal decision-making, trial design, and strategic planning early in the development of DMTs.

Model Framework

The model was constructed as an **individual patient simulation** to simulate the clinical and economic outcomes of patients newly diagnosed with PD.

- Characterizes disease progression in terms of sequential changes in key clinical scales using a set of **interrelated predictive equations** for progression of MDS-UPDRS and UPDRS subscale scores
- Captures both the **short-term benefits of symptomatic treatments**, and their long-term limitations, such as increasing off-time and the associated complications of therapy
- Predicts the **long-term benefits of DMTs** due to slowing the rate of disease progression as distinct from symptomatic improvements

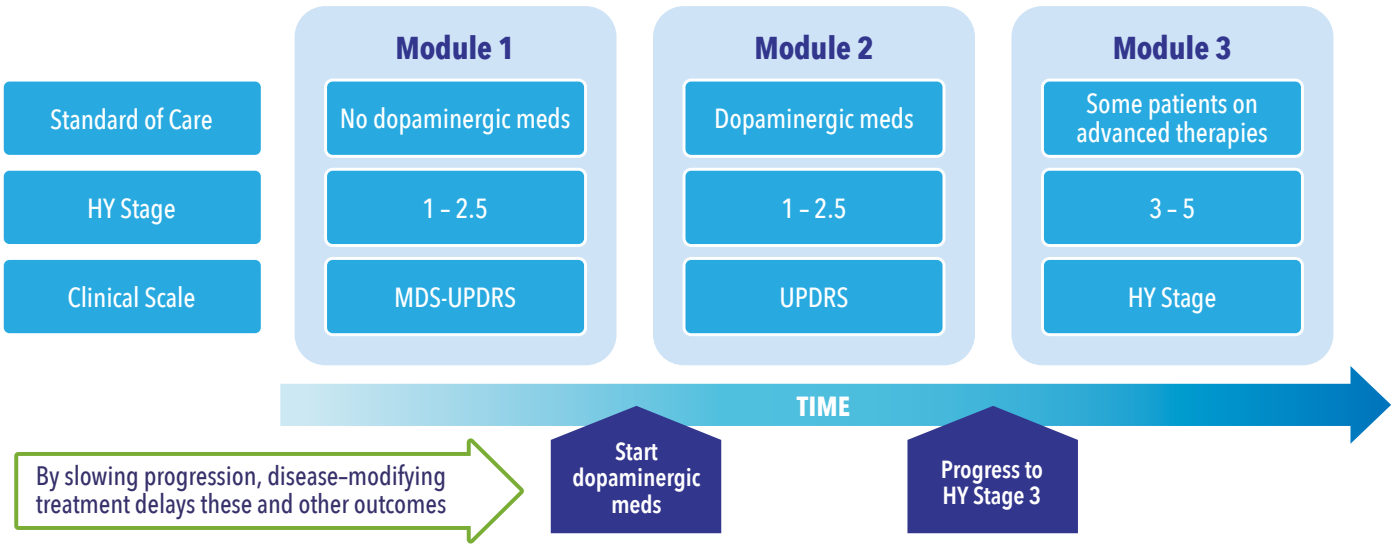
The simulated patient characteristics influencing disease progression include age, sex, and disease duration, as well as the initiation of dopaminergic medications or advanced therapies (e.g., deep brain stimulation). This simulation was implemented in Microsoft Excel® and uses the discretely integrated condition event (DICE) approach.[4] The progression and management of PD is therefore conceptualized as a combination of evolving conditions (age, MDS-UPDRS, UPDRS, Hoehn and Yahr [HY], costs, and utilities) and events (distinct points in time where conditions change, such as medications, discontinuation, institutionalization, or death).

Disease Progression

PD is a slow progressing disease and therefore no single dataset with longitudinal MDS-UPDRS or UPDRS data was available that followed patients from diagnosis to the advanced stages of the disease. New predictive equations were developed by analyzing two data sources to model disease progression for newly diagnosed patients. These were then combined with additional published sources to inform long-term progression, mortality, utilities, and costs.[5-7]

- The model has **three modules for distinct phases of the disease progression**, each based on a different data source (See Figure 1). Mappings between various scales maintain internal consistency.
- A series of **new predictive equations were developed based on longitudinal data** obtained from Parkinson's Progression Markers Initiative (PPMI)[8] for MDS-UPDRS scales and the National Institute of Neurological Disorders and Stroke (NINDS) Exploratory Trials in PD Long-Term Study[1] (NET-PD LS-1) for the UPDRS scales.[9,10]

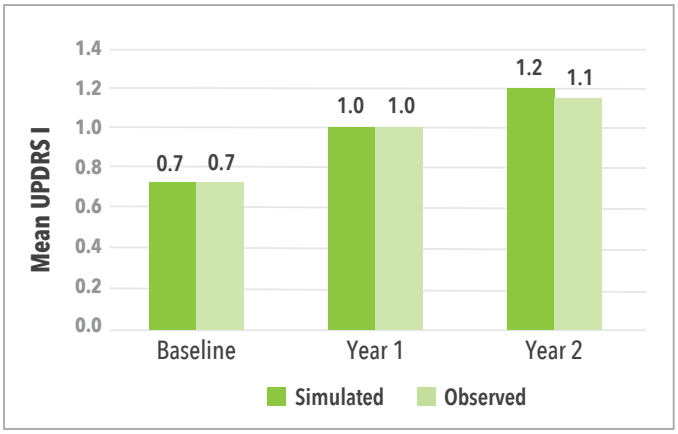
Figure 1. Overview of Disease Progression Modules

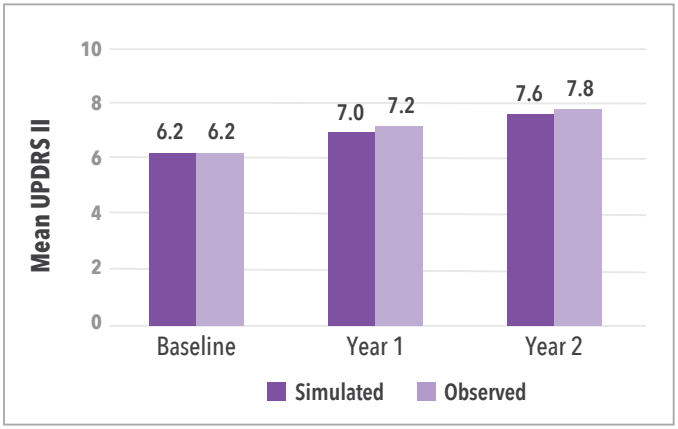


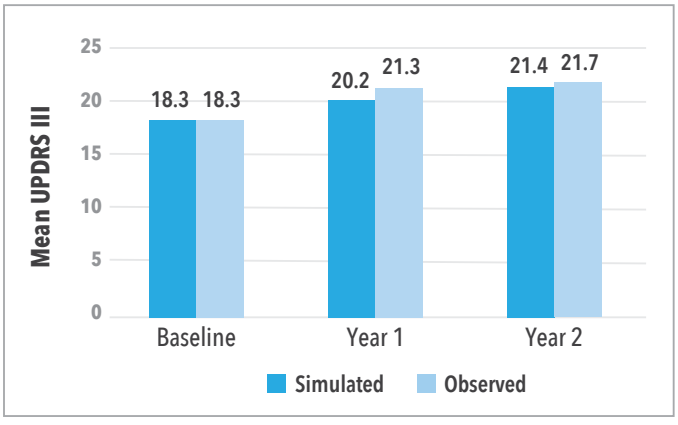
HY: Hoehn and Yahr; MDS-UPDRS: Movement Disorder Society-Unified Parkinson's Disease Rating Scale; UPDRS: Unified Parkinson's Disease Rating Scale

- Profiles of newly diagnosed patients were generated by jointly sampling correlated characteristics from PPMI (mean age 61.2 years, male 65%, duration six months, treatment-naïve).
- A new predictive **equation was developed to estimate EQ-5D-3L**-derived utilities, capturing motor and non-motor symptoms.
- Progression from HY Stage 3 was based on study published by Johnson et al.[11]

Figure 2. Simulation of UPDRS Scale Scores Over Time for a Newly Diagnosed Cohort: Comparison of Simulated Mean Change from Baseline with Observed Outcomes







UPDRS: Unified Parkinson's Disease Rating Scale

Validation

Extensive validation of the projections and technical verification was a key step in the development of this new disease simulator. The analyses illustrated the model appropriately simulated progression for both treatment-naïve and treatment-experienced patients.

The progression equations were first individually confirmed by comparing the predicted and observed scores each year post-baseline to ensure the predictions were aligned. These equations were then implemented in the model, and the simulated outcomes were confirmed to align with the observed longitudinal data for three cohorts:

- Treatment-naïve patients (PPMI data)
- Patients on PD medication at baseline (NET-PD LS-1 data)
- Treatment-naïve patients based on an external source (PRECEPT data)[12]

In the simulation, the predicted values from one equation are used as predictors for correlated measures; therefore, this step assessed the joint validity of the equations once implemented in the model. One limitation to the project was that the PPMI data set was used to develop the functions for projecting treatment-naïve progression, as well as for validation of the model. However, the equations developed from the NET-PD LS-1 for progression after initiation of dopaminergic medications were validated against an external data source (See Figure 2).

Discussion

The newly developed equations supported a de novo model framework suitable for conducting simulations from early in the disease and captures the progression of both motor and non-motor symptoms. Additional validations and refinements to this simulator are ongoing. The model can be used early in a drug development program to conduct scenario analyses to inform internal decision-making and strategic planning. This might include simulating the potential benefits of a new DMT and how certain design decisions could impact the likelihood of success of a trial. The influence of varying key clinical trial design assumptions can be simulated such as:

- Inclusion or exclusion criteria applied to select specific sub-populations (e.g., treatment-naïve, age range, HY stages, etc.)
- Mean change in MDS-UPDRS or UPDRS (individual subscales or combinations)
- Trial duration
- Sample size and dropout rates

This tool facilitates conducting exploratory analyses by varying key parameters, such as the durability of health benefits (i.e., immediate loss or gradual waning of benefits)

and treatment stopping rules. The results from these scenarios can help to understand the key drivers of cost-effectiveness and identify important data gaps to inform evidence generation planning for each market. Assessing the likely pricing to be cost-effective at various willingness-to-pay thresholds can often be informative. For example, running scenarios can generate an evaluation of the economically justifiable price (i.e., the price at which the estimated incremental cost-effectiveness ratio is equal to the selected cost-effectiveness thresholds).

The model was systematically validated against the source data and an external data set. Long-term access to additional data sources from other populations would provide a more complete understanding of the generalizability of the equations developed. This project has allowed us to construct a new framework that is extremely flexible and customizable, allowing users to generate their own scenarios without the need to interact with the complex programming within the model.

This framework facilitates running simulations of a proposed clinical trial protocol, and comparison of the likely results, with many alternative options and assumptions for the design, patient population, and outcome measures. Early modeling can also support identifying gaps in the data available and defining the critical questions to prioritize addressing in order to meet the requirements of health technology assessment groups and help plan for payer discussions. These types of simulations early in development can support optimizing value demonstration for new innovative therapies for a complex disease and increase the likelihood the final value proposition will be accepted by both regulators and payers. ■

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Implementation Science: A Primer

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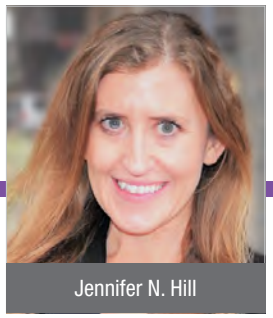
What is Implementation Science?

The hook that implementation scientists often use to drive home the importance of their work is that it takes an average of 17 years for evidence to be implemented into practice and only 14% of original research will reach patients.[1,2] But what is implementation science?

While there are several different definitions of implementation science, it is broadly defined as the scientific study of methods to promote systematic uptake of research findings and other evidence-based practices into routine practice, and hence, to improve the quality and effectiveness of health services and care.[3] It is also referred to as dissemination and implementation research or knowledge translation.[4]

Who are the stakeholders and what is the value proposition?

Everyone benefits from implementation science, including hospital administrators, providers and other healthcare professionals, pharmacists, health insurers, policymakers,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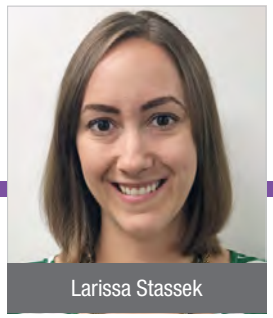
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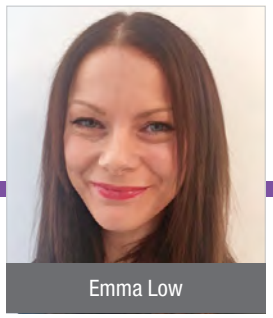
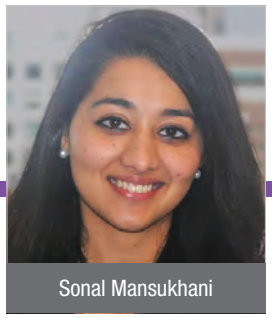

Emma Low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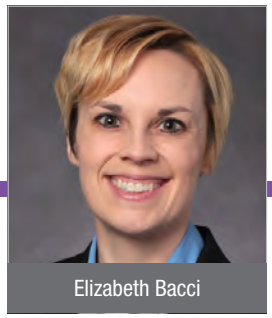

Elizabeth Bacci

regulators, pharmaceutical companies, caregivers, and, most importantly, patients.

The value of implementation science is becoming clearer as we deal with resource constraints. Utilization and evaluation of evidence-based strategies is essential to ensuring that investments in research are contributing to increased use of evidence while maximizing healthcare value and improving public health.[5,6,7]

Implementation Science Study Designs

What does an implementation science study look like?

Clinical research and implementation science share similarly rigorous approaches to scientific study. While clinical trials are largely focused on establishing effectiveness (tolerating), implementation science is focused on understanding and addressing barriers and facilitators to the uptake of evidence-based practices and interventions in the context in which they are being introduced.[8]

Implementation can be considered throughout the research pipeline, but implementation science studies may come after, or in combination with, effectiveness studies (See Figure 1). These combination studies are considered hybrid designs and there are three different types.[9] Hybrid designs are usually most appropriate for studies with minimal risk interventions (i.e., those with at least some evidence of effectiveness and strong face validity, to support use of the intervention in a new way such as setting, population, or method of delivery).[10]

- **Hybrid Type I** designs are primarily focused on testing and collecting evidence of the clinical intervention while gathering some data on implementation, such as acceptability or feasibility.
- **Hybrid Type II** designs typically place an equal emphasis on testing the clinical intervention and the implementation strategy.
- **Hybrid Type III** designs are typically focused on testing the implementation strategy, such as fidelity and adoption, while collecting some data on effectiveness.

Selecting a hybrid design depends on the level of evidence available on the intervention, the trial population and information available to support the implementation strategy. In an implementation trial, the scientists have an evidence-based intervention or practice that needs uptake, and the implementation expert is testing hypotheses regarding modified strategies for uptake in a new setting, as well as fidelity to those plans.[11]

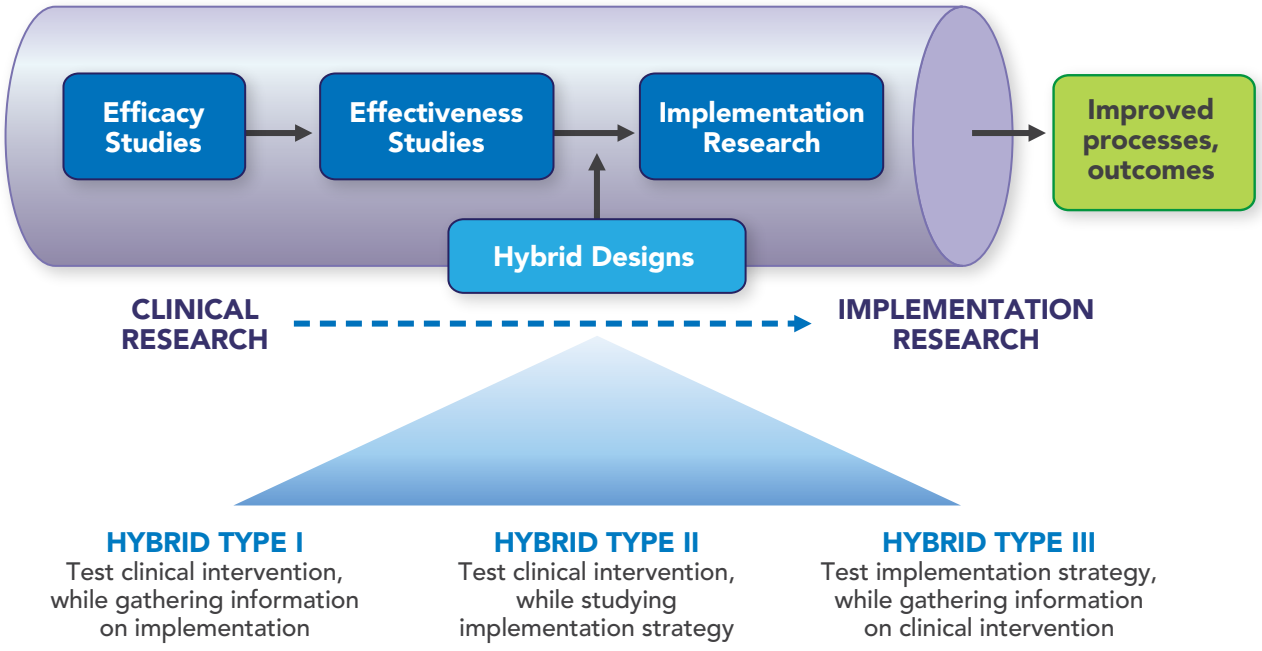
The Role of Continuous Quality Improvement

Continuous Quality Improvement (CQI) involves incremental and iterative assessments of improvement based on small and/or large changes to processes or delivery of evidence-based practices or interventions. Goals may include, but are not limited to:

- Improvement of processes (e.g., system or clinic levels)
- Individual-level outcomes (e.g., patient, clinician)
- Regulatory outcomes (e.g., improved safety)[13]

Designs or methodologies for these types of improvement studies may include Plan-Do-Study-Act (PDSA)[14] cycles or Six Sigma (which follows the problem-solving process

Figure 1. Research Pipeline and Hybrid Designs[8,12]



of Define, Measure, Analyze, Improve and Control [DMAIC]).[15] In CQI studies, improvements are made, the effect of those improvements are assessed, and the cycle is repeated until the desired outcome is achieved.[13] Data collection strategies used in this study are similar to program evaluation or implementation studies, but the cycle for analysis is typically much quicker as the feedback is fed directly back into the study and immediately acted upon.[16,17]

Methods and Data Collection

Implementation science studies can be retrospective (e.g., large scale comparative case studies or retrospective assessment of factors impacting implementation) or prospective in design, (e.g., collecting data during an implementation trial for the purposes of testing specific hypotheses) or may be a combination of both. These studies may also be guided by a framework or theory that informs the design and conduct of the study, the design of data collection instruments, and the reporting of study findings.

Implementation science studies typically employ a mix of methods such as use of quantitative data (e.g., administrative data or data produced from databases or systems, closed-ended survey questions or measures, source documents, etc.) and qualitative data (e.g., interviews or focus groups, open-ended survey questions, meeting notes/minutes, etc.). Due to the diverse nature of implementation study designs and objectives, a variety of analytic approaches may be used to assess data from these various sources, including traditional statistical and/or qualitative approaches, rapid analysis techniques,[16,17] or triangulation of the data from the various data sources.[18,19]

Data collected within an implementation study are often complex and may be collected at several different levels such as system level (governmental or policy), organizational level, site level (provider team or group level), and the patient level.[20] Outcomes may include, but are not limited to, knowledge or attitude change, behavior change, health-related outcomes or changes, process-related changes, and policy or system-related changes.

How does program evaluation fit in?

Program evaluation can be, and often is, considered under the umbrella of implementation science. Program evaluations may be designed retrospectively, prospectively, or both, and are usually guided by an evaluation framework. Program evaluations typically involve engaging stakeholders, sometimes from multiple groups, in describing and establishing the design of an evaluation. They include identifying key questions, indicators to measure key outcomes, and collection of data from many different sources such as existing data/documents or newly collected data from surveys, focus groups, or interviews. Program evaluation requires a synthesis of the findings while considering the needs of the stakeholder, as well as a review and agreement of the conclusions of the evaluation among the stakeholder groups. This review of conclusions is a critical step to ensure that the results of the evaluation will be used for program improvement. It is important that the results produced from a program evaluation tie back to the purposes identified early in the evaluation and that the results are provided in a way that can be used and shared broadly with other stakeholder groups.

Example Implementation Science Studies

The following sections provide examples of how to utilize implementation science to address different research needs.

DAILY ORAL (AT-HOME) TREATMENT VS. INJECTABLE (IN-CLINIC) TREATMENT

Population: Two studies, both of patients and providers, with one undertaken in the United States and one in Europe

Challenge: How to most effectively implement a new, long-acting injectable treatment that requires regular visits to the clinic, as opposed to daily oral medication self-administered at home, which is the current standard of care. Due to the different route of treatment and the need for more frequent clinic visits, the sponsor was interested in identifying barriers and facilitators involved in making this treatment shift.

Approach: Both studies utilized implementation science frameworks within their design. The US-based study used the Consolidated Framework for Implementation Research (CFIR)[21] whereas the European-based study utilized the Exploration, Preparation, Implementation and Sustainment Framework (EPIS) alongside outcomes guidelines developed by Proctor et al.[22] Similarly, both studies utilized a mixed methods approach involving individual surveys and one-on-one interviews. The US-based study adopted a single arm approach with all sites receiving the same implementation support, including eight monthly facilitation calls with clinic staff. The European-based study used a two-arm study design in which the standard arm sites received traditional implementation support, and the enhanced arm sites received additional meetings and trainings. The latter arm also participated in CQI calls involving the development of plans to address challenges.

Stakeholders: Patients, doctors, nurses, and administrative clinic staff responsible for implementing the treatment, and the sponsor.

Key Findings: Through the surveys, interviews, and facilitation or CQI calls, stakeholders offered feedback on facilitators and barriers to successful implementation. This has allowed the research team and sponsor to better understand who is best suited for the new treatment, what types of clinics and settings may need additional support in implementation, and strategies for patients and clinics to be more successful in the transition to this new treatment. The study findings will be used to help advise and support clinical sites in the effective implementation of this new treatment in a real-world setting.

CAN A HEALTHCARE APP IMPACT CLINICAL OUTCOMES?

Population: Patients attending a specialty care clinic and providers at the speciality care clinic

Challenge: Evaluate a new app designed to track potential patient symptoms and exacerbations of new symptoms over time, provide resources to patients, and increase the ability of patients to communicate with their care team.

Approach: The patient interface is linked to a clinician dashboard where patient responses are tracked and responded to by the patient's clinical team in real time. Using a mixed methods design, including techniques such as one-on-one qualitative interviews with patient and clinical site users, patient surveys, and other quantitative usage metrics, evidence can be evaluated with the hope of improving the quality of the electronic system in clinical practice and determining if the app impacted clinical outcomes.

Key Findings: The results of this study will be disseminated in early 2022.

STUDYING PROGRAM IMPACT THROUGH RETROSPECTIVE AND PROSPECTIVE DATA

Population: Individuals from funding partner's organization, individuals from leadership at program partner, and individuals from the field involved in the program

Challenge: Evaluate a program to understand its impact since inception (retrospective data) as well as at the current stage (prospective data). Though the program has been funded for nearly five years, efforts to study the impacts have been largely informal. A dedicated evaluation was requested to support decisions that would inform future funding.

Approach: The evaluation followed the Centers for Disease Control and Prevention framework for program evaluation[23] which focuses on producing results that are the most salient while reinforcing the integrity and quality of the evaluation. The framework involves engaging stakeholders, describing the program, focusing the evaluation design, gathering credible evidence, justifying conclusions, ensuring use, and sharing lessons.

Stakeholders: The funding partner that provided guidance on aspects of program development and the partner responsible for the conduct of the program.

Key Findings: The evaluation provided key information on areas of strength and challenge within the program and areas of greatest impact. The findings and recommendations produced from the program evaluation were immediately used in presentations to high-level decision makers for the purpose of informing conversations about priorities for future focus.

Conclusion

Implementation science studies often consider multiple factors that may serve as barriers and/or facilitators at the system level, site level, or individual level. Analyses may include a mix of existing data or data collected specifically for the purposes of the assessment. Data may also be collected from a variety of sources, over multiple timepoints throughout an assessment and may carry over into a long-term assessment of sustainability. Implementation science plays a critical role in producing evidence-based strategies and supporting the uptake of evidence-based practices and interventions, with the goal of improving healthcare and patient outcomes. ■

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What You Need to Know About Real-World Databases in Japan

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Valuable information for real-world evidence generation can be gleaned from healthcare databases, and the number of databases available continues to expand. Knowing the right data to answer the right question is critical in effective study design. While much is known about use and access of data through Europe and North America, the expanding interest in research in Asia-Pacific presents a new challenge in understanding the uses and challenges of new databases. Japan's health system and corresponding healthcare databases provide a unique challenge. This article focuses on outlining the Japanese healthcare system, its available real-world databases, and insights into their effective use.

Overview of the Japanese Healthcare System

Japan has universal healthcare coverage for citizens via social health insurance. There are three sub-systems: National Health Insurance (for the self-employed), Employee Health Insurance (for employees), and the

Special Scheme for the Aged (for individuals age 75 and older). The insurance systems cover most medical services, in most cases paying 70% of the cost of covered care, with the remaining costs borne by the insured. In some cases, elderly costs are covered at a higher percentage, up to 90%. In all cases, however, the insured pays out of pocket for over-the-counter drugs, normal pregnancy and delivery care, vaccines, and "lifestyle" treatments such as cosmetic surgeries.

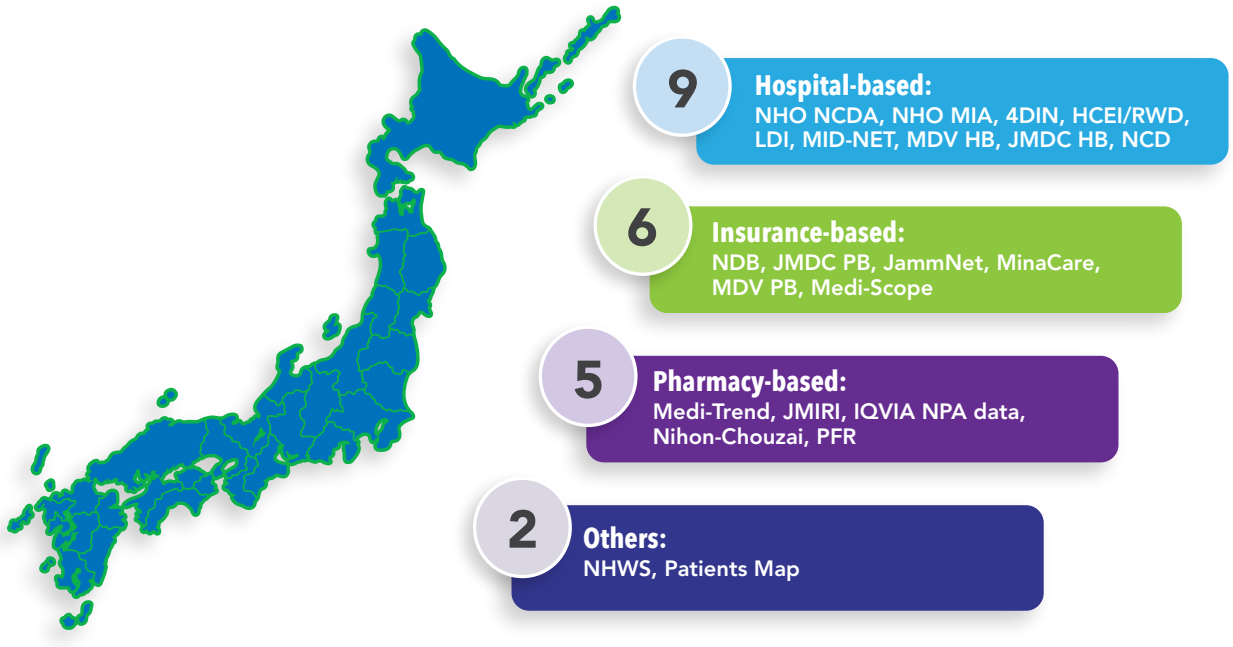
Because Japanese employees tend to stay with the same employer for many years, Japan has robust healthcare data compared to nations where employees change jobs or health insurers more often. Annual check-ups are provided by employers at no cost to employees and include blood work, a chest X-ray, height and weight measurements, and vision, hearing, urine, blood pressure, and obesity tests. There is also the option to pay for an annual "Ningen Dock," a day-long or overnight stay in a hospital for a full health work-up, including an endoscopy, cancer screenings, X-rays, and other tests. Generally, Japanese patients do not have a primary care physician and referrals are not required to see a specialist; however, specialist visits are more expensive without a referral. Patients must consult a doctor for each prescription refill and new prescriptions are often for only two weeks at a time. Prescriptions for long-term or chronic conditions may be given for up to a year, excluding narcotics.

Since insurance claims are submitted by patients and healthcare facilities monthly rather than for each encounter, researchers can see which claims were submitted when but not necessarily the order in which care was given. Japan primarily uses the fee-for-service system; however, a diagnosis procedure combination (DPC) payment system unique to Japan was introduced in 2003 to improve healthcare standards and transparency, and overall institutional performance. Inpatient claims rely on the DPC payment system that groups patients according to diagnosis categories. Inpatient DPC hospitals charge a flat rate, which is calculated by multiplying the rate by the length of the stay, plus additional costs for surgeries or other procedures. Outpatient care is fee-for-service.

Available Real-World Databases

There are 22 databases in Japan that are regularly used in pharmacoepidemiology research (See Figure 1). These data can be classified as either hospital-based (41%), insurance-based (27%), pharmacy-based (23%), or other sources, such as surveys (9%). Eighty-two percent of these data include information on outpatient visits, with 64% including information on medications dispensed in the outpatient setting. Sixty-four percent of the databases include inpatient stay data, with 59% including information on medications dispensed in-hospital. Most databases (64%) record diagnoses using the International Classification

Figure 1. Available Pharmacoepidemiology Databases in Japan



NHO: National Hospital Organization; NCDA: NHO Clinical Data Archives; MIA: Medical Information Analysis; 4DIN: a hospital-based database owned by 4DIN; HCEI/RWD: Health, Clinic, and Education Information Evaluation Institute/Real-World Data; LDI: Life Data Initiative; MID-NET: Medical Information Database Network; MDV: Medical Data Vision; HB: Hospital Based; JMDC (formerly named Japan Medical Data Center Co., Ltd); NCD: National Clinical Database; NDB: National Database of Health Insurance Claims and Specific Health Check-ups; PB: Payer-Based; JMIRI: Japan Medical Information Research Institute; NPA: National Prescription Audit; PFR: a pharmacy-based database owned by 4DIN; NHWS: National Health and Wellness Survey Database

of Diseases, Tenth Revision (ICD-10) system, which has been used in Japan since 1995. Nearly half (41%) of the databases indicate whether a laboratory test was ordered, but only 36% record test results.

Pharmaceutical companies have access to most of the healthcare databases in Japan. Those most easily accessed (i.e., direct access to the data through a license or one-off payment) include: HCEI/RWD, LDI, MDV (hospital and payer-based), JMDC (hospital and payer-based), Minacare, Medi-Scope, Medi-Trend, JMIRI, IQVIA, Nihon-Chouzai, PFR, NHWS, and PatientsMap. However, some databases, such as JammNet, are only available through indirect access, while others are only accessible to licensed or academic researchers. The databases with the most clinical information (e.g., laboratory, genetic, diagnostics and physiological test results) include NHO NCDA, 4DIN, HCEI/RWD, LDI, MID-NET, MDV, NCD, and NHWS.

The number of people included in each database varies (See Figure 2). The NDB has data on 120 million people, nearly the entire Japanese population. Other databases with significantly large population coverage include the JMIRI (39 million), MDV (33 million), IQVIA (33 million), and HCEI/RWD (21 million).

Considerations and Recommendations

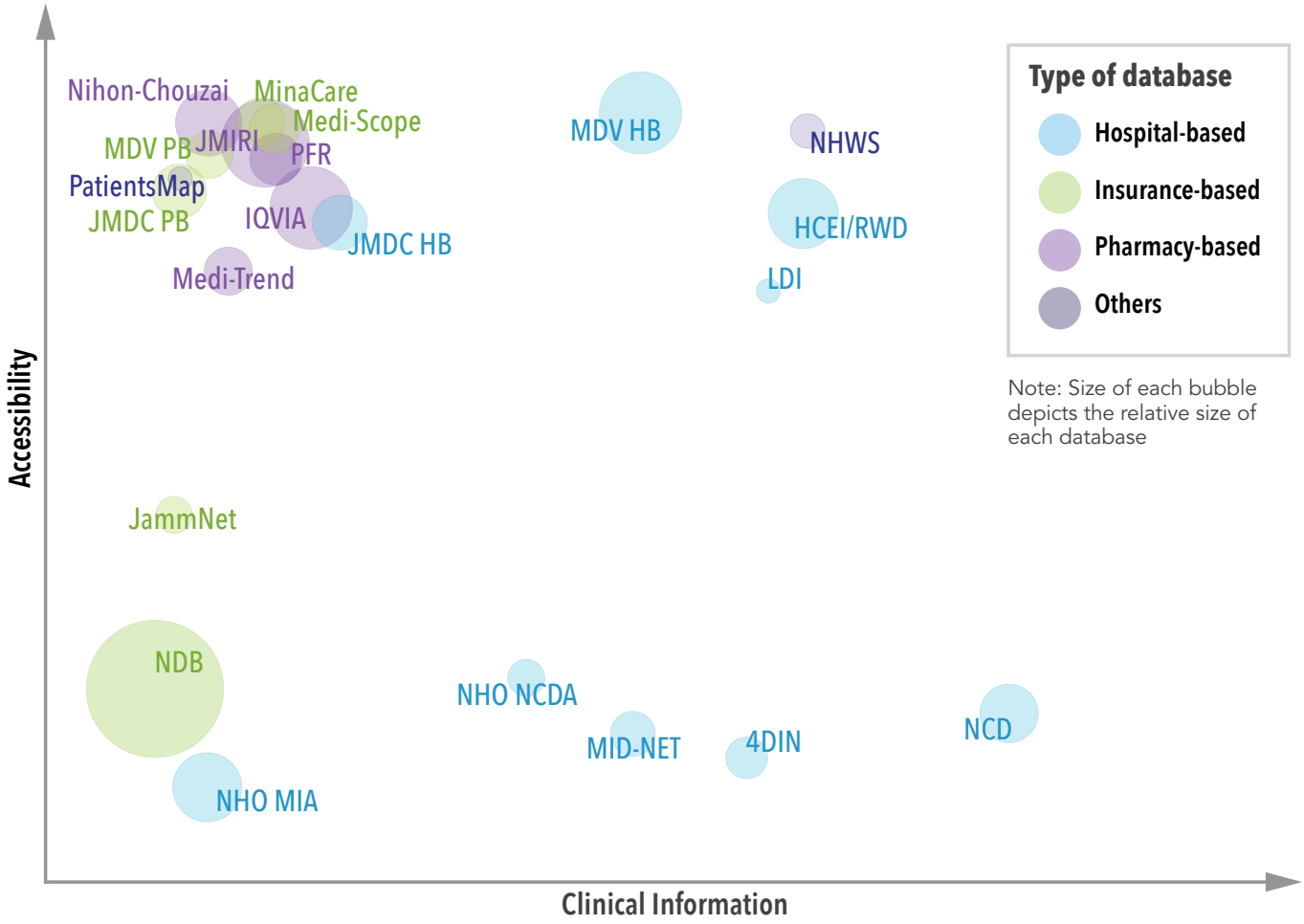
Japan has several robust healthcare databases that are proving to be valuable in real-world evidence generation. However, there are also some unique challenges in using this data. Here are some key considerations and recommendations in using Japanese data.

Data Access

Many databases have limitations on their availability for outside researchers. For example, NDB, NCD, 4DIN, MID-NET, and the NHO datasets are not directly accessible to pharmaceutical companies. There are also logistical restrictions. For example, some provide the data on a flash drive and there are restrictions on shipping outside Japan.

Recommendation: Collaborate with local researchers who can access these data.

Figure 2. Japan Database Assessment



Note: Size of each bubble depicts the relative size of each database

Language Barriers

Relevant clinical documentation is often in Japanese. Specifically, treatment guidelines for rare diseases, drug package inserts, data dictionaries, diagnosis, and receipt codes dictionaries are often not available in other languages. Access to this information is critical for appropriately reflecting clinical practice patterns in Japan during the design and data interpretation phases of a study.

Recommendation: Work with a Japanese translator with knowledge of the database being used in the study.

MDV and JMDC

MDV and JMDC are most used by pharmaceutical companies for pharmacoepidemiology research in Japan.

The MDV database includes medical health insurance claims dating back to April 2008, with both inpatient and outpatient information. It also includes encounters from 399 out of 1,700 DPC hospitals, covering approximately 23.5% of the total number of acute care beds in Japanese hospitals. Prescriptions administered in-hospital and prescriptions dispensed in the outpatient setting are included, as well as laboratory test results.

The JMDC data includes inpatient, outpatient, and pharmacy claims derived from all healthcare services under health insurance systems since 2005. It houses data on diagnoses, medications administered in-hospital, medications dispensed at pharmacies, tests and procedures performed, duration of hospitalization, and direct medical costs for resources used. As of April 2020, the database includes data from 7.3 million salaried workers and their families. Clinical variables, such as laboratory test results, are not available. The age distribution of the population included in JMDC is: 0 to 17 years old = 23%; 18 to 64 years old = 74%; and 65 to 74 years old = 3%. Unemployed patients are not represented at all.

Longitudinality of the Data

It can be difficult to track patients in most Japanese hospital-based databases because visits to other institutions within the data network cannot be linked as each facility uses a unique identifier. In an insurance-based claims database, patients retain the same identifier if they maintain the same insurance policy.

Recommendation: When designing a study, if it is important to adjust for confounding variables at index, or if continuous follow-up of patients is required, then the use of insurance-based claims is recommended.

Data Coverage

Data from insurance-based claims are limited to only working-age patients and their dependents. However, hospital-based databases have their own limitations. For example, large hospitals and hospitals that admit patients with more severe conditions, such as DPC-designated hospitals, may be overrepresented.

Recommendation: Consider the target population in a study before selecting a data source. If the study primarily focuses on the elderly population, use a hospital-based database.

Data Source Quality

For some databases, especially hospital-based claims databases, demographic information such as weight, height, and other variables like smoking status may be missing. Discharge summaries at DPC-designated hospitals may lack information that is not relevant for reimbursement purposes, even if the variable exists in the database. In addition, laboratory test results are available in hospital-based databases, such as MDV, but the set of institutions providing this information might be limited.

Recommendation: Restricting the analysis to patients with available data should be carefully considered as this could strongly impact the generalizability of the analysis.

Conclusion

Several Japanese databases, such as MDV and JMDC, are available to researchers and are frequently used to conduct real-world studies. A careful assessment of each database's strengths and limitations is highly recommended before selecting a database for use in a study. Additionally, the structure of the Japanese healthcare system and the way that care is delivered to patients is unique compared to other countries in North America and Europe. It is particularly important to understand these factors or to collaborate with local researchers, as they may influence both the study design and interpretation of evidence derived from real-world studies. ■

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Pre-Approval Information Exchange (PIE)
Is It Time for More PIE?

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The use of pre-approval information exchange (PIE) has been on the rise the past couple of years. While the final version of the US Food and Drug Administration's (FDA) Drug and Device Manufacturer Communications With Payors, Formulary Committees, and Similar Entities – Questions and Answers Guidance for Industry and Review Staff released back in June 2018 really set things into motion, the release of Version 4.1 of the Academy of Managed Care Pharmacy (AMCP) Format for Formulary Submissions in December 2019 has led to an expanded use of PIE and an increased demand for pre-approval AMCP dossiers (i.e., Unapproved Product Dossiers and Unapproved Use Dossiers), PIE slide decks, and other PIE materials.[1,2]

What is PIE?

PIE is information that can be shared with healthcare decision makers (HCDMs), such as payers, prior to the FDA approval of a new product (i.e., an unapproved product) or a new indication for a currently approved product (i.e., an unapproved use).[2] It does not require an unsolicited request from an HCDM and is typically shared in a proactive manner.[1,3]

Why Do HCDMs Want PIE?

HCDMs want to receive information about new products and new indications prior to FDA approval.[1,2] Such information helps HCDMs to more accurately plan for future drug approvals and reimbursement decisions, and forecast their future budgets.[1]

Information Related to Product Pricing

While HCDMs would like information on the price of a product, it is seldom provided by manufacturers prior to FDA approval. That being said, if a manufacturer is seeking a new indication for a currently approved product, the known price of the approved product should be included in PIE materials.[1] If the price of a new indication of an approved product is expected to be different than the price of a currently indicated use, this should be mentioned.[1]

If a specific price is not available, or if the manufacturer chooses not to share it, there are other pieces of economic information such as price ranges, economic models, and target patient population sizes that HCDMs consider useful for forecasting their budgets.[1,2] While a price range may be provided by manufacturers, and Version 4.1 of the AMCP Format provides example price ranges that can act


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as a guide, this approach is uncommon.[1] Similarly, most manufacturers do not share economic models as part of PIE materials, potentially because they may include outcomes or assumptions related to the effectiveness and/or safety of the unapproved product or indication.[1] In contrast, providing an accurate estimation of the size of the target patient population is a common approach. Sharing this information can give HCDMs an idea of how many people will realistically make use of a new product or indication.

Other Types of Information

In addition to information related to product pricing, HCDMs are also interested in receiving other types of information: general information about the product, information about the clinical studies supporting the product, and the timelines for product approval.[1,2] Knowledge about the product and its key clinical studies makes HCDMs aware of which products are seeking FDA approval, and the timelines for FDA approval let HCDMs know when a new product or new indication will start to directly affect their budgets.

Why Should Manufacturers Share PIE?

Even though manufacturers are not required to develop and share PIE materials,[1,2] doing so can provide many benefits. Providing PIE materials allows the manufacturer to raise awareness and share information about new products and new indications prior to FDA approval. It is also possible that providing PIE may help manufacturers gain access, achieve earlier access post-approval, and prevent unwanted restrictions.[3]

If manufacturers choose to provide PIE to HCDMs, HCDMs will not only have knowledge about new products and new indications, but also be able to compare them. Using PIE, HCDMs can compare new products with products that are already approved. In addition, PIE also allows HCDMs to compare two unapproved products with different timelines for FDA approval.[3] If one manufacturer is expecting product approval in six months and another is expecting approval in two months, providing PIE will allow HCDMs to review both products simultaneously, despite the difference in FDA approval timelines.[3] In fact, it is possible that HCDMs may ultimately choose to pay for the product with the longer approval timeline instead of the product with a shorter approval timeline if they feel that it provides more benefits to patients.[3]

What Information May Be Shared in PIE Communications?

Information that can be shared during PIE discussions has been outlined by the FDA and includes:[2]

- Product information (e.g., mechanism of action)
- Information about the indication(s) being sought
- Information about the patient population being examined
- The anticipated timeline for FDA approval of the new product or indication
- Information on product pricing
- Patient utilization projections and/or prevalence data
- Product-related programs or services and patient support programs
- Factual presentations of the design and results of clinical studies

While the focus of PIE communications is generally on the manufacturer's product, information on the current state of the field in general (e.g., disease burden, unmet need, current treatments, treatment guidelines) can be included in PIE communications. While sharing information on treatment guidelines is not specifically mentioned in the FDA guidance or Version 4.1 of the AMCP Format,[1,2] most manufacturers choose to share this information so that HCDMs can start to think about how a new product or new indication will fit into the current treatment paradigm. For example, if the product will be used after another therapy or in place of another therapy.

Thus far, most of the information that has been included in PIE communications has been publicly available. While data on file can be shared at the discretion of the manufacturer,[1] most manufacturers have chosen not to share data on file in PIE communications. This is partially due to concerns about confidentiality.[3] However, developing PIE materials has provided a reminder that there are many publicly available sources of information that can be shared as part of PIE communications. Press releases, published manuscripts, information from ClinicalTrials.gov, published study protocols, response letters from manufacturers' medical information departments, and conference abstracts, posters, and oral presentations have all found their way into various PIE materials.

While a value proposition may be used to guide the type of information that will be used to develop PIE, it cannot be directly incorporated into PIE materials or other PIE communications. Instead, the information presented in PIE communications must be factual, objective, and unbiased; no characterizations, conclusions, or claims about an unapproved product or indication may be made or implied.[1,2] Therefore, PIE communications cannot state or imply that a new product or a new indication of an approved product fulfills a current unmet need. However, factual comparisons relating to endpoints and statistics can be made in PIE communications, and the FDA guidance provides examples that highlight some of the differences between providing factual comparisons and making a claim, characterization, or conclusion about an unapproved product or unapproved indication.[2]

Finally, all PIE materials should include a clear statement that the new product or new indication is not approved by the FDA, and that the safety and effectiveness of the new product or new indication has not been established.[1,2]

How Can PIE Be Communicated?

There are several ways in which PIE can be communicated. Pre-approval AMCP dossiers and PIE slide decks are two of the most common. Other options for communicating PIE include:

- Response letters to medical information requests[3]
- AMCP PIE webinars[3]
- Press releases
- Brochures that describe a product or clinical trial
- Flashcards that describe a clinical trial[3]
- Links to ClinicalTrials.gov
- Conference abstracts, posters, and oral presentations
- Published manuscripts and study protocols

The FDA guidance does not address who can or should deliver PIE to HCDMs.[2] Therefore, any representative from the manufacturer can deliver PIE to an HCDM or other appropriate payer audience.[3] In general, the field team of the manufacturer delivers PIE materials and communicates them to HCDMs, usually during an in-person discussion or a webinar.[3] One common example is the medical science liaison, but other team members including account managers, account executives, field medical team members, and health economics/outcomes research liaisons can also communicate PIE materials.[3] During and after the communication, payers can provide feedback and ask questions.

While the FDA does not give specific recommendations regarding exactly when PIE can be communicated prior to approval,[2] it is normally communicated 6 to 24 months prior to the anticipated product approval date.[1]

Learnings From the Past Year

More and more manufacturers have developed internal processes (e.g., review by medical, legal, and regulatory teams) for reviewing and approving PIE materials. While some parts of the process, such as the desire to use publicly available information in PIE communications, are consistent across manufacturers, each manufacturer also seems to have its own unique methods built into their approach.

One common conversation that has occurred during the past year centers around the belief that pre-approval AMCP dossiers cannot be shared proactively. That is not the case. While post-approval AMCP dossiers (i.e., Approved Product Dossiers) can only be provided in response to an unsolicited request (i.e., reactively), pre-approval AMCP dossiers may be provided by the manufacturer in either a proactive or reactive fashion.[1]

While many manufacturers choose to provide pre-approval AMCP dossiers reactively instead of proactively, that is starting to change. Indeed, some manufacturers have decided to share pre-approval AMCP dossiers proactively, sometimes as a follow-up after a PIE engagement (e.g., an in-person discussion or a webinar). If a manufacturer does not wish to provide a pre-approval AMCP dossier proactively, there are several other PIE materials that they can share with HCDMs in a proactive manner. These materials often contain information that is similar to the information contained within pre-approval AMCP dossiers. Finally, some manufacturers have started to use a mixed approach, depending on the specific product, where they share pre-approval dossiers proactively for some products and reactively for other products.

Finally, while most manufactures have ultimately been reluctant to share information on product pricing, it has been a topic of frequent discussion. For example, there have been discussions about whether to share information about potential cost offsets provided by a product (e.g., decreased length of hospital stay) prior to FDA approval. At this time, it is not clear if there will be a future increase in the sharing of information related to product pricing in PIE communications. However, the current perspective may change as manufacturers become more comfortable with PIE and incorporate it more routinely into their market access strategy.

Conclusions

Just a couple of years ago, many manufacturers were hesitant to develop and share PIE materials. However, even though PIE materials are not required,[1,2] many have found that they are useful tools for facilitating communications with HCDMs. Since it is possible that sharing PIE could benefit many new products and indications, we recommend that manufacturers consider the available options and think about the approach that aligns best with their strategy. ■

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Four Common Missed Opportunities When Designing and Developing a REMS Program

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A Risk Evaluation and Mitigation Strategy (REMS) is a complex and evolving safety program. Although the US Food and Drug Administration (FDA) ultimately determines if a REMS program is necessary, there may be more opportunities than you might realize to shape the development of your program. Proactive engagement with the FDA, for example, can make a critical difference in reducing timelines, limiting confusion, and agreeing to reasonable requirements. Here we discuss four common missed opportunities when developing a REMS program.

What Is a REMS?

The FDA requires a REMS for certain products with serious safety concerns to help ensure the benefits of the product outweigh the risks to the patient. While all FDA-approved pharmaceutical products have labeling that informs healthcare providers of the product's risks, only a small percentage require a REMS.[1] Each REMS includes safety measures unique to the safety risks associated with a particular product or class of products. The requirements may include elements to assure safe use (ETASU) or simply distribution of a medication guide or a communication plan (See Figure 1). ETASU may be required when other elements are not considered sufficient to mitigate serious risk(s). Examples of ETASU include prescriber certification, pharmacy certification, patient enrollment, evidence or documentation of safe use conditions (e.g., confirmation

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Figure 1: Types of Risks REMS Requirements Aim to Mitigate[2]

Risk Example	Possible REMS Action
Serious Infection	Patient education on initial warning signs prior to prescribing
Severe Allergic Reaction	Healthcare provider must be certified prior to administering the product
Liver Damage	Liver function monitoring while patient is taking the drug
Severe Birth Defects	Negative pregnancy test prior to dispensing each prescription

of pregnancy testing or other monitoring results) prior to dispensing, or patient participation in a registry.

If ETASU are required as part of a REMS, a plan for implementing the ETASU will need to be developed. This plan may include a website and contact center to facilitate certification and enrollment and the creation of a database for collecting and maintaining appropriate data.

MISSED OPPORTUNITY 1

A Delayed Start

The FDA requires, reviews, and approves REMS programs, but sponsors must design and develop their own REMS programs. These programs may be large, complex, resource-intensive, and may involve multiple sponsors (e.g., in the case of a single shared REMS, a consortium of multiple companies).

Many sponsors make the mistake of only beginning development of their REMS programs when the FDA requests it. We recommend sponsors take a proactive approach, ideally starting design and development of REMS programs at least six months before submitting an application (e.g., new drug application [NDA], abbreviated new drug application [ANDA], biologics license application [BLA]). If a REMS is required, the NDA cannot be approved without final documents, including the REMS document, REMS supporting document, and REMS materials (e.g., stakeholder letters, brochures, enrollment forms).

While the FDA may release a sponsor from their commitment to have a REMS, or remove certain components of the REMS if they determine the extra measures are no longer necessary to ensure a product's benefits outweigh its risks, ETASU REMS or certain components of other REMS programs may continue to be required throughout a product's "life" on the market.

Waiting until late in the approval cycle to begin designing your REMS may put unnecessary strain on your resources and timelines, lead to rushed development of your REMS, and limit your opportunities to negotiate the specific REMS requirements with the FDA. A late start could also mean a delay in your product's approval, particularly when there are extensive FDA comments to work through in response to your submission.

But how do you know if the FDA will impose a REMS? Determining the likelihood of a REMS can be tricky. The FDA issued guidance in 2019 that outlined six factors to consider in determining the necessity of a REMS:[3]

1. The seriousness of any known or potential adverse events that may be related to the product and the background incidence of such events in the population likely to use the product
2. The expected benefit of the product with respect to the disease or condition
3. The seriousness of the disease or condition that is to be treated with the product
4. Whether the product is a new molecular entity
5. The expected or actual duration of treatment with the product
6. The estimated size of the population likely to use the product

The FDA guidance acknowledges, however, that determining the necessity of a REMS is complex and specific to the particular product.[3] Analysis of previously approved REMS programs for products in the same class (i.e., same mechanism of action) or with similar safety profiles can help provide insight into whether a REMS may be necessary for your product. For example, for each Chimeric antigen receptor (CAR) T-cell therapy approved in the US thus far, the FDA has required a REMS. Therefore, if you plan to submit an NDA/BLA for a CAR T-cell therapy, it is safe to assume a REMS will be required. Products with serious safety concerns (e.g., birth defects, life-threatening infection, or vision loss) may require more complex REMS requirements.

MISSED OPPORTUNITY 2

Failure to Proactively Engage with the FDA

If you think a REMS might be required for your product, it is advantageous to begin to strategize what you would like to propose to the FDA and engage in those discussions as early as possible. Many sponsors are hesitant to proactively contact the FDA, but, in our experience, the FDA not only encourages early outreach, they welcome the opportunity to engage in open, two-sided dialog. Proactive engagement allows you to approach the FDA with your

recommendations and gives the FDA something to react to. On the other hand, a more passive approach (i.e., waiting for the FDA to lay out what is required) may limit your ability to control the discussions.

By taking the initiative and providing your recommendations to the FDA, you may be able to speed up timelines, limit confusion, secure agreement, understand requirements, and set reasonable expectations.

MISSED OPPORTUNITY 3

Early Engagement with a Third-Party Partner

Designing and developing a REMS is a complex process involving multiple stakeholders and requiring experts in many functional areas from epidemiology, risk management, and regulatory affairs to finance, information technology, and medical writing. Strong project management is also critical for a successful REMS program.

It's important to determine whether your organization can manage those resources internally, especially if you're building your first REMS program. Not all organizations have existing staff, or the ability to hire new staff, with these skillsets. You will need to assess the capabilities and availabilities of resources from several functional areas and determine whether they have specific experience with REMS, not just in their respective areas of expertise. Also, you may not need full time staff if you only have one or two products with REMS programs in your company.

Alignment of REMS resources is also critical. Internal departments may have different agendas and decision-making processes. It's important to establish and align the various goals across the organization. A third-party vendor can help streamline that process by creating and managing one governance committee that can help bring your organization into alignment. Additionally, if you are a member of a single shared REMS, a Project Management Office vendor is critical to objectively manage complex logistics, finances, and meetings; guide consensus planning; and oversee voting and decision making. Outsourcing functions can give you the expertise you need when you need it.

MISSED OPPORTUNITY 4

Not Negotiating with the FDA

Once the FDA determines a REMS is necessary for a product, manufacturers must design their specific REMS. While the need for a REMS is rarely up for negotiation, the scope of what the REMS includes is something you may be able to influence if you have a strong rationale; after all, the FDA does not want to create undue barriers to access or burden patients, caregivers, or the healthcare delivery system with the REMS requirements. In our experience, the FDA has been open to these discussions, which can lead to decreased burden on stakeholders as well as sponsors. Negotiations may continue after submission of the application (e.g., NDA, ANDA, BLA) and REMS documents.

Early and ongoing negotiations with the FDA may not only inform your activity during the very limited implementation window, they may give you a stronger voice in how the details of your implementation are built out, help you avoid a delayed launch if you encounter implementation issues, or handle unexpected feedback from the FDA. During this time, comments and revisions from the FDA should be incorporated into REMS documents while you are building your infrastructure (i.e., contact center, database, and website) and processes so that you are ready to go live once approval is received.

A clear plan for assessing the REMS must be established as part of REMS design and development of the REMS submission documents. After implementation, ongoing assessments evaluate the effectiveness of the REMS. These assessments have tight timelines for submission (i.e., 60 days from data cut-off to report submission), so it is essential to thoroughly understand the metrics you have committed to reporting. Early conversations with the FDA can, once again, help you avoid unwanted surprises and potentially influence the reporting process.

Conclusion

While the elements of a REMS program are mandated by the FDA, there are ways you can influence not just the approval timeline but the scope of the REMS. Early and ongoing engagement, using a third-party to manage the process, and negotiating with the FDA can help limit confusion, clarify expectations, and build consensus on reasonable requirements. This, in turn, will decrease the burden on you, the sponsor, as well as, the burden on patients, caregivers, and the healthcare delivery system. ■

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Everything Old is New Again
Classic Epidemiologic Concepts in a Pandemic Age

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Introduction

2000 was the Year of the Rat, SARS-CoV-2, and the Epidemiologist. Some of these epidemiologists have university degrees; many got their training through social media and earnest research. Those of us in the business often share stories of mothers who once proclaimed our jobs "a mystery" but now hold forth on subjects like vaccine efficacy and herd immunity.

There's a fourth – and dare we say sizable – category of credentialed epidemiologists who are revisiting the classic concepts of our discipline, long filed away because we were focused on cancer, neurodegenerative diseases, age-related macular degeneration, and so on. Nothing like a pandemic to bring us all back into the classroom of Infectious Diseases 101. In that spirit, what follows is a brief primer on pandemic-related topics.

Endemic, Epidemic, or Pandemic: It's a Matter of Location

You may have heard these terms at one time or another: *endemic, epidemic, pandemic*. As you move alphabetically through them, they increase in scale and scope.

Endemic derives from the Greek *endēmios* (native) based on *dēmos* (people). An endemic is an illness that belongs to a specific location or group, and endemics are a constant presence in these locations. Malaria is endemic to parts of Africa and dengue fever is endemic to certain regions of Africa, Central and South America, and the Caribbean.[1]

Epidemic derives from the Greek *epi* (upon) and *dēmos* (the people). An epidemic affects a larger than expected number of persons within a community, population, or region in a specified period of time. When COVID-19

Margaret Richards

Table 1. A Time-Lapse of Selected Epidemics and Pandemics: The Last ~700 years[3,4,5,6]

Disease Time Period	Pathogen	Death Toll	Historical Notes
Black Death *(Bubonic Plague)* 1347 – 1666	*Yersinia pestis* bacteria spread by rats and fleas	200 million	The children's rhyme "Ring around the rosy, a pocket full of posy; ashes, ashes; we all fall down!" is a reference to the [rosy] bubonic rash, the [posy] perfumed handkerchief needed due to the terrible odor of the victims, and death [ashes and falling down]. Figure 1 shows the clothing worn by plague doctors during the outbreaks.
New World Smallpox 1520 – present	*Variola major* virus	56 million	Historians cite the colonial weaponization of smallpox via infested blankets gifted to Native or Indigenous Americans.
Yellow Fever Summer 1793	Virus spread by mosquitoes	100,000–150,000 Philadelphians	Alexander Hamilton contracted yellow fever early in the epidemic. Philadelphians covered their faces with handkerchiefs dipped in vinegar to prevent breathing in contaminated air.
Cholera Pandemics 1817 – 1923	*Vibrio cholerae* bacteria	1 million+	John Snow, founding father of epidemiology and data visualization/mapping, got his start studying cholera. There is a pub in the SoHo neighborhood of London (next to the famous Broad Street Pump) where you can drink a pint in Snow's honor.
Spanish Flu 1918 – 1919	H1N1 virus spread by pigs	40–50 million	George W. Bush read *The Great Influenza: The Epic Story of the Deadliest Plague in History* by John M. Barry (2004) in 2005 and reportedly became obsessed with the need to prepare for a possible pandemic.
HIV/AIDS 1981 – present	Virus spread by chimpanzees	25–35 million	Another must-read book on the epidemiologist's shelf: *And the Band Played On: Politics, People, and the AIDS Epidemic* by Randy Shilts (1987).
Swine Flu 2009 – 2010	H1N1 virus spread by pigs	200,000	This strain represented a unique combination of influenza viruses not previously seen in humans or animals.
Ebola 2014 – 2016	Ebolavirus spread by wild animals	11,000	The 1995 movie *Outbreak*, starring Dustin Hoffman, Rene Russo, and Morgan Freeman, focuses on an outbreak of a fictional Ebolavirus in Zaire and California.
COVID-19 2019 – present	Coronavirus spread by bats	2.7 million *(as of March 22, 2021)*	The virus with so many hooks, both literally and figuratively: COVID-19 toes, nose, and tummy. Infection without symptoms is possible. Multiple mutations. Collisions between policy and science.

was limited to Wuhan, China, it was an epidemic. Once it started to spread globally, it became a pandemic. As you contemplate the term epidemic, you can visualize how to break down epidemiology (and epidemiologist). The official definition of epidemiology is "the study of the distribution and determinants of health-related states or events in specified populations, and the application of this study to the control of health problems."[2] But if that's a mouthful, at your next dinner party or lunch with your mom, you can simply say: "Epidemiology is the study of epidemics, and I study epidemics."

A **pandemic** is an epidemic that is spread over multiple countries or continents. A pandemic is an epidemic with a passport. Pan is the Greek prefix signifying all or everything. It has been said that pandemics occur every 100 years or so, and that we were long overdue for COVID-19. History does not quite support a 100-year cycle, however. Table 1 offers a look at some of the most significant epidemics and pandemics of the last 700 years.

Figure 1. The Plague Doctor's Outfit[7]

The clothing worn by plague doctors was intended to protect them from airborne diseases (miasma) during outbreaks of the Bubonic Plague in Europe. It is seen as a symbol of disease and/or death.

The typical costume consisted of an ankle-length overcoat and a bird-like beak mask which was filled with purported medicinal, sweet, or strong-smelling substances (e.g., dried flowers, lavender, juniper berry, cloves), along with gloves, boots, and a wide-brimmed hat.

The wide-brimmed leather hat indicated their medical profession. The doctors used wooden canes to point out areas needing attention and to examine patients without touching them.

Table 2. R_0 for Selected Diseases

Disease	R_0	Disease	R_0
Measles*	12 – 18	1918 Influenza	1.4 – 2.8
Chickenpox	10 – 12	COVID–19	0.4 – 5.7**
HIV/AIDS	2 – 5	Ebola***	0.3 – 0.8

*Measles spreads via breath, cough, or sneeze because the virus is aerosolized. You can catch measles by being in a room where a person with measles had been more than 2 hours earlier (this is a serious contagion).

**Estimates vary since we are still learning about COVID-19.[8]

***Ebola has a relatively low R_0 because it is transmitted through close, direct contact with infectious bodily fluids. You may recall the tremendous fear when the first case was reported in the United States. That is because Ebola, once contracted, is 40%-90% fatal. The case-fatality ratio for COVID-19, by contrast, is 2% globally.

R_0 and R: Measuring Transmissibility

R_0, pronounced R naught, is the basic reproduction number (rate) and refers to the contagiousness and transmissibility of infectious disease pathogens. R_0 is an estimate of the speed at which an infectious disease currently (it can change) spreads through a given population. Simply put, it is the number of people, on average, one person can infect. These unlucky recipients are called secondary cases.

Typically, R_0 is <1 if the disease is controlled or not spreading. If R_0 >1, the disease can spread (perhaps exponentially, depending on value) to a wider population, potentially creating an epidemic or pandemic. The R naughtiest (see what we did there?) pathogen is measles, because one person with measles can infect 12-18 secondary cases.[9]

R_0 is normally calculated based on duration of contagiousness, the likelihood of transmission between the infected and susceptible individual, and contact rate. R_0 is further impacted by geo-environmental factors, public health policies and enforcement (mask-wearing, quarantining, physical distancing), and the presence of immunity (via illness or vaccination). R_0 applies only to a population in which everyone is vulnerable.

That's where the effective reproductive number, or R, comes in. Rarely will a population be totally vulnerable to infection, as is assumed by R_0. Some contacts will be immune due to prior infection or immunization. Therefore, not all contacts will become infected and the average number of secondary cases per infectious case will be lower than R_0. R is the average number of secondary cases per infectious case in a population made up of both susceptible and non-susceptible hosts. If R>1, the number of cases will increase. If R=1, the disease is endemic, and if R<1 the number of cases will decline.

R is estimated as the product of R_0 and the fraction or percent of the host population that is susceptible (x). The equation is: $R = R_0(x)$. For example, if R_0 for COVID-19 is 4 and 75% of the population of interest is immune, the R for COVID-19 in that population is 4 x 0.25 = 1. Under these circumstances, a single case of COVID-19 would produce an average of one secondary case. To successfully eliminate a disease from a population, R must be < 1. See Table 2 for more information about R_0 and selected infectious diseases.

Modeling Infection: The Compartment's the Thing

Kermack and McKendrick, wishing to explain the rapid rise and fall in the number of infected patients observed in epidemics such as the plague in London from 1665-1666 and cholera in London in 1865, developed mathematical models for disease spread.[10] These compartmental models employ mathematical modeling of infectious diseases to try to predict how a disease spreads, the total number infected, or the duration of an epidemic. The population in question is assigned to compartments with labels such as Susceptible (S), Infectious (I), or Recovered/Removed (R) (SIR model) and individuals progress between compartments[11] (See Figure 2). There are many types of models in addition to SIR. They include SEIR, SPQEIR, and MSIR wherein E=Exposed, P=Protected, Q=Quarantined, and M=Maternal Immunity.

The models estimate various epidemiological parameters such as R_0. Models can show how different public health interventions affect the outcome of the epidemic. These include how mask-wearing or physical distancing may alter the course of transmission, how vaccines will impact the pandemic, and what we can expect from viral mutations or variants.

One of the most practical uses of any compartmental model is to monitor R_0, R, and the number of cases predicted

in the coming weeks or months. Sponsors want to know where to target clinical trials or studies and public health officials need to be prepared for the potential onslaught of cases that will stress various parts of the healthcare system. Although these models are far from perfect, they can be an important tool to aid in epidemic or pandemic planning and response.

Everything Vaccine: Efficacy, Effectiveness, Etc.

Vaccine efficacy is the percent reduction in disease occurrence in a vaccinated group compared to an unvaccinated group under optimal conditions (i.e., a randomized controlled trial). When we look at efficacy, we are asking "Does the vaccine work?" **Vaccine effectiveness** assesses the ability of a vaccine to prevent outcomes of interest in the real world. When we look at effectiveness, we are asking "Does the vaccine help people?"

The basic formula for vaccine efficacy is written as:

$$VE = \frac{ARU-ARV}{ARU} \times 100\%$$

where VE=vaccine efficacy, ARU=attack rate among unvaccinated, and ARV=attack rate among vaccinated persons. Attack rate refers to the percentage of an at-risk population that contracts the disease of interest – however disease is defined – during a specified period. To calculate the relative risk (RR) of developing the disease for vaccinated people compared to unvaccinated people, the equation is VE=1-RR x 100%. This is a classic cohort design: we assemble two groups of people with different exposures (vaccination) and watch for the development of disease (e.g., COVID-19).

Vaccine effectiveness, on the other hand, is typically estimated as 1 minus the Odds Ratio, or 1-OR x 100%. We start with a disease (COVID-19) and look back at exposure (vaccine); this is a classic case-control design. Case-control studies cannot establish causation because the lack of randomization means that we must be wary about misclassification, confounding, and other biases. The most we can say in case-control designs is that there is an association between outcome and exposure. In the past few decades, the test-negative design (TND) has come into vogue for measuring vaccine effectiveness.[13] TND is a variation of the case-control design in which all participants meet a pre-specified, syndromic case definition, such as cough or shortness of breath plus one other COVID symptom, and a diagnostic assay is used to differentiate cases from controls. The TND offers two advantages: it is less burdensome because controls can be assembled while identifying cases, and it reduces bias and confounding due to similar healthcare use patterns between cases and controls.

Figure 2. A Typical SIR Model[12]

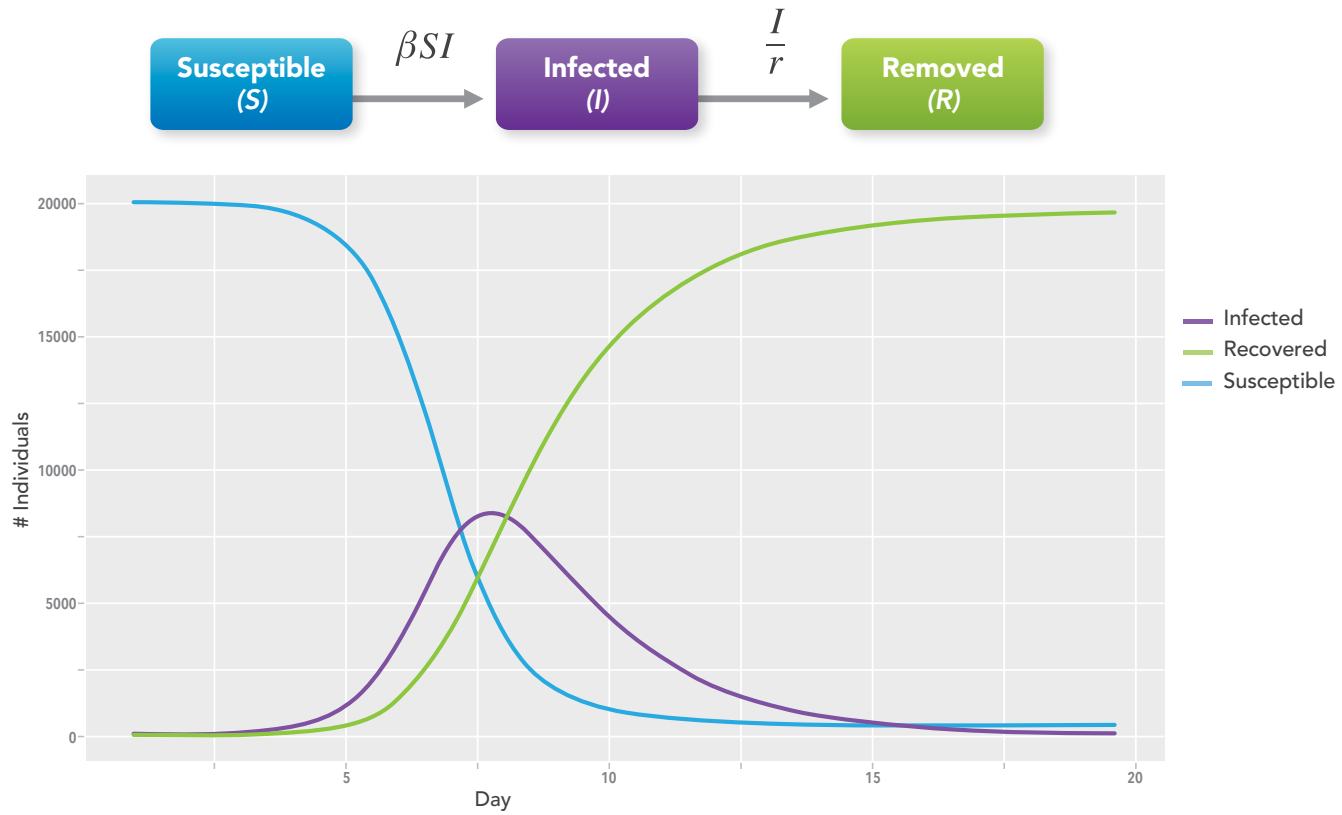


Figure 3. Delivering the Vaccine

Many locations around the US are standing up vaccination sites in empty stadiums with multiple lanes for drive-up injection.

While the pandemic continues, this is a very safe and efficient means of immunizing many people at once.

COVID-19 Vaccines

Much has been written about the efficacy of the first batch of COVID-19 vaccines granted Emergency Use Authorization. There has also been some anxiety over the safety of vaccines that seem to have been developed in months rather than years. Thus far, serious adverse events appear to be rare and it's important to note that some of these new platforms have been in development for many years.

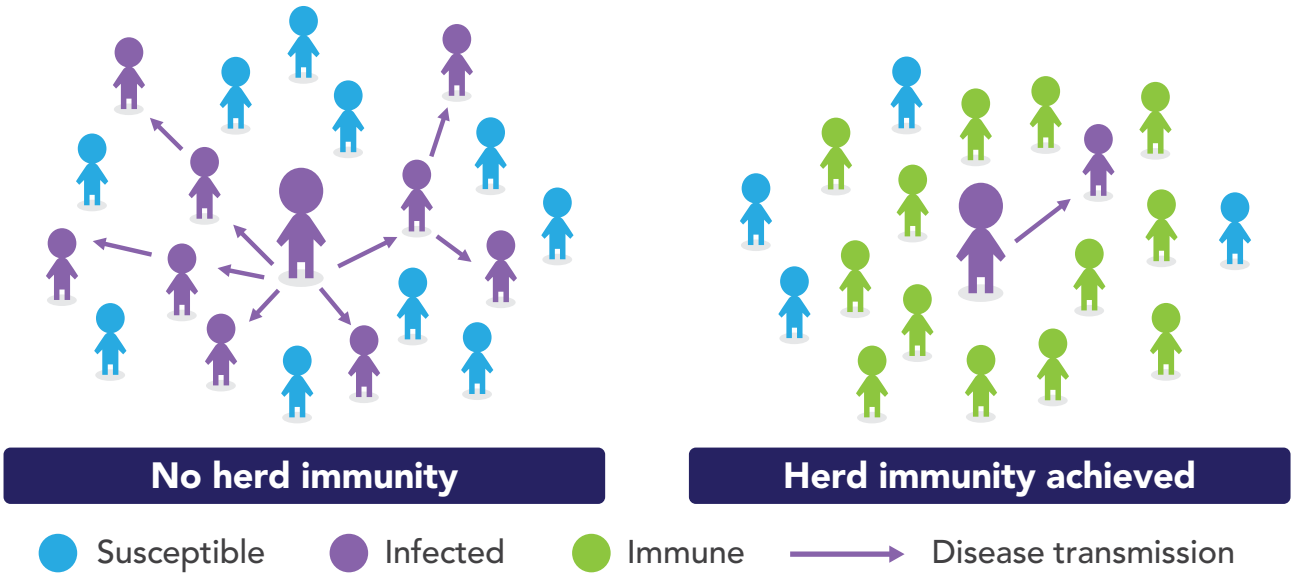
The Pfizer-BioNTech and Moderna vaccines reported stunning overall efficacies (> 90%) whereas Johnson & Johnson and Oxford-AstraZeneca had somewhat lower efficacy (65%-70%). For context, influenza vaccines, in any given year, are 20-60% effective in preventing flu onset. Recently, the Mayor of Detroit declined an allotment of the Johnson & Johnson vaccine, indicating that he would hold out for "better vaccines" for his city.[14,15] Others are adamant that all vaccines are equal in preventing hospitalization and death and advise that, "the best vaccine is the one you get."

Although the latter is undoubtedly, unequivocally true, these vaccines are not created equal. They are all important tools in our COVID-19 toolbox, but some are more effective at preventing symptoms whereas others are more effective at preventing severe outcomes. Their collective Phase 3 trials were not conducted in the same way, in the same locations, at the same time, or with the same outcomes assessed. Some vaccines require two doses compared to one dose; some have cold-storage requirements vs. regular refrigeration; and some expire quickly once thawed whereas others have a longer shelf-life. Bottom line: the world needs all available vaccines because vaccinating a large percentage of the population will move us closer to herd (or hive) immunity.

Herd (or Hive) Immunity: How and When

The phrase "herd immunity" first appeared circa 1910 in the work of American livestock veterinarians concerned about contagious abortion (i.e., epidemics of spontaneous miscarriage) in cattle and sheep.[16] Herd immunity occurs when a significant proportion of the population (the herd) has been vaccinated, or are immune due to previous

Figure 4. What Does Herd (Hive) Immunity Look Like?[19]



Source: GAO adaptation of NIH graphic. | GAO-20-646SP

infection, resulting in protection for susceptible individuals. The more individuals who are immune, the lower the likelihood that a susceptible person will encounter the infection. It is more difficult for diseases to spread when the chain of infection is slowed or interrupted.[17]

The herd immunity threshold is the proportion of a population that must be immune (to any degree, as there are gradations of immunity) for an infectious disease to become stable. When stability is reached, each case leads to, at most, a single new case (R <=1) and the infection stabilizes within the population. If the threshold for herd immunity is surpassed, then R<1 and the number of cases of infection decreases (See Figure 4).

Often, herd immunity is quoted to be around 80%, but it depends on both R_0 and R. For COVID-19, we don't yet know what herd immunity will look like, where that threshold may lie, and if it will involve lifetime or seasonal immunity. The classically trained epidemiologist will point out that we cannot know what the herd immunity level will be until the outbreak has passed. While the outbreak is ongoing, we can make only educated guesses.

Social scientists suggest that we use the phrase hive immunity rather than herd immunity since a herd connotes mindless queuing and a sacrificial march to the slaughterhouse whereas a hive connotes intelligent cooperation and planned activity.[18]

COVID-19: Love it a Little

In the 1991 movie *Backdraft*, Captain Donald Rimgale (played by Robert DeNiro) tells trainee Brian Caffrey (played by William Baldwin) that fire, "… is a living thing, Brian. The only way to beat it is to think like it. Some guys on this job, the fire owns them, makes 'em fight it on its level, but the only way to truly kill it is to love it a little."

Fast forward to 2020. Virologists, social scientists, and epidemiologists suggest that using words or phrases such as *war*, *lockdown*, and *warp speed* militarize and distance us from the virus. Instead, we need to view COVID-19 as teaching us its viral mysteries. We must be students of the virus and its transmission, either as new recruits or as veterans revisiting our discipline. We must be willing to turn on a dime and pivot as needed to understand this clever bit of genetic material in all its cunning and elusive adaptation. We can fear and loathe COVID-19, but the only way to quell this pandemic is to get intellectually close to the virus; to respect it and maybe even love it a little. ■

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Evidera's Presentations Accepted at **ISPOR 2021 Virtual**

PLENARY SESSION

Public Health ... Economics?

Caro JJ, Ryan M, Tegnell A, Thumath M

SPOTLIGHT SESSION

SP4: Public Health Economics - Can We Model It?

Caro JJ, Eichenbaum M, McKibbon W, Vassall A

ISSUE PANELS

Mixed Methods Research: Using Embedded Qualitative Interviews to Enhance Interpretation of Clinical Trial Outcomes

Kimel M, Knoble N, **Dias-Barbosa C**, Eliason L

IP10: Accounting for Preference Heterogeneity in Stated Preference Studies: Moving from Methods to Practice to Decision Making – the Issue of Developing Useful Guidance

Heidenreich S, Boeri M, Hess S, Janssen E

PODIUM PRESENTATIONS

PB4: Patient Perspectives on Implementation of a Long-Acting Injectable Antiretroviral Therapy Regimen in HIV US Healthcare Settings: Final Month 12 Results from the CUSTOMIZE Study

Flamm J, Garris C, D'Amico R, Dalessandro M, **McHorney CA**, Mansukhani SG, Benson P, Thedinger B, Salazar D, Tanda N, Fricker J, Czarnogorski M

EM3: Robustness of External Control Arm: WHEN to Use Them

Ladouceur M, **Colby C**, **Okala S**, **Yue B**

POSTERS

BIOLOGICS/BIOSIMILARS/ REGENERATIVE MEDICINE

PBI3: Comparative Efficacy of Bimekizumab for the Treatment of Moderate to Severe Plaque Psoriasis - A Network Meta-Analysis

Armstrong A, Reich K, Warren RB, Taieb V, **Fahrbach K**, **Kazmierska P**, **Betts M**, **Neupane B**, Kiri S, Gordon K

CANCER

PCN78: A Set of Systematic and Targeted Reviews to Identify the Burden of Iron Chelation Therapy in Myelodysplastic Syndromes

Oliva EN, Huey K, **Deshpande S**, **Turner M**, Chitnis M, Schiller E, Tang D, Jones S, Shah F

PCN114: Investigating Secular Trends in the Survival of Melanoma Patients in England

Ramond A, Carroll R, Vekeria S, **Nordstrom B**

PCN217: Health State Utility Values of Patients with Locally Advanced or Metastatic Urothelial Carcinoma- Analysis Based on the JAVELIN Bladder 100 Trial

Kapetanakis V, **Rakonczai P**, **Benedict Á**, Cislo P, Chang J

DIABETES/ENDOCRINE/ METABOLIC DISORDERS

PDB46: A Best-Worst Scaling Preference Study: The Mealtime Insulin Experience for People with Diabetes in US and UK

Paczkowski R, Poon JL, **Cutts K**, Osumili B, Piras de Oliveira C, Hankosky ER, **Gelhorn H**

INFECTIOUS DISEASES

PIN75: Women's Perspectives of Long-Acting Injectable Antiretroviral Therapy in US HIV Healthcare Settings from the Customize Study

Salazar D, Thedinger B, Benson P, Garris C, **Stassek L**, Mansukhani SG, D'Amico R, Adeyami T, Dalessandro M, Petty L, Czarnogorski M

NO SPECIFIC DISEASE

PNS119: Real-World Evidence Generation in Japan - Uses and Challenges

Graham S, Laurent T, **Simeone J**, Kuwatsuru R, Hirano T, Phillips R, Isomura T

PERSONALIZED & PRECISION MEDICINE

PPM1: Trends in US Public-Private Payer Market Access Dynamics of Precision Medicine Molecular Diagnostics

Iliadi Alexiou A, **Stewart R**

SYSTEMIC DISORDERS/CONDITIONS

PSY16: A Systematic Literature Review of the Relationship Between Serum Ferritin and Outcomes in Beta-Thalassemia

Shah F, Huey K, **Deshpande S**, **Turner M**, Chitnis M, Schiller E, Yucel A, Moro Bueno L, Oliva E

PSY22: A Systematic Literature Review of the Relationship Between Serum Ferritin and Outcomes on Myelodysplastic Syndromes

Oliva E, Huey K, **Deshpande S**, **Turner M**, Chitnis M, Schiller E, Tang D, Jones S, Shah F

MEDICAL DEVICES

PMD10: A Prospective Qualitative Analysis of the Medicare Coverage of Innovative Technology (MCIT) Access Pathway- Opportunities, Considerations, and Implications of Streamlined Breakthrough Device Market Access

Miller M, **Stewart R**, **Iliadi Alexiou A**

RARE & ORPHAN DISEASES

PRO62: Qualitative Interviews to Assess the Content Validity of A Novel Raynaud Diary In Patients With Systemic Sclerosis

Domsic R, Vampola C, **Stassek L**, **Pokrzywinski R**, Furst D, Chung L, Steen V, Mayes M, Shah A, Molitor J, Nagaraja V, Oliver K, Benton W, Khanna D

Upcoming Presentations

ATS 2021

May 14-19, 2021 | VIRTUAL CONFERENCE

ePOSTER

Systematic Review of Real-World Effectiveness and Safety Studies of Mepolizumab in Treating Severe Eosinophilic Asthma

Israel E, Canonica GW, Brusselle G, Yang S, Howarth P, **Martin A**, Koufopoulou M, Smith SG, Alfonso-Cristancho R

JSN 2021

May 19-22, 2021; Kyoto, Japan

ORAL PRESENTATION

Japanese Clinical Trial Participants' Experiences of Migraine and Erenumab Treatment

Hasebe M, Takashima T, Igarashi H, **Duenas A**, **Dias-Barbosa C**, Chandler D, Yoshida R, Numachi Y, Adachi K, **Hareendran A**

EHA 2021 Virtual

June 9-17, 2021 | VIRTUAL CONFERENCE

ABSTRACT ONLY

Validation of Algorithms to Identify First-Line Therapy (Induction and Maintenance) for Multiple Myeloma for Use in Electronic Healthcare Databases

Berger A, Ailawadhi S, **Shah S**, **Fraeman K**, **Saragoussi D**, **Buus R**, **Nguyen B**, Cherepanov D, Romanus D

McGill University Pharmacoepidemiology Courses Summer Session 2021

June 14-18, 2021 | VIRTUAL

SHORT COURSE

EPIB 654 - Pharmacoeconomics for Health Technology Assessment

Caro JJ

DIA 2021

June 27-July 1, 2021 | VIRTUAL CONFERENCE

ePOSTER

A COVID-19 Epidemiologic Model to Enhance Efficiency Through Evidence-Based Site Selection for Vaccine & Treatment Trials

Caro JJ, **Schaumberg D**

SHORT COURSE

Best Practices for Business Communications: How to Communicate with Maximum Impact

Chen D

SESSION SPEAKER

Early Access Programs as Real-World Data Generators: An Additional Source of Data in the Pre-Approval Phase

Speas E

IAS 2021

July 18-21, 2021 | VIRTUAL CONFERENCE

ePOSTER

CAB+RPV LA implementation Outcomes and Acceptability of Monthly Clinic Visits Improved During COVID-19 Pandemic Across US Healthcare Clinics (CUSTOMIZE: Hybrid III Implementation-Effectiveness Study)

Czarnogorski M, Garris C, **Stassek L**, Mansukhani S, D'Amico R, Dalessandro M, Williams W, Wu S, Wohlfeiler M, Flamm J, Benson P, Zurawski C, Bosse M

ORAL PRESENTATION

CUSTOMIZE: Overall Results from a Hybrid III Implementation-Effectiveness Study Examining Implementation of Cabotegravir and Rilpivirine Long-Acting Injectable for HIV Treatment in US Healthcare Settings; Final Patient and Provider Data

Czarnogorski M, Garris C, D'Amico R, Flamm J, Sinclair G, Wohlfeiler M, Mena L, Dalessandro M, McHorney C, Mansukhani S, Williams W, Merrill D, Spreen W

Recent Presentations

SID 2021 Meeting

May 3-8, 2021 | VIRTUAL CONFERENCE

ePOSTER

Using Electronic Health Records to Evaluate Factors Associated with Treatment Escalation in Psoriasis

Rhoads JL, Malatestinic W, Burge R, **Ganz ML**, Saravanan S, Duffin KC

APA Annual Meeting

May 1-3, 2021 | VIRTUAL CONFERENCE

POSTER

A Systematic Literature Review of Schizophrenia Clinical Practice Guidelines: Recommendations on Acute and Maintenance Antipsychotic Treatment

Correll CU, **Martin A**, Patel C, Goulding R, Kim E

ePOSTER

Systematic Review of Schizophrenia Clinical Practice Guidelines: Recommendations on use of Long-acting Injectable Antipsychotics in the United States

Correll CU, **Martin A**, Benson C, Goulding R, Kim E

European Myeloma Network Meeting

March 3-6, 2021 | VIRTUAL CONFERENCE

ePOSTER

Patient-Reported Experiences During and Following Treatment with Belantamab Mafodotin (Belamaf) for Relapsed/Refractory Multiple Myeloma (RRMM) in the DREAMM-2 Study

Eliason L, **Correll J**, **Martin ML**, Cardellino A, Opalinska J, Piontek T, Gorsh B, Sapra S, Popat R

Gene Therapy for Rare Disorders

February 22-25, 2021 | VIRTUAL CONFERENCE

ISSUE PANEL

Evaluating Challenges Encountered in Small Patient Number Trials

Miller T, Chung D, Lin J, Shaywitz A

PODIUM

Real-World Assessment of Commercialization Strategies for Rare Disease Gene Therapies

Stewart R

WCLC

January 28-31, 2021 | VIRTUAL CONFERENCE

POSTER

Real-World Treatment Patterns and Sequencing of Immunotherapy and Chemotherapy Based on PD-L1 TPS in European Patients with mNSCLC

Gower MN, **Patel SM**, **Janowicz EG**, **Anderson DJC**, **Capart P**, **Stoyanov N**, **Nguyen B**, **Combest AJ**, Ognar RG

REMS Summit

January 19-22, 2021 | VIRTUAL CONFERENCE

ISSUE PANEL

Evaluate if your Organizations REMS Program Should be Outsourced or Developed Internally

Cheslow D, Ancell J, Gopu K, Elhoregy K

San Antonio Breast Cancer Symposium

December 8-11, 2020 | VIRTUAL CONFERENCE

POSTER

A Real-World Evidence Study of Treatment Patterns Among Patients with HER2-Positive Metastatic Breast Cancer

Collins J, **Nordstrom B**, Kwong J, **Murphy B**, Pavilack M

ACNP Virtual Meeting

December 6-9, 2020 | VIRTUAL CONFERENCE

POSTER

Effect of Esketamine Plus Standard of Care (SOC) vs SOC on Time to Remission of Depressive Symptoms in Patients with Major Depressive Disorder with Acute Suicidal Ideation or Behavior: Results from a Pooled Analysis of Aspire I and II

Fu DJ, Zhang Q, **Shi L**, Borentain S, **Guo S**, Mathews M, Anjo J, Nash A, O'Hara M, Canuso CM

ASH Annual Meeting of the American Society of Hematology

December 5-8, 2020 | VIRTUAL CONFERENCE

POSTER

Patient-Reported Experiences During and Following Treatment with Belantamab Mafodotin (Belamaf) for Relapsed/Refractory Multiple Myeloma (RRMM) in the DREAMM-2 Study

Eliason L, **Correll J, Martin M**, Cardellino A, Opalinska J, Piontek T, Gorsh B, Sapra S, Popat R

ICPE All Access Special COVID-19 Sessions

December 3, 2020 | VIRTUAL MEETING

ORAL PRESENTATION

A COVID-19 Epidemiologic Model to Enhance Trial Efficiency through Evidence-Based Site Selection for SARS-COV-2 Vaccine Trials

Schaumberg DA, **Ishak KJ**, **Roiz J**, **Moller J**, **Caro JJ**

PCR London Valves

November 22-24, 2020 | VIRTUAL CONFERENCE

ePOSTER

Procedural Stroke in Transcatheter Aortic Valve Replacement Poses a Substantial Cost Burden to Medicare

Alkhouli MA, **Ganz ML**, **Mercaldi K**, Amorosi SL, Feng C, Christen T, Kapadia S

PROMIS International Conference

October 25-27, 2020 | VIRTUAL CONFERENCE

ORAL PRESENTATION

Methodology for Selecting and Evaluating Items from PROMIS® Item Banks to Develop Novel Short-Form Questionnaires

Blum SI, **Stassek L**, **Bushnell DM**, Lee S, Shaw JW, **Martin ML**

ASN American Society of Nephrology Kidney Week

October 22-25, 2020 | VIRTUAL CONFERENCE

ePOSTERS

Patient and Clinician Preferences for Hyperkalemia Treatment: A Qualitative Study

Israni R, **Brooks A**, **Tervonen T**, Huang J, Szerlip H

Preferences for Anemia Treatment Among Chronic Kidney Disease Patients Not on Dialysis

Alexandre AF, Morga A, **Thomas C**, **Krucien N**, **Tervonen T**, Jiletcovici A, **Marsh K**

Recent Publications

Agarwal SK, Soliman AM, **Pokrzywinski RM**, Snabes MC, **Coyne KS**. Clinically Meaningful Reduction in Dyspareunia is assoc. w/ Improvements in HRQoL Among Women w/ Moderate/Severe Pain assoc. w/ Endometriosis: A Pooled Analysis of Phase 3 Trials of Elagolix. *J Sex Med.* 2020 Dec;17(12):2427-2433.

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