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# THE EVIDENCE FORUM

FALL 2020

## Looking Forward in Drug Development

**TOPICS INCLUDE**

- Post-Marketing Safety Registries
- Health Technology Assessment During COVID-19
- Clinical Trial Site Selection During the Pandemic
- Transformation of Clinical Trial Design and Operations
- *And Much More!*

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# COVID-19 Symptom Reports
## Comparing and Contrasting Three Groups of Patients


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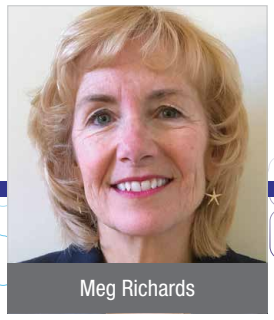
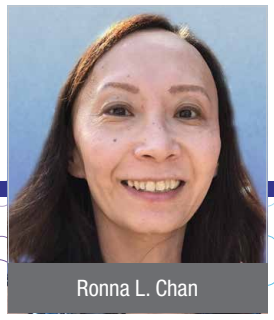
The COVID-19 pandemic has taught us much about the novel virus, and one of the more remarkable lessons is the variation in symptom presentation. Aside from the expected cough, muscle aches, and fever,[1] there have been reports of "COVID tummy" (nausea, vomiting, diarrhea), "COVID taste loss," and "COVID toes" (painful red lesions on the feet).[2] Symptoms vary with age, general health status, and severity of COVID-19 infection, but according to some very recent research, the core symptoms present in a consistent order. University of Southern California (USC) researchers examined rates of symptom incidence collected by the World Health Organization (WHO) for over 55,000 confirmed COVID-19 cases in China. They modeled a sequence that begins with fever, moves to cough and muscle pain, then on to nausea, vomiting, and diarrhea.[3] It's a "head-to-toe" or "North-South" progression, more or less.

Evidera has had the opportunity to support a number of COVID-19 research projects, one recently completed. The study included two cohorts of patients at several primary care clinics in early summer of 2020 in the southwest United States (US). Cohort A consisted of patients presenting with suspected COVID-19, whereas Cohort B consisted of


Meg Richards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patients with previously polymerase chain reaction (PCR)-confirmed COVID-19 diagnosis. The suspected cases were interviewed and tested the day of presentation whereas the confirmed cases were interviewed within five days of diagnosis. Study participants were presented with a core symptom checklist and were asked to recall the day of symptom onset. Although they were not asked about symptom order, we hypothesized that because all patients were newly symptomatic, they would report more fever, cough, and muscle aches than later onset gastrointestinal symptoms. We were curious if the Cohort A patients who ultimately tested negative had a different profile than the Cohort A patients who ultimately tested positive, and how their profile might differ from Cohort B patients. The results are summarized in Table 1.

Of the 110 patients in Cohort A presenting with suspected COVID-19, 28 (25%) tested positive. Positive patients were more ethnically diverse than those testing negative (43% versus 22% Hispanic or Latinx) and were in a narrower age

Table 1. Comparison of Patient Profiles for Cohort A and Cohort B

| | Cohort A* | | | | Cohort B** | |
|---|---|---|---|---|---|---|
| | Positive N=28 | | Negative N=82 | | Positive N=25 | |
| **Characteristic / Symptom** | **No.** | **%** | **No.** | **%** | **No.** | **%** |
| **Demographic** | | | | | | |
| Gender (Female) | 17 | 61% | 50 | 61% | 7 | 28% |
| Race (White) | 23 | 82% | 72 | 88% | 24 | 96% |
| Ethnicity (***not*** Hispanic or Latinx) | 16 | 57% | 64 | 78% | 18 | 72% |
| Age in years (median, range) | 45 | 21-72 | 43 | 19-80 | 43 | 19-80 |
| **Symptom-related^** | | | | | | |
| Headache | 18 | **64%** | 42 | 51% | 11 | 44% |
| Chills or shakes | 16 | **57%** | 24 | 29% | 7 | 28% |
| Muscle aches | 16 | **57%** | 30 | 37% | 17 | **68%** |
| Cough | 15 | 54% | 46 | **56%** | 14 | 56% |
| Fever > 100° F | 15 | 54% | 33 | 40% | 15 | **60%** |
| Fatigue | 12 | 43% | 44 | **54%** | 16 | **64%** |
| New loss of taste or smell | 12 | 43% | 10 | 12% | 4 | 16% |
| Sore throat | 12 | 43% | 46 | **56%** | 8 | 32% |
| Diarrhea | 7 | 25% | 21 | 26% | 2 | 8% |
| Nausea/vomiting | 7 | 25% | 17 | 21% | 1 | 4% |
| Shortness of breath | 4 | 14% | 22 | 27% | 3 | 12% |
| Chest pain | 2 | 7% | 18 | 22% | 2 | 8% |
| Abdominal pain | 1 | 4% | 9 | 11% | 0 | 0% |
| Wheezing | 1 | 4% | 11 | 13% | 1 | 4% |
| Symptom duration in days (median, range) | 4 | 1 - 9 | 4 | 1 - 163 | 7 | 1 - 16 |
| Symptom count# (median, range) | 5 | 2 - 9 | 4 | 1 - 9 | 3 | 0 - 11 |

*Cohort A consisted of patients presenting with suspected COVID-19. Suspected cases were interviewed and tested the day of clinic presentation.

**Cohort B consisted of patients with previously PCR-confirmed COVID-19 diagnosis. Confirmed cases were interviewed within five days of diagnosis.

^Symptoms are sorted in order of decreasing frequency by the first column of patients, the Cohort A-positive patients. Top three symptoms in each column are bolded for ease of relative ranking.

#Two of the Cohort B patients were either asymptomatic or could not recall symptom history.

range (21-72 years versus 19-80 years). The most frequently reported symptoms for Cohort A-positive patients were headache, chills, and muscle aches, whereas for Cohort A-negative patients, cough, sore throat, and fatigue were the most common complaints. Number of symptoms and symptom duration were similar between the Cohort A-positive and -negative subgroups, with the exception of one reported (verified) symptom duration of 163 days for a patient who ultimately tested negative.

The most interesting contrast, perhaps, is between the Cohort A-positive patients and the Cohort B (positive) patients. Although Cohort A-positive patients were predominantly female (61%), Cohort B patients were predominantly male (28% female). Cohort A-positive patients were more racially diverse than Cohort B (82% versus 96% White, respectively). The most commonly reported symptoms for Cohort B included muscle aches, fatigue, and fever. Although Cohort A-positive patients reported a larger number of symptoms than Cohort B (a median of five versus three, respectively), reported duration of symptoms among Cohort A-positives was shorter than Cohort B (a median of four versus seven days, respectively.) It is likely that the Cohort B patients were more distant from symptom onset and diagnosis such that a longer reported duration of symptoms (and some recall bias) would not be unexpected.

Looking across the positives, it appears that the earlier symptoms in the USC-proposed progression – fever, cough, muscle pain – are indeed more prominent in these newly diagnosed/recently diagnosed COVID-19 patients than the later symptoms involving the GI tract. This holds true even for the Cohort A-negatives. It is interesting that sore throat – a rather nonspecific symptom of respiratory illness – is prominent among the negatives. Perhaps those who ultimately tested negative were actually suffering with rhinovirus or allergies. There are anecdotal reports of persons wishing to be tested for COVID-19 infection who manufacture symptoms in order to secure a test where tests remain in scarce supply.

Our interpretation of these data is limited by several factors. First, this is a cross-sectional convenience sample of patients from two study sites and with two sets of entry criteria (known to be COVID-19 positive versus presenting for COVID-19 work-up.) Patients who chose to participate may be quite distinct from those who were approached for participation but refused (we did not have the resources to collect information on refusals). Furthermore, we did not collect information on order of symptoms, severity of symptoms, or impact of illness on patients' lives; these would be interesting endpoints to examine in future studies.

COVID-19 continues to teach, or as some have said, "to school," us.[4] Virologists submit that instead of using language that suggests "waging war" against the coronavirus, we embrace the notion that COVID-19 is tutoring us. Undoubtedly, the lessons we learn will continue well into 2021 and beyond. ■

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# An Initial Framework to Describe and Classify Integrated Scientific Advice Procedures

## Trends and Developments

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### ISA and the Value of Multiple Stakeholder Engagements

Multi-stakeholder involvement with patients, regulators, and health technology assessment (HTA) bodies is fundamental in the development of evidence generation plans for the success of new technologies.[1] Medical treatment developers can seek to optimize their plans via Integrated Scientific Advice (ISA), through which

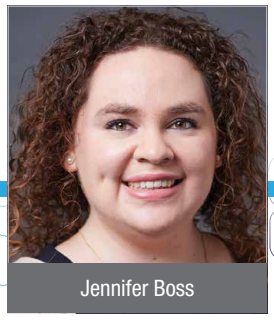
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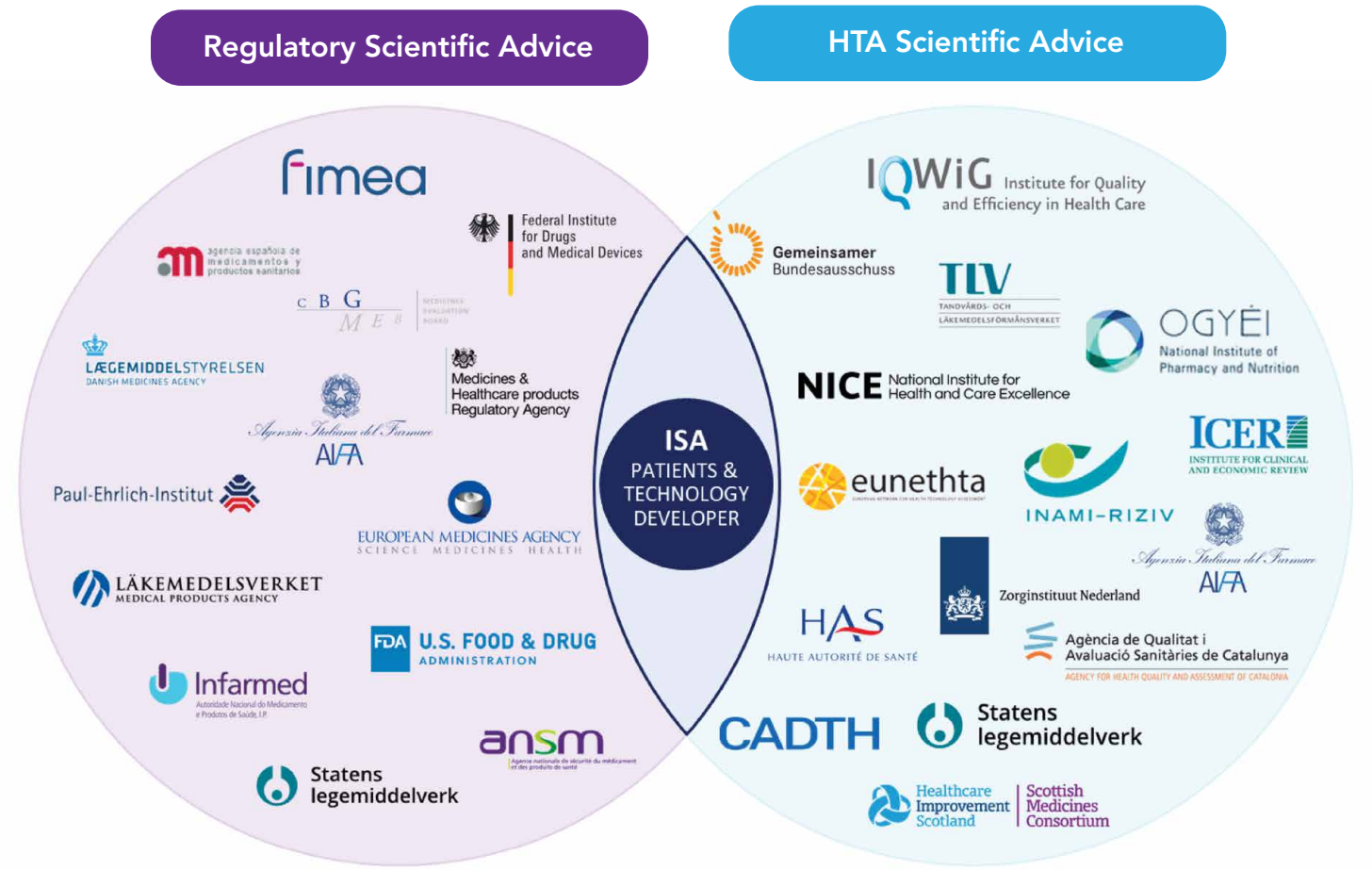
**Figure 1.** Integrated Scientific Advice




regulators, HTA bodies, and payers (See Figure 1) are able to provide constructive feedback, enabling developers to create a robust evidence package that is relevant to all stakeholders, including patients, clinicians, regulators, HTA bodies, and payers, paving the way for timely access.[1]

Since the establishment of the first HTA early advice procedure in 2009, the number of options available to treatment developers has dramatically increased. In addition to the options for ISA offered by national regulatory agencies and HTA bodies, several multinational programs have emerged such as the European Network for Health Technology Assessment (EUnetHTA) Early Dialogues and the National Institute for Health and Care Excellence (NICE)-Canadian Agency for Drugs and Technologies in Health (CADTH) parallel advice. These formal, national and multinational interactions can be further supplemented through informal advice with former members of the agencies via advisory meetings and roundtables, among other engagements. Different combinations of formal and informal engagements can also be sought to maximise the value of these interactions while at the same time meeting key internal objectives, deadlines, and resource requirements (See Figure 2).

Despite being a relatively recently established procedure, there is emerging evidence of the benefits of ISA for developers.[2] Agreement between stakeholders on evidence generation topics discussed during the scientific advice procedure has generally been high, especially among HTA bodies where a consistently high level of agreement is observed.[2, 3] While the views of European Union (EU) HTA bodies and regulators can vary, choice of treatment comparator is the only domain where a meaningful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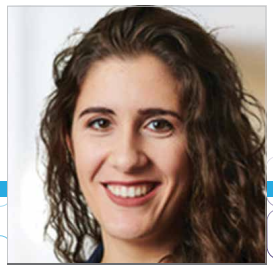
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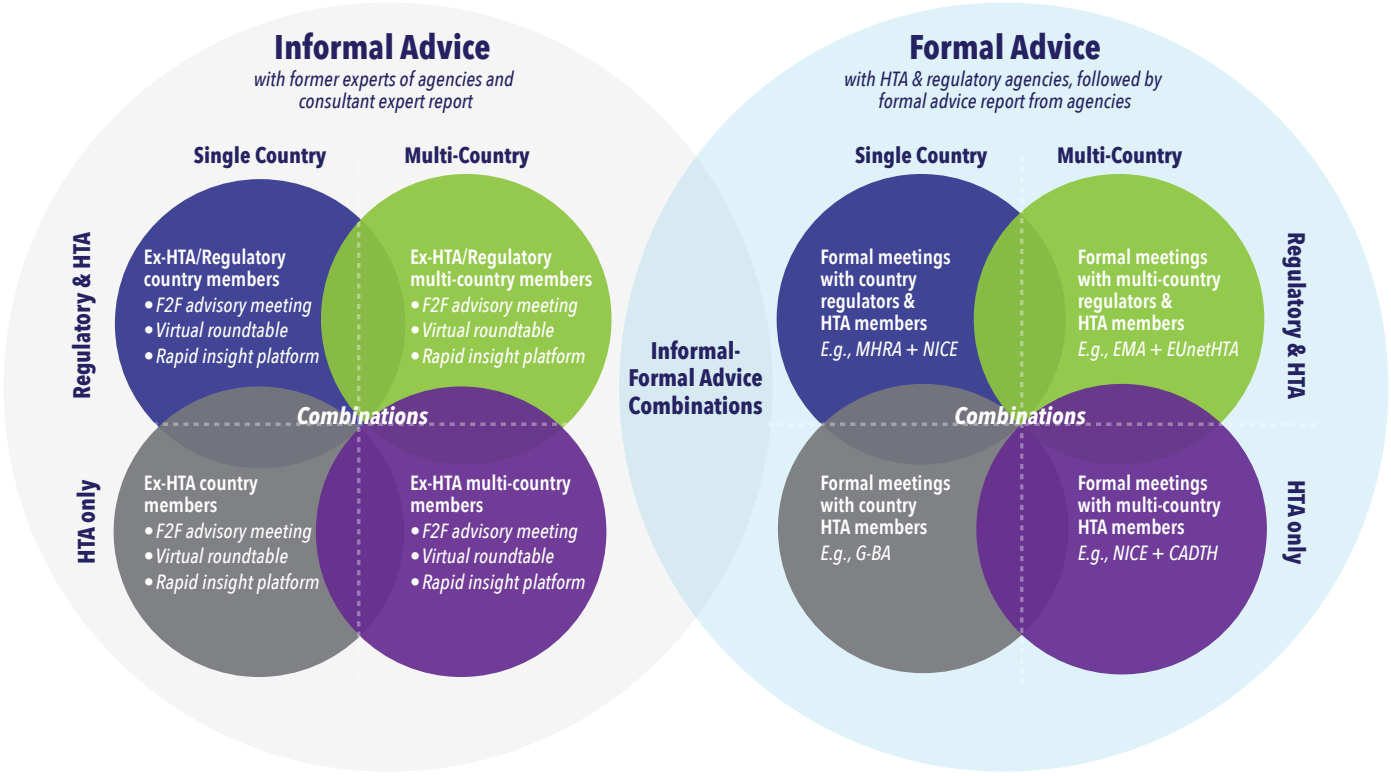
**Figure 2.** Integrated Scientific Advice Combinations




F2F = face to face; MHRA = Medicines and Health Care products Regulatory Agency; NICE = National Institute for Health and Care Excellence; EMA = European Medicines Authority; EUnetHTA = European Network for Health Technology Assessment; G-BA = Federal Joint Committee; CADTH = Canadian Agency for Drugs and Technologies in Health

variance in agreement has been found.[2, 3] Treatment developer compliance with provided advice is higher for regulatory advice than for HTA advice, especially when the stakeholders have limited alignment on their advice.[2, 3]

The benefits of ISA to developers fall into four main streams (See Figure 3)[1,2]:

**De-risking**: Companies can obtain external validation of their clinical development plan. This is particularly useful for medicines with transformative potential, are first-in-class, there is complexity or uncertainty in the approach to clinical development, and where there is a lack of clinical or HTA guidelines.

**Engagement**: The process provides an opportunity for early engagement across market access stakeholders; for example, incorporating a patient representative can provide crucial insights into the unmet need and patient burden associated with a given indication, which may challenge pre-conceived notions around the need for new therapeutic innovation.

**Alignment**: The process requires the cross-functional involvement of clinical, biostatistics, regulatory, market access, health economics, and outcomes research within a company. This early cross-functional engagement may lead to improved internal alignment during the preparation process, exposure of functions to the HTA decision making process, as well as educating different functions on the HTA appraisal process and market access, leading to greater internal harmony on the future development of other treatments.

**Timely patient access**: The opportunity to seek scientific advice with multiple stakeholders and refine the evidence generation plan and launch strategy in response to feedback ensures fewer technical hurdles at the final HTA submission. There is emerging evidence of the positive impact of obtaining early ISA on the subsequent achievement of positive HTA recommendations.[1-4]

While early engagement with regulatory bodies for advice on clinical and non-clinical development plans to demonstrate the safety and efficacy data required for marketing authorization is well established, the involvement of HTA bodies in scientific advice is relatively recent. The first HTA advice procedure was only established in 2009 compared with the much earlier establishment of regulatory advice in 1995. HTA bodies provide advice on the evidence requirements to demonstrate relative effectiveness and economic value of a new product in clinical practice compared with the current standard of care (See Table 1). HTA bodies can also provide direction on relevant comparators, outcomes of interest, evidence quality, and relevance of routine clinical practice. As for HTA appraisals, the patient perspective is increasingly being incorporated at the advice stage.

Figure 3. ISA Streams of Engagement

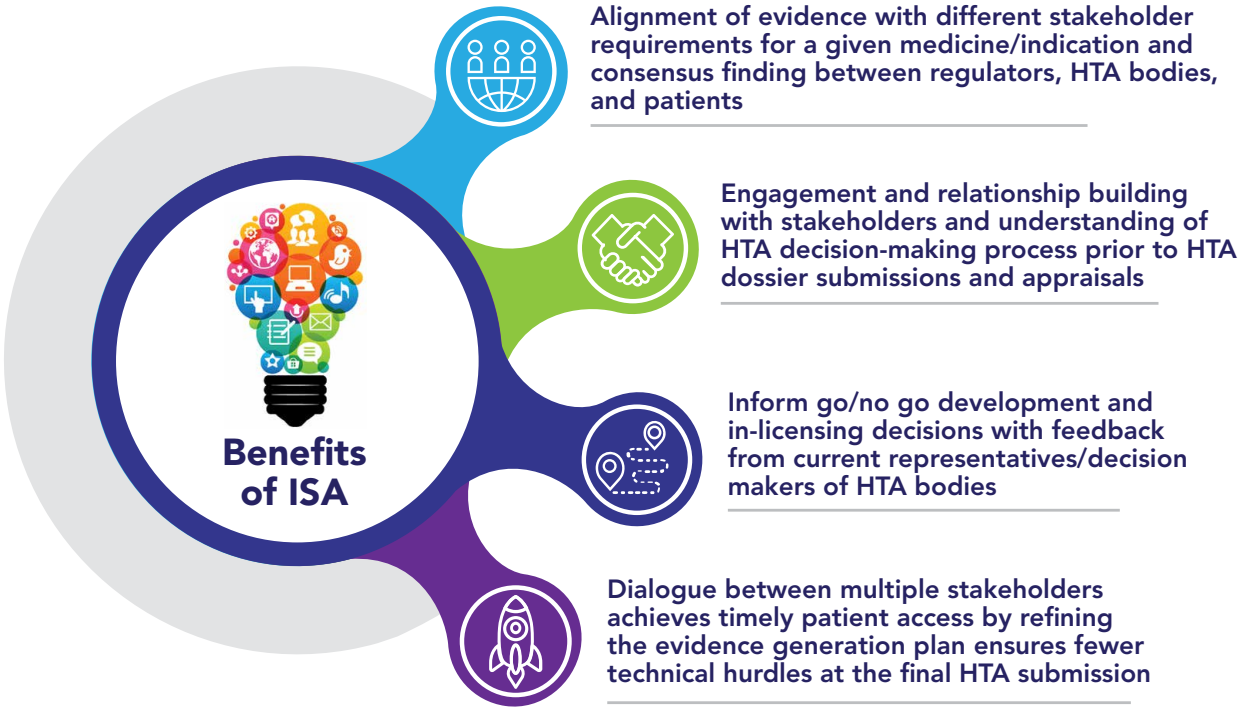



Table 1. Overview of HTA Scientific Advice Processes[1]

| | Parallel Consultation | Joint National Regulatory-HTA Scientific Advice | EUnetHTA Multi-HTA Early Dialogue | Individual HTA Scientific Advice |
|---|---|---|---|---|
| **Overview** | EMA and EUnetHTA advice for up to five countries (EUnetHTA countries plus two additional HTA bodies) | Joint national regulatory-HTA advice from one selected country | Multi-HTAs dialogue with HTA bodies | Single HTA body |
| **Content Considered** | • Clinical development plan<br>• Economic assessment | • Clinical development plan<br>• Economic assessment<br>• Clinical data (certain HTAs only) | • Clinical development plan<br>• Economic assessment | • Clinical development plan<br>• Economic assessment<br>• Clinical data (certain HTA only) |
| **Outcome** | EMA: The Regulators' Final Advice Letter<br>EUnetHTA: Consolidated pathway—final written consolidated HTA recommendations<br>Individual pathway—individual reports as per Individual HTA Scientific Advice | Advice report (MHRA/NICE)<br>Minutes (BfArM/G-BA) | Final written report document in response to questions | Full report (NICE)<br>Minutes (HAS, G-BA) |

MHRA=Medicines and Healthcare products Regulatory Agency; NICE=National Institute for Health and Care Excellence; BfArM=Federal Institute for Drugs and Medical Devices; G-BA=Federal Joint Committee; HAS=French National Authority for Health

Table 2. Categories of ISA Procedure Characteristics

| Eligibility and Type of Procedure | Process for Procedure | Briefing Book Requirements | Meeting Advice Deliberations | Advice Reporting and Follow-up |
|---|---|---|---|---|
| Describes more general aspects of the procedure<br>• Eligibility<br>• Fees | Takes into account the detail of undertaking the procedure<br>• Type of advice<br>• Steps required<br>• Timeframe for engagement | Considers technical aspects of the briefing book<br>• Structure of briefing book<br>• Data requirements<br>• Restrictions (if any)<br>• Timelines for submission | Looks at aspects of advice meeting<br>• Format and structure<br>• Timelines<br>• Venue<br>• Participants | Outlines the format of reporting and follow-up opportunities<br>• Document<br>• Content covered<br>• Timelines<br>• Follow-up engagement opportunity |

## The ISA Framework

With the growing availability of ISA there is a need to describe and classify ISA procedures to support comparisons and identify the value of the differing programs, similar to the HTA framework developed by Hutton et al.[5,6] Evidera has developed an initial and detailed framework to compare formal ISA procedures, due to be presented at ISPOR Europe 2020 in November. A key aim of this framework is to provide details on the different services that are offered to companies seeking advice in a standardised format, thus making it possible to compare across ISA offerings.

Hutton et al.[5,6] developed an analytical framework to describe and classify the requirements used to justify the reimbursement of pharmaceuticals by health systems. This comprehensive analytical framework provides a landmark to collect information on characteristics of HTA systems in a more systematic way. This methodology enables us to move toward a consensus on the key characteristics of HTA bodies, thereby facilitating cross-country comparison.

Using the Hutton HTA framework as our base, we performed a desk review of websites, public domain sources, and interviews with agency representatives to inform an internal workshop; the result was the creation of an analytical framework for ISA procedures that describes and classifies procedures based on identifiable categories for comparison. Available ISA procedures were compared using the framework and current trends and developments identified. We previously described the impact of COVID-19 on ISA procedures in an earlier white paper titled "Integrated Scientific Advice during the COVID-19 Pandemic: A Status Update on Key Programs in North American and Europe," allowing us to also include the impact of COVID-19 into our framework. All programs had or continue to have at least some procedural modifications, with EUnetHTA, Canadian, and Italian procedures being subject to temporary suspensions. Other modifications included:

- Shift to online meetings and option for written advice only
- Capacity restrictions and prioritization of therapeutically critical technologies
- Accelerated procedures for therapeutically critical indications
- Further detail on company evidence generation plans required, e.g., real-world evidence (RWE) and patient-reported outcomes (PRO) sections

Based on our investigations, we developed an ISA framework that classifies the characteristics of ISA procedures into five distinct categories (See Table 2).

The proposed framework was then validated by analysing various ISA offerings within individual countries and globally. The results from this analysis will be presented at ISPOR Europe 2020. In brief, general trends included:

- Increased demand for ISA and resulting agency capacity issues
- Impact of COVID-19 leading to changes in existing procedure processes and development of new offerings, including:
  - Prioritization of COVID-19-related or therapeutically critical technologies
  - Acceleration of processes (e.g., new fast-track options)
  - Change of meetings to virtual format

- More detailed submission requirements, such as companies needing to submit patient-reported outcomes and post-launch evidence plans

While more research is ongoing, the proposed framework has enabled our team to identify key risks arising from the COVID-19 situation as well as changes and trends for some of the key ISA procedures globally. Given the differences between each procedure and the complexities of the engagements, it is important for companies to assess all options before requesting ISA, with a keen understanding of their objectives, the expected value to be gained from different engagements, and any potential associated risks.

By providing the basis for comparative assessment between ISA procedures, this framework is aimed at helping to navigate the diversity of these procedures and identify the most appropriate approach to ISA based on a company's asset and strategy. ■

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# Health Technology Assessment During the COVID-19 Pandemic

## An Update and Recommendations for Moving Forward

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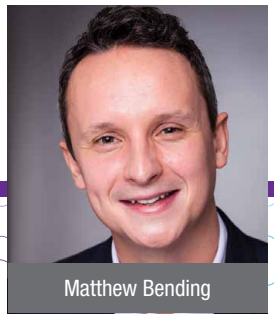
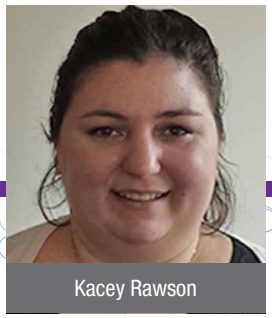
The global COVID-19 pandemic has infiltrated every aspect of daily life with long-lasting effects expected across all sectors, including health technology assessment (HTA) and the market access of pharmaceuticals. Healthcare treatment developers must brace themselves for considerable delays to clinical trials, re-prioritization of pipeline products, and a shift change in normal working practices. As a follow-up to our investigation on the impact of COVID-19 on integrated scientific advice procedures (See "Integrated Scientific Advice during the COVID-19 Pandemic: A Status Update on Key Programs in North American and Europe" in the Spring 2020 issue of *The Evidence Forum*), we now focus on another key area of risk to the commercialization of a new HTA and price negotiations.


Jennifer Boss


Matthew Bending


Kacey Rawson

## HTA Overview

Health technology assessment is a multidisciplinary process that uses explicit methods to determine the value of a health technology at different points in its lifecycle.[1] The purpose is to inform decision making in order to promote an equitable, efficient, and high-quality health system.[1] Distinct from integrated scientific advice which takes place at an earlier stage in the product lifecycle during evidence generation planning (See "An Initial Framework to Describe and Classify Integrated Scientific Advice Procedures: Trends and Developments" in the Fall 2020 issue of *The Evidence Forum*), HTA is an evaluative approach that assesses the impact on society of health technologies and informs decision making regarding the reimbursement of drugs and other health technologies.[2] Since its creation in the 1990's, HTA has become widely implemented across health systems globally and is now a key stage for successful market access.[2] As one indicator of its use, the term "health technology assessment" was entered into Google Ngram Viewer, which displays a graph showing how that phrase has occurred in a corpus of books (e.g., British English, English Fiction, French) over a selected period of years. The frequency with which the phrase is used in books highlights how quickly the terminology has become adopted (See Figure 1). Indeed, justification of reimbursement is now commonly referred to as the fourth hurdle to obtaining a product license after demonstration of product quality, efficacy, and safety.

Throughout 2020, the COVID-19 pandemic has resulted in changes to the status of HTA as institutions reallocate resources to respond to outbreak-related requests and healthcare practitioners provide care to those affected by the pandemic. While there are resulting delays and disruptions to various HTA programs across countries, there are still options available for sponsors seeking assessment and appraisal.

## Status of HTA During the Pandemic

A summary of the status of key HTA programs in North America, Europe, and the Asia-Pacific region is presented in Table 1. COVID-19 has had a varying impact on market access across the HTA programs in terms of changes to the format and timeframes of assessment meetings (whereby interactions between the HTA body, sponsor, and Evidence Review Group are held), and prioritization of technologies by the institutions.

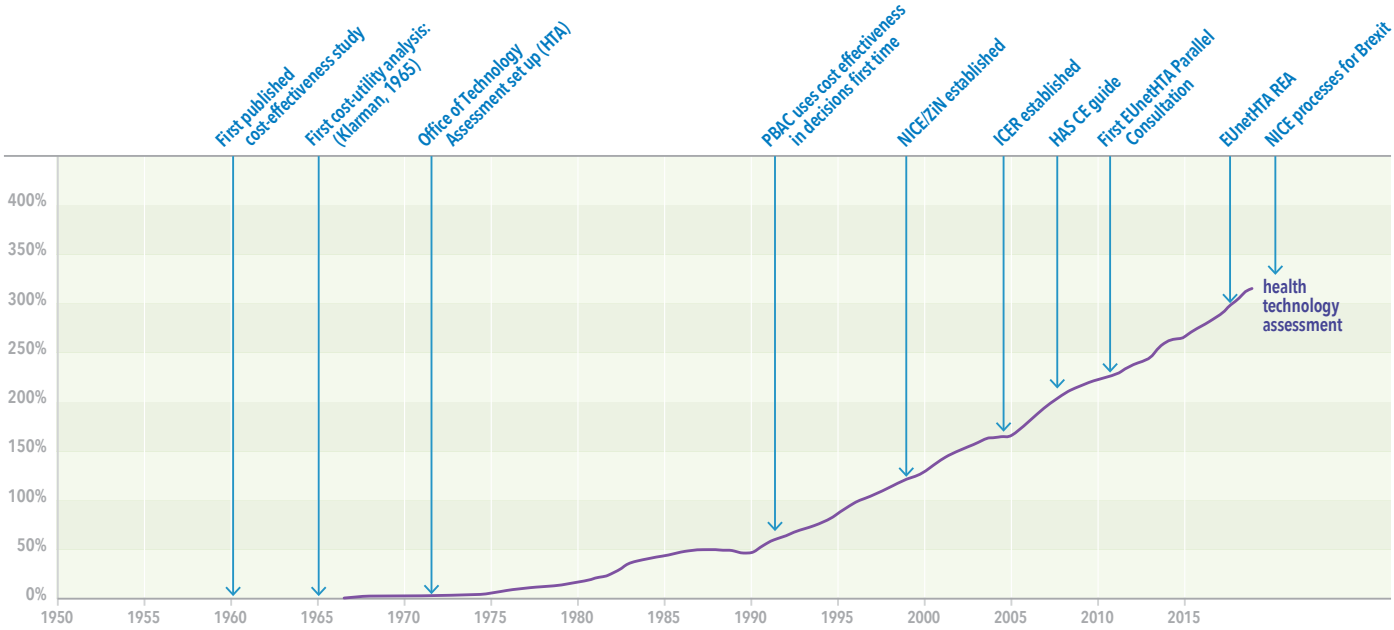
### Format

The most widespread change is the switch of meeting format from in-person to virtual which has been implemented across each program by all institutions.

### Timeframe

In terms of timeframes, some institutions are conducting their HTA programs as normal with minimal or no impact on assessment timeframes, including the Pharmaceutical Benefits Advisory Committee (PBAC; Australia), Canadian Agency for Drugs and Technologies in Health (CADTH; Canada), Federal Joint Committee (G-BA; Germany), Italian Medicines Agency (AIFA; Italy), National Centre for Pharmacoeconomics (NCPE; Ireland), and Dental and Pharmaceutical Benefits Agency (TLV; Sweden). Other institutions have temporarily suspended their HTA programs during the pandemic, including the Spanish Interministerial Medicinal Products Pricing Committee (CIPM; Spain).

**Figure 1.** Citation of the Term "Health Technology Assessment" in Books Between 1950 and Today




CE = Cost-effectiveness; PBAC = Pharmaceutical Benefits Advisory Committee; NICE = National Institute for Health and Care Excellence; ZIN = National Health Care Institute; ICER = Institute for Clinical and Economic Review; HAS = Haute Autorité de santé (French National Authority for Health); EUnetHTA = European Network for Health Technology Assessment; REA = Relative Effectiveness Assessment

Although the HAS in France did not suspend meetings, priority therapeutic areas for assessment have been identified (COVID-19, oncology, pediatrics, or any medication in a serious disease with high unmet need) and products which do not fall into these categories are expected to be delayed.

In the United Kingdom, the All Wales Medicines Strategy Group (AWMSG; Wales), National Institute for Health and Care Excellence (NICE; England), and Scottish Medicines Consortium (SMC; Scotland) had temporarily suspended all appraisal meetings for varying lengths of time during the first and second quarters of 2020; however, all three institutions have now resumed their HTA programs which are running with delays (note that the SMC is not currently accepting new submissions or resubmissions). Similarly, the Institute for Clinical and Economic Review (ICER) in the United States (US) also temporarily suspended assessment meetings, but activities have now resumed with a 90-day delay in assessments as of April 2020.

### Prioritization of Specific Therapy Areas

Multiple institutions have announced prioritization of certain therapeutic areas for assessment, including products for COVID-19 (including HAS, AIFA, NICE, EUnetHTA, and ICER) or therapeutically critical products for oncology, pediatrics, or diseases with a high unmet need (HAS and NICE).

## Short-term Implications

The most immediate challenge facing HTA agencies as they resume normal operations is to clear the backlog of appraisals. For HTA programs such as those at NICE and SMC which have resumed meetings following temporary suspension, delays of at least six months are expected through 2021 (especially for products in non-prioritized therapeutic areas). Although some HTA agencies are trying to help with backlog through the prioritization of disease areas with high unmet need, the criteria for prioritization is not always transparent and this approach is not consistent between the agencies assessed. As a result, considerable variations in delay timeframes across different indications and markets is to be expected.

**Recommendation**: The exact impact of the predicted delays on the launch timelines of specific products remains to be seen; however, pharmaceutical companies should be reassessing country launch waves, cross-country launch sequencing, and competitor launch forecasting for all late stage products in order to identify new opportunities and prepare for emerging challenges.

## Mid-term Implications

All countries assessed have now adopted virtual meetings with face-to-face interactions postponed for the foreseeable future. Therefore, market access teams must adjust their preparations from a face-to-face to a virtual platform. In a virtual setting, it becomes more difficult to communicate within your own team, react to non-verbal cues, and to generate a level of familiarity among attendees. In addition, those attending the meeting will be more reliant on pre-submitted written materials.

**Recommendation**: Clear and concise value communication across all written deliverables should be prioritized alongside virtual negotiation preparedness training with affiliate teams. Some best practices include:

- Restart computer at least 30 minutes before the meeting with HTA and keep all unnecessary applications closed (including email, as it can be distracting)
- Test video and audio the day before (e.g., Zoom, the platform used by NICE, allows the ability to do a test meeting to check audio and video)
- Keep a separate chat open outside of the HTA meeting for within-team communication
- Ensure microphone is muted when not speaking
- Be aware of one's location and surroundings, ensuring no distractions, room lighting is adequate, etc.
- Dress as you would for a face-to-face meeting

The development of virtual negotiation playbooks, negotiation guidelines, and mock negotiations will enable affiliate teams to suitably prepare for this new setting.

## Long-term Implications

The COVID-19 pandemic has put healthcare systems around the world under considerable pressure, and a long-term shift in priorities is predicted across all countries. In addition, the considerable financial cost of dealing with the pandemic will mean healthcare budgets will be even more constrained. This is anticipated to create knock-on effects for pharmaceutical companies; greater difficulty in proving the value of new medications for market access approval, tougher pricing negotiations, and stricter volume restrictions are expected. A lower willingness to pay due to COVID-19 will likely lead to greater evidence requirements in submission dossiers during a time when conducting additional clinical trials is difficult. It is also possible changes to formal or informal thresholds of budget impact and/or cost-effectiveness or international reference pricing approaches may also be forthcoming. NICE, for example, has already announced changes to the HTA appraisal process based on learnings from changes to working practices during the pandemic.[3]

**Recommendation**: An end date to the prioritization of certain disease areas was not provided by any of the HTA agencies assessed for this article. Therefore, one can only speculate on what this means for the future of prioritization, but it is possible that agencies will move to a new model where products meeting a defined set of criteria no longer need formal appraisal as a way to free up resources

long term. Early and continued engagement with HTA bodies will provide useful insights into this evolving payer landscape. While early stage interactions with HTA and regulatory bodies in the form of integrated scientific advice is emerging to be very beneficial, it may be invaluable during this period of growing uncertainty. As we published previously, many agencies are still offering scientific advice services (albeit remotely) helping companies to understand stakeholder needs and refine their evidence package. In addition, it will be important for pharmaceutical companies to be open to alternative and innovative access arrangements, and aligned customer engagement across the local health ecosystem will be essential to successfully negotiate all stakeholders and decision makers. This will require complex analysis, planning, and engagement at a local level, valuing the contribution of each role. ■

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Table 1: Status of HTA Programs During the COVID-19 Pandemic

| Country/ Region | Institution | COVID-19 Impact on: | | | Changes in Access Priorities | Long-term Implications |
|---|---|---|---|---|---|---|
| | | | Meeting Timetables | Meeting Location | | |
| **Australia** | PBAC[4] | | **No change** to timing | All meetings being run **virtually** | N/A | N/A |
| **Canada** | CADTH[5,6] | | **No change** to timing | All meetings being run **virtually** | N/A | N/A |
| **Europe** | EUnetHTA[7-9] | | **Significant delays** as assessments related to COVID-19 are prioritized | All meetings being run **virtually** | Priority therapeutic area throughout remainder of duration of Joint Action 3 (end of May 2021): COVID-19 | Unclear when non-COVID-19 related assessments will resume normally |
| **France** | HAS[10] | | N/A | All meetings being run **virtually** | Priority therapeutic areas for assessment: COVID-19, oncology, pediatrics, or any medication in a serious disease area with high unmet need | N/A |
| **Germany** | G-BA[11] | | **No change** to timing; New amendment to allow a **written voting procedure** | All meetings being run **virtually** | N/A | N/A |
| **Ireland** | NCPE[12] | | **No change** to timing | N/A | COVID-19 Evidence Review Group for Medicines established | N/A |
| **Italy** | AIFA[13,14] | | **No change** to timing | All meetings being run **virtually** | COVID-19 products | National: N/A<br>Regional: Market access delays are expected at regional level due to staff shortages and re-prioritization of resources |
| **Spain** | CIPM[15] | | All meetings **suspended** from 4 March 2020 | All meetings being run **virtually** | N/A | National: N/A<br>Regional: Market access delays are expected at regional level due to staff shortages and re-prioritization of resources |

**KEY:** = no impact = some impact = significant impact

| Country/ Region | Institution | COVID-19 Impact on: | | | Changes in Access Priorities | Long-term Implications |
|---|---|---|---|---|---|---|
| | | | Meeting Timetables | Meeting Location | | |
| **Sweden** | TLV[16] | | **No change** to timing | All meetings are being run **virtually**; TLV is not currently receiving any external visits | N/A | While operations are continuing as usual with virtual meetings, a continuity plan has been developed to prioritize activities if necessary |
| **UK** | AWMSG[17] | | All meetings **suspended** from March to May 2020; Meetings **resumed** from 16 June 2020 | All meetings being run **virtually** | N/A | N/A |
| **UK** | NICE[18] | | All meetings **suspended** for April and May 2020; Meetings **resumed** from 1 June 2020 | All meetings being run **virtually** | Priority therapeutic areas for assessment: therapeutically critical (e.g., oncology) and COVID-19 | Beginning May 2020, the technical report is replaced by a modified version of the Evidence Review Group (ERG) report so that it is presented in an issues-based style; further changes to the NICE appraisal process are expected in June 2021 |
| **UK** | SMC[19] | | All meetings **suspended** from 22 May 2020; Meetings **resumed** from August 2020 in phased approach | All meetings being run **virtually** | **First phase** of resuming meetings will focus on existing applications that were being processed during the suspension. Some applications may be fast tracked to advice following a review by the SMC Executive. **Second phase** will see the SMC Executive agree on which submissions to review, given the unmet need and availability of other medicines. This is only a temporary step, with the SMC hoping to resume full review of all submissions once the backlog has been cleared. | No new submissions or resubmissions being accepted at the current time |
| **US** | ICER[20, 21] | | All meetings **suspended** for 90 days beginning in April 2020; All meetings were planned to resume following this pause | N/A | ICER announced adaptations to their value assessment framework for COVID-19-related products to ensure more timely responses | |

**KEY:** = no impact = some impact = significant impact

AIFA = Italian Medicines Agency; AWMSG = All Wales Medicines Strategy Group; CADTH = Canadian Agency for Drugs and Technologies in Health; CIPM = Spanish Interministerial Medicinal Products Pricing Committee; CT = Transparency Commission; ERG = evidence review groups; EUnetHTA = European Network for Health Technology Assessment; G-BA = Federal Joint Committee; HAS = la Haute Autorité de santé; HTA = health technology assessment; ICER = Institute for Clinical and Economic Review; N/A = not available; NCPE = National Centre for Pharmacoeconomics; NICE = National Institute for Health and Care Excellence; PBAC = Pharmaceutical Benefits Advisory Committee; SMC = Scottish Medicines Consortium; TLV = Dental and Pharmaceutical Benefits Agency.

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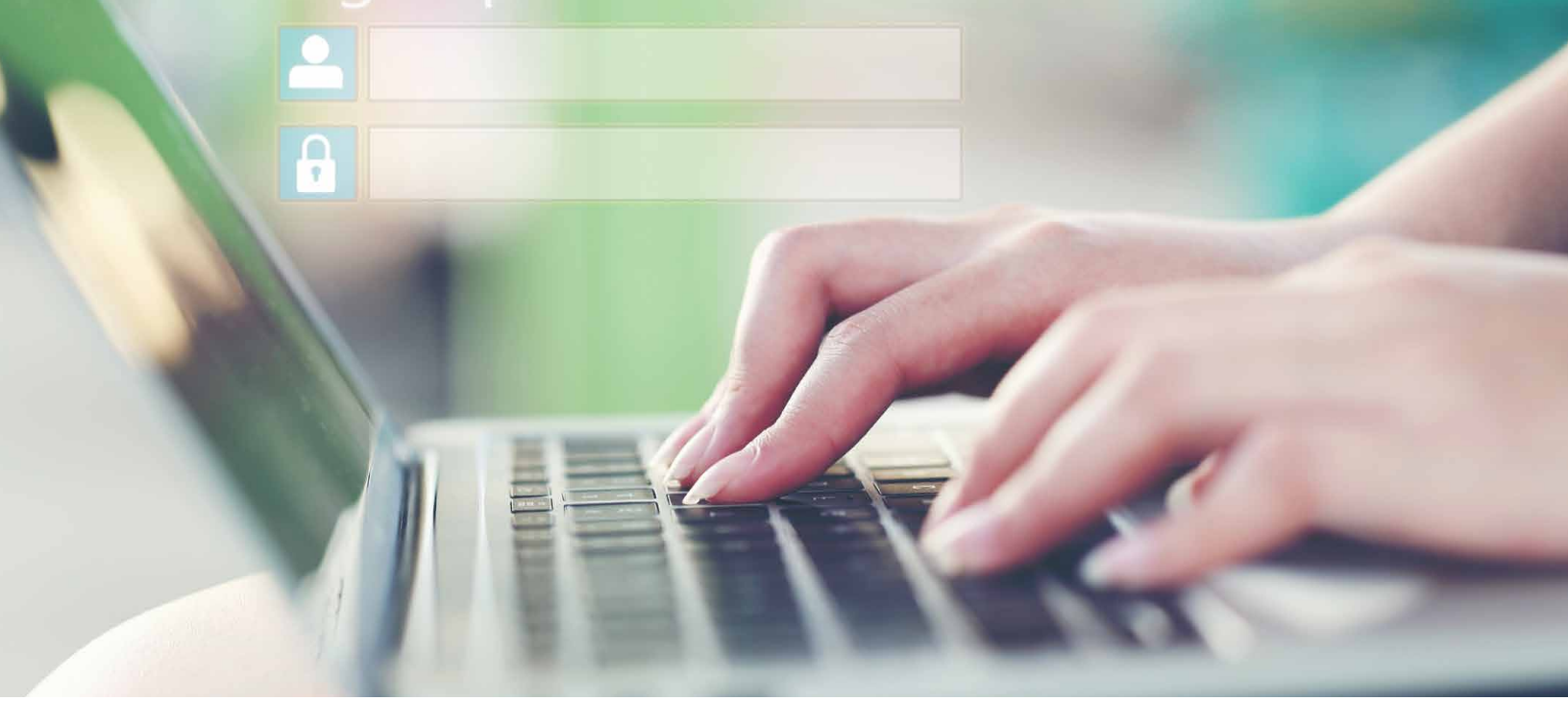

# Post-Marketing Safety Registries
## What, When, Why, How?


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Most often, drug safety studies have a longitudinal cohort study design to describe drug utilization over time and to characterize the risk functions of safety events of interest. Retrospective or historical cohort studies, using retrospective data sources such as medical chart reviews or electronic healthcare databases (e.g., claims or electronic medical records), are often a preferred approach since they have reputedly shorter timelines and lower budgets. Conversely, registries, which are based on a prospective cohort design, might often be viewed as a burdensome approach. However, a post-marketing safety registry can generate an important added value if it is built for the right objectives in the right circumstances.

### What is a Registry?

A registry can be defined as "an organised system that uses observational methods to collect uniform data on specified outcomes in a population defined by a particular disease, condition or exposure."[1] Practically, a patient registry is a particular case of a prospective cohort study, which can be open-ended, where the data collection is systematic and usually relies on data arising from routine clinical assessments. Patient registries are not necessarily built for a specific objective but may be built as a framework or data source for sub-studies in the therapeutic area of interest.[2,3] This definition corresponds well to "disease registries," where patients are included if they are diagnosed with a specific disease, with no restriction on how those patients are managed and treated. Disease registries are frequent in rare diseases and have several applications, such as quantifying and characterizing


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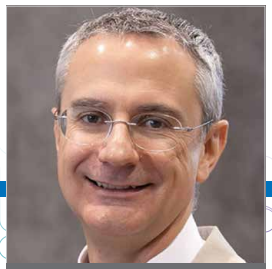
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the patient population, evaluating burden of illness, and describing standard of care.

However, registries in the context of post-marketing safety evaluation aim at evaluating the safety of a specific drug and are most of the time "product registries," where patients are included if they are routinely prescribed a certain drug or group of drugs. Product registries can also be described as prospective cohort studies of patients exposed to one or several drugs.

## Why and When to Propose a Product Registry as a Post-Marketing Safety Study?

It may happen that regulatory authorities in one or several geographies request a registry as a post-marketing safety study requirement. A preferred option is always for a market authorization holder to be proactive and take the first step in proposing a safety study to the authorities when planning risk management activities. The choice of the study design should ideally be based on:

1. Assessment of the safety risks that will need to be studied in the post-marketing period based on best knowledge of the drug's safety profile
2. Translation of the safety risks into research questions
3. Assessment of potential existing data sources to address the research questions
4. Appreciation of study design possibilities to best address the research questions

Figure 1 shows the different possible study objectives by type of approach.

A registry can be proposed based on the following cumulative criteria:

- Study objectives calling for prospective longitudinal data collection
  - Longitudinal and especially long-term patient follow-up
  - Detailed description of safety data (e.g., serious adverse events, suspected adverse drug reactions, suspected unexpected adverse drug reactions)
  - High granularity of safety data (e.g., severity, outcomes)
  - Detailed clinical data required
  - Patient-reported outcomes are of interest
- Circumstances calling for a targeted prospective primary data collection
  - Rare disease
  - Disease not identifiable in an electronic healthcare database
  - Absence of available or appropriate electronic healthcare database
  - Need to monitor safety in "real-time" and regularly report to authorities (e.g., interim analyses, yearly updates to regulatory authorities)

Figure 1. How Registries and Other Sources of Longitudinal Data Address the Main Safety Study Objectives

| | Data Source of Longitudinal Data | Objectives and Outcomes | | | | |
|---|---|---|---|---|---|---|
| | | Drug Utilization | Overall Safety | Specific Safety Risks | Adverse Events vs. Adverse Reactions | Effectiveness |
| Prospective Cohort Design | Registries | Yes (excl. off-label use e.g., in disease registries) | Yes (via AE reporting) | Yes (incl. seriousness, severity, causality, outcome) | Yes | Yes (incl. PROs) |
| Retrospective Cohort Design | Chart Reviews | Yes (incl. off-label use) | No | Yes (incl. seriousness, outcome; granularity limited by availability of data in medical charts) | Yes, but availability and granularity variable depending on chart data | Yes (excl. PROs except if done routinely and recorded in medical charts) |
| | Electronic Healthcare Databases | Yes (incl. off-label use) | Possible (via analysis of diagnostic codes) | Frequency only (excl. seriousness, severity or causality; granularity limited by diagnoses coding system) | Possible in some US electronic health records (e.g., via data mining) | Depending on availability of effectiveness criteria (excl. PROs) |

AE = Adverse Event; PROs = patient-reported outcomes

Figure 2. EMA and FDA Positions on Post-Marketing Registries

| Attribute | EMA | FDA |
|---|---|---|
| Acceptability | High | High |
| Status | PASS (or PAES) | • As part of a REMS<br>• As a PMR outside of a REMS (includes pregnancy registries) |
| Exhaustivity | Not expected | Possible if part of a REMS (e.g., drug distribution conditional to registry enrollment) |
| Safety Outcomes | • Important identified risks<br>• Important potential risks<br>• Important missing information | • AEs, SAEs<br>• SARs, SUSARs |
| Effectiveness | • Yes, if the study is a PAES<br>• Possible as a secondary objective in a PASS if not jeopardizing the collection of safety data and maintaining an acceptable data collection burden | • Yes (e.g., long-term outcomes)<br>• Including differences vs. clinical trial data |
| Comparator | Depending on circumstances | Depending on circumstances |
| Use of Existing Registries | Highly recommended if possible | Possible |
| Countries | • EU countries (with representation of diverse EU geographies)<br>• Possibility to include non-EU countries in the case of rare diseases (≤50% of patients) | US |

AEs = adverse events; PASS = post-authorization safety study; PAES = post-authorization efficacy study; PMR = post-marketing requirement; REMS = risk evaluation and mitigation strategy; SAEs = serious adverse events; SARs = suspected adverse reactions; SUSARs = suspected unexpected serious adverse reactions

Acceptability of registries is high in all geographies. Figure 2 shows the European Medicines Agency (EMA) and United States Food and Drug Administration (FDA) positions on registries based on regulatory guidances[4,5] and our experience. In other geographies, prospective cohort studies are generally well received and are sometimes a preferred approach or a requirement, especially in countries where electronic healthcare databases are not available (e.g., in India or in Mexico).[6]

## What are the Key Registry Design Considerations for a Post-Marketing Safety Study?

### Inclusion Criteria: Incident Users or Prevalent Users?

Part of the objectives of a safety registry is to describe or confirm the risk function of one or several risks. For this reason, a key design point is the inclusion of new (or incident) users, in other words the inclusion of patients when they first initiate treatment with the drug of interest (or the comparator drug, if any). This is a key feature to avoid immortal time bias[7] and depletion of susceptibles.[8]

However, in the case of rare disease, there is a need from both the market authorization holder (MAH) and regulatory authority perspective to collect as much data as possible. In this circumstance, it might be required that patients already treated outside of randomized controlled trials (e.g., through long-term safety follow-up studies or early access programs) who transition to routine treatment with the newly commercialized drug be included in the registry. These patients (prevalent users) already treated with the drug of interest for quite some time can increase the pool of longer-term drug exposure data. However, as such patients need to remain on treatment to qualify for study inclusion at the time of registry initiation, the resulting study population tends to be selected because those who died or discontinued the drug (e.g., due to AEs) prior to the enrollment into the registry are excluded.

The recommendation in that case is to ensure and clarify in the study synopsis that these patients will be analyzed separately and that there will be no pooling of the data from incident and prevalent users for the analysis of safety risks. Accordingly, the sample size calculation should be based on incident users only, and prevalent users should be included as additional participants (resulting in a greater overall sample size).

### Follow-Up Duration

#### Fixed Follow-Up Duration or Fixed Study Duration?

Although it would seem quite straightforward to apply the same follow-up duration to all patients, this approach has the following caveats:

- The safety events of interest are observed in relation to the drug, so the period of interest is the exposure to the drug. The exposure duration is bound to vary from patient to patient and cannot be determined per protocol in a non-interventional study.
- Some patients might die or drop-out, thus truncating their follow-up.
- Proposing a fixed patient follow-up duration can delay the end of the study (e.g., if most of the patients have been included in the first half of the enrollment period and only a few patients have been included at the end of the enrollment period).
- Some safety events of interest may take several years to develop, even after exposure to the drug has ceased.

The recommended approach is usually to define an enrollment period and an end of study period which ensures an optimal minimal follow-up duration for the last patient included (See Figure 3). This approach allows accounting for the variable exposure period among patients; for censoring, which is common in any prospective follow-up; and, allows the assessment of the incidence rate of safety events (with exposed person-time at risk as the denominator), including long-term safety events of interest.

### *Follow-Up: How Long is Long-Term?*

Registries are frequently aiming at assessing the long-term safety of drugs. But what does long-term mean? It depends, of course, on the expected length of treatment, the underlying pathogenic mechanisms and timing of occurrence of the safety events, and on the patient life expectancy related to the disease. Long-term safety will apply to chronic diseases and long-term treatments. Although no clear definition is given, a consensus is that long-term follow-up is usually five years or more.

### *Beyond Exposure: Should the Follow-Up Extend Post-Discontinuation of the Drug of Interest?*

It is implicit in a post-marketing safety registry that the safety assessment will focus on the exposure period (period when the patient is exposed to the drug, from initiation to discontinuation). However, it is important to raise the question of the post-discontinuation follow-up, based on current level of knowledge on pharmacokinetics and other considerations (e.g., carcinogenicity, risk of withdrawal syndrome, potential reversibility of effect). Even when safety risks are expected to be very low or inexistent post-discontinuation based on these criteria, a short post-discontinuation follow-up period is usually well-received.

Practically, it is not always expected to pursue the same level of data collection in the post-discontinuation follow-up period: a simple remote point of contact with the site, patient, or family can provide enough information regarding the main safety events and vital status.

Figure 3 gives an example of study design based on a fixed study duration approach, including post-discontinuation follow-up.

**Figure 3.** Post-Marketing Safety Registry Design Example

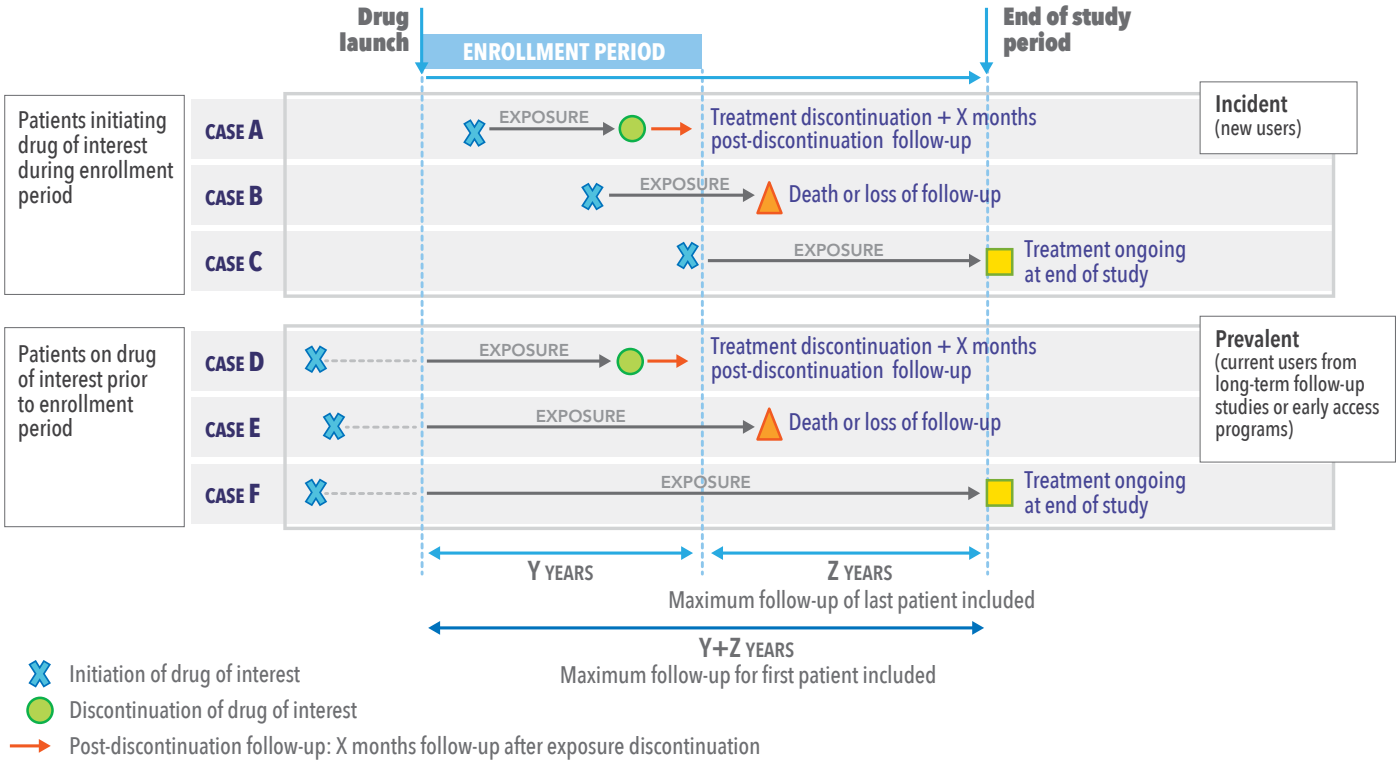
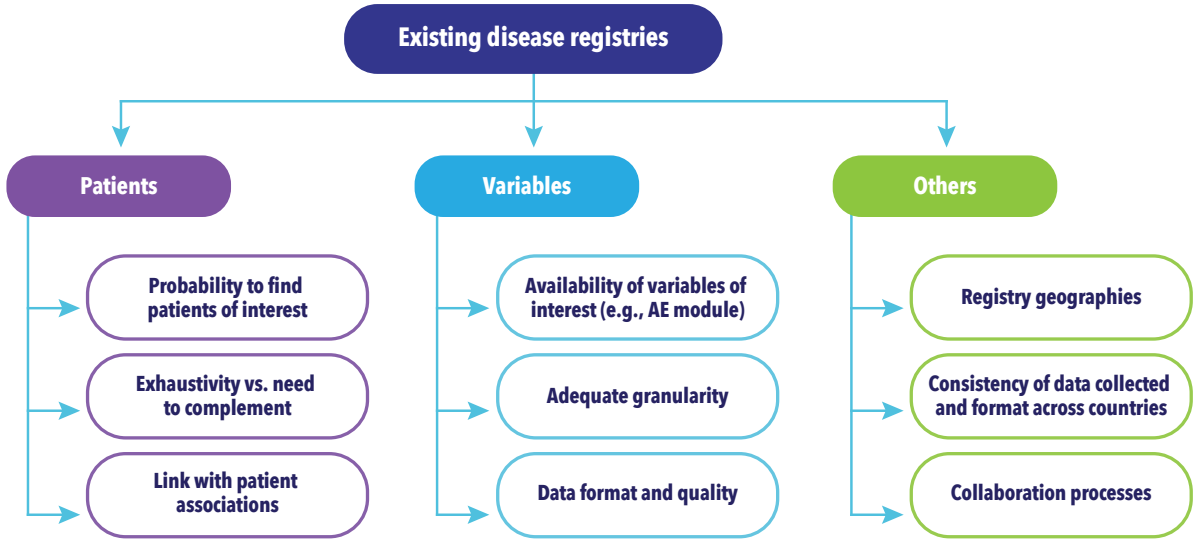


**Figure 4.** Main Considerations When Assessing Possible Collaboration with an Existing Registry




### Comparator or No Comparator?

The inclusion of a comparator group in a post-marketing safety registry is an important strategic decision. When possible and relevant, including such a group is often favored and requested by the EMA and FDA (although more seldomly in Asia and Latin America).

The relevance of adding a comparator group depends on several factors, such as:

- Presence of a clear standard of care on the market (one or several drugs) in the same indication, involving the same monitoring procedures
- Results of any head-to-head clinical trials
- One of the safety events of interest could be due to a drug class effect

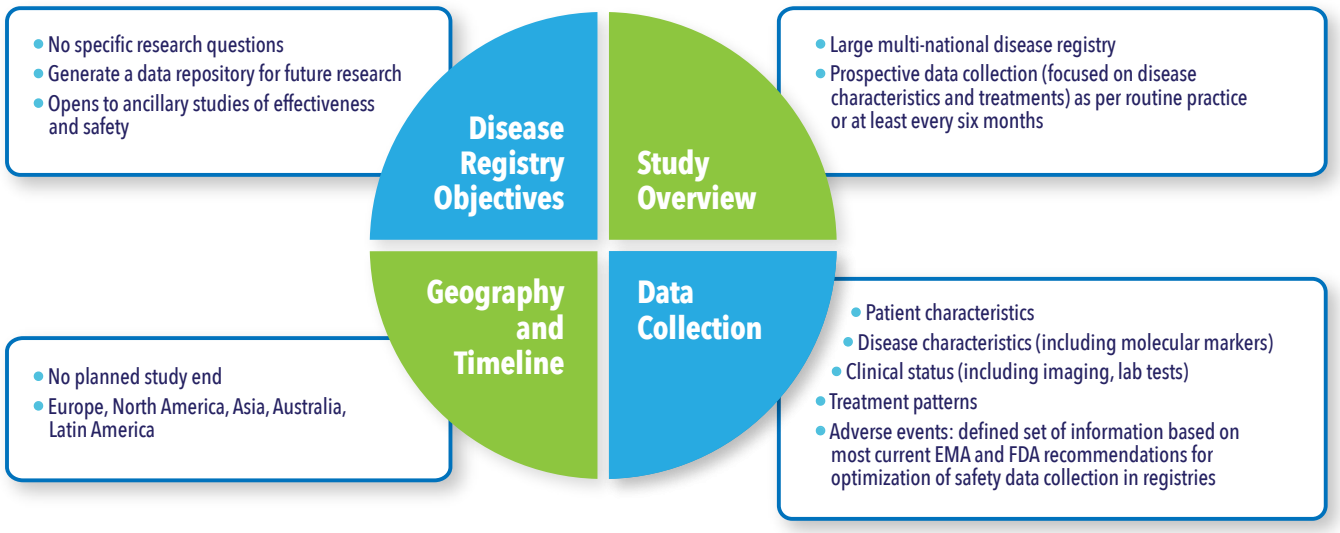
In situations where a comparative study design is not possible or not relevant (e.g., drug of interest is first-in-class or first-in-indication), it can be useful to benchmark the incidence of the safety events of interest against the background risks (e.g., given in European risk management plans, or calculated concomitantly to registry analyses based on other data sources).

## How to Optimize a Post-Marketing Safety Registry Design Using Existing Disease Registries

### Use of Existing Disease Registry

In some therapeutic areas (e.g., oncology or rare diseases), disease registries are established to better describe the natural history of the disease and its outcomes under current standard of care treatments. Most of the time, these registries are established at the initiative of academic

**Figure 5.** Case Study: Disease Registry Set-Up as a Platform for Future Research



clinical centers, sometimes with the collaboration of patient associations or advocacy groups. While post-marketing safety registries are usually product registries, it is important to consider upfront whether to collaborate with existing disease registries in the same therapeutic area and in the geographies of interest, or establish a new registry, for the following reasons:

- Post-marketing safety registries might compete for enrollment with disease registries (with a risk of patient under-enrollment and selection bias in the product registry)
- Post-marketing safety registries might compete for data collection with disease registries (e.g., a patient participating in a disease registry could also be eligible for a post-marketing safety registry, thus potentially duplicating the data collection burden for the site).

The EMA identified this situation as early as 2015 and has since suggested that existing registries could be used as a potential data source for post-marketing safety assessments, under certain conditions (e.g., quality requirements, collection of relevant data[9]). To this purpose, the patient registry initiative was launched and has yielded recent developments, such as conclusions of a workshop with different stakeholders, launch of a registry qualification process, and issuance of a draft guidance for public consultation.[10-12] In our experience, the EMA is encouraging MAHs to explore the possibility of using existing registries and to collaborate with existing registries when possible. Figure 4 shows the main topics for discussion when considering collaborating with an existing registry.

Based on the analysis of these criteria, several strategies can be envisioned:

- No possibility to use existing registries (in this case, a strong justification should be given)
- Possibility of using the existing registry, but the registry needs to be complemented (e.g., with patients from other countries, by recruiting patients outside of the registry to achieve the targeted sample size, or with collection of additional key variables not collected in the registry)
- Possibility of using the existing registry as the only source of data

The best approach is to make early contacts with the registry owners to be able to evaluate any potential gap and to discuss any improvement steps (regarding geographical reach, data collection, EMA qualification) which would prove beneficial to both the MAH and the registry owner.

Figure 6. Case Studies of Post-Marketing Safety Registry Designs

| Case Study | Objectives/ Outcomes | Study Periods | Comparator | Complementary Data Sources | Geographies | Effectiveness Outcomes |
|---|---|---|---|---|---|---|
| **Oncology Indication** | • Adverse events of special interest including seriousness, severity, causality<br>Overall safety (AEs) | • Fixed study duration<br>Post-discontinuation follow-up | Yes | No | EU and ex-EU | Yes, as a secondary objective |
| **Rare Oncology Indication–First-in-Class** | • Overall safety (AEs, ADRs) | • Fixed study duration<br>Minimum study duration determined by expected life expectancy | No | No | US | Collected |
| **Rare Pediatric Disease–First-in-Class** | • Long-term safety<br>Adverse events of special interest | • Fixed study duration<br>Post-discontinuation follow-up | No | No | EU + US | Collected |
| **Rare Pediatric Disease–Other Drugs in Indication, but Unique Monitoring Scheme** | • Adverse events of special interest (+impact of risk minimization measures) | • Fixed study duration<br>Post-discontinuation follow-up | Benchmark on background risk | Existing registry – to complement with de novo data collection | EU | Collected |
| **Rare Disease–Other Drugs in Indication but New Mode of Action** | • Adverse events of special interest<br>Long-term safety<br>Utilization | • Fixed study duration | Yes | Existing registry – potential to be the only data source | EU + US | Yes, as an objective |

### Building a Disease Registry to Optimize Future Post-Marketing Safety Studies

Conversely, when building a new disease registry, the possibility to use this registry as a data source for future post-marketing safety studies is ideally integrated from the outset in the study design (See Figure 5). Industry sponsors can indeed decide to invest in a disease registry in order to have a platform of data to leverage for different purposes, including safety assessment.

## Conclusion

Post-marketing safety registries, although thought to represent about 10% of post-marketing safety studies, will still be needed in several circumstances (e.g., rare diseases, high granularity of safety data, lack of existing electronic healthcare database). In these cases, beyond providing post-marketing safety data, these registries provide useful long-term information on treatment utilization and effectiveness outcomes that can be used outside of a regulatory safety environment.

The growing experience with this kind of safety registry (See Figure 6) allows the sponsor to anticipate and address the regulatory authorities' requirements; it also ensures maximal leveraging of existing disease registries, and optimization of the study design to ensure the study objectives are achieved with the best balance between regulatory, scientific, and operational considerations. ■

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# Rare Diseases and Orphan Drugs
## Where are We Now?


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While rare diseases are individually uncommon, they collectively represent a major burden to society as well as to the patients concerned. Overall, more than 7,000 such diseases are known, affecting an estimated total of 30 million to 40 million people in the European Union (EU) and 400 million worldwide.[1,2] The definition of rare diseases differs across jurisdictions, although it is typically based on prevalence estimates. For example, rare diseases are defined as those affecting <200,000 people in the United States (US),[3] and <1 in 2,000 people in the EU,[4] with conditions affecting <1 in 50,000 in the EU being additionally classified as "ultra-rare."[5] Patients with rare diseases face immense difficulties in accessing treatment,[6] particularly due to the lack of effective options for many conditions. Where therapies do exist, challenges associated with current regulatory and reimbursement frameworks contribute to the limited access to care. Here we discuss the current state of moves to address this situation.

### What's the Problem?

Traditionally, the very small patient populations with each rare condition have made rigorous clinical trials of new therapies unfeasible or financially unviable.[7] The conduct of clinical trial programs is further hampered by a lack of fundamental knowledge about key aspects of many rare diseases, including their epidemiology and natural history. Also, the heterogenous disease landscape with regard to their pathophysiology, symptom presentation, and disease characteristics can make it particularly difficult to recruit enough patients to sufficiently power a clinical trial.[8]

The resulting low level research activity and associated lack of specific licensed and reimbursed treatments for many rare diseases has promoted the use of the term "orphan


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disease" when referring to such conditions.[6] To address these evidence and therapeutic gaps in rare diseases, legal frameworks have been established in many countries to promote the development and commercialization of treatments (often called "orphan drugs").

## Incentives for Orphan Drug Development

Understanding, awareness, and interest concerning rare diseases have grown in recent decades, resulting in various policies and incentives to encourage manufacturers to develop treatments for these conditions.[1,6] Orphan designation (or status) was formally defined in the US through the Orphan Drug Act 1983, and in the EU as part of the specialized pathway for application of orphan medicinal product (OMP) designation (based on Regulation (EC) No. 141/2000).[4,9] This legislation dictates that for a drug to be awarded orphan designation, it must meet specific criteria focusing on a condition's prevalence, the absence of existing treatment options, and the high costs of drug development (which the manufacturer may not be able to recoup through sales) (See Table 1). However, orphan designation does not confer marketing authorization. Instead, such designation represents part of the research and development stage of drug development by providing a framework for evaluating a drug's efficacy and safety profile.

Once orphan drug status has been awarded, both the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) support drug development for rare diseases through financial incentives such as tax credits, the waiver of future fees, or market exclusivity (for 7 years in the US and 10 years in the EU). Regulatory agencies also provide support through scientific advice, particularly on the conduct of tests and trials to demonstrate the efficacy, safety, and quality of the drug being considered for marketing authorization.[10] Designated drugs may be considered for specific approval pathways that are not limited to orphan treatments (e.g., the FDA's accelerated approval pathway or EMA's conditional approval).

## Requirements for Regulatory and Reimbursement Assessment

Regulatory and reimbursements pathways follow standardized processes to assess candidate new medicines and depend heavily on evaluation of clinical trial data. However, these two types of pathways differ from each other and across territories with regards to their evidence requirements for these products. This can pose major challenges for both manufacturers and authorities, especially in the context of rare diseases, where the value of a drug may not be easy to demonstrate through traditional clinical and cost-effectiveness measures.

Regulatory bodies, such as the EMA and FDA, mainly consider evidence on the therapeutic effects and safety of a drug. The need for such data may help explain why, despite the significant increase in the number of granted orphan

**Table 1.** Criteria for Orphan Designation by the EMA and FDA

| EMA[4,11] |
| --- |
| The medicinal product is intended for the diagnosis, prevention, or treatment of a life-threatening or chronically debilitating condition.<br><br>The condition does not affect more than five in 10,000 persons in the [European] Community when the application is made, or without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment.<br><br>There exists no satisfactory method of diagnosis, prevention, or treatment of the condition in question that has been authorized in the Community or, if such method exists, the medicinal product will be of significant benefit to those affected by that condition.<br><br>An application for designation may however be submitted for a new therapeutic indication for an already authorized medicinal product. In this case, the marketing authorization holder shall apply for a separate marketing authorization which will cover only the orphan indication(s). |
| **FDA[3]** |
| The disease or condition for which the drug is intended affects fewer than 200,000 people in the US or, if the drug is a vaccine, diagnostic drug, or preventive drug, the persons to whom the drug will be administered in the US are fewer than 200,000 per year, or for a drug intended for diseases or conditions affecting 200,000 or more people, or for a vaccine, diagnostic drug, or preventive drug to be administered to 200,000 or more persons per year in the US, there is no reasonable expectation that costs of research and development of the drug for the indication can be recovered by sales of the drug in the US.<br><br>A sponsor may request orphan drug designation of a previously unapproved drug or of a new use for an already marketed drug. In addition, a sponsor of a drug that is otherwise the same drug as an already approved drug may seek and obtain orphan-drug designation for the subsequent drug for the same rare disease or condition if it can present a plausible hypothesis that its drug may be clinically superior to the first drug. |

designations in recent years, only a few of these have ultimately resulted in licensed products.

An even broader range of evidence is generally needed to support reimbursement submissions, including comparative efficacy and safety and, often, the cost effectiveness of a drug in a local healthcare setting. Some health technology assessment (HTA) bodies also require good quality-of-life data to demonstrate the burden of a disease and the impact of its treatment on patient-reported outcomes.[12] In many instances, orphan drugs go through the same assessment processes as those without this status. The extensive requirements for these evaluations can pose problems for manufacturers' evidence-generation strategies for orphan drugs, and this may contribute to the lack of HTA submissions for such treatments.[13,14] Specific frameworks have emerged in recent years to specifically address such challenges.

## Demonstrating Clinical Benefit

Consideration of clinical trial evidence remains the cornerstone of technology assessments both for orphan and non-orphan drugs. However, demonstrating the effectiveness of an orphan drug can be difficult given the lack of knowledge of the pathophysiology of many diseases, difficulties in recruiting enough patients for clinical trials, and a general lack of established active comparators. Many trials often also lack well-defined clinical endpoints, which is compounded by the often short follow-up duration in such studies. Surrogate endpoints are frequently used in clinical studies in support of applications for marketing authorization and can be helpful in identifying clinical benefits in circumstances where small sample sizes preclude demonstrating definitive effects on longer-term or hard clinical endpoints, such as disease progression or survival.[15] However, the correlation between surrogate endpoints and hard clinical endpoints is often unclear and there may be insufficient data for endpoint validation.[16-18]

In light of these limitations, real-world evidence is increasingly used as a source of long-term clinical data or to facilitate researching treatments for rare diseases for which clinical trial data are often sparse.[19]

### Demonstrating Cost Effectiveness

Conducting health economic evaluations of potential treatments for rare diseases may be hard due to challenges similar to those encountered when aiming to establish a clinical benefit.[14,20] Also, companies conducting such evaluations to seek reimbursement for their orphan drugs are often confronted with an unfavourable incremental cost-effectiveness ratio (ICER) that reflects high treatment costs and uncertainties around the clinical benefit. In addition, there is general acknowledgement by HTA bodies, such as the National Institute for Health and Care Excellence (NICE) and the Scottish Medicines Consortium (SMC), that quality-adjusted life years (QALYs) – a standard measure of treatment effect – do not necessarily capture all elements needed to adequately and comprehensively demonstrate the added value of orphan drugs. Accordingly, in addition to accepting higher ICERs, NICE and the SMC commonly consider other evidence sources, such as patient experience, during the evaluation process.[21]

### Differences in HTA Requirements

Difficulties in preparing reimbursement submissions due to differences between HTA bodies in their evidence requirements (e.g., regarding the acceptability of surrogate endpoints or the need for patient-reported, as well as clinical, outcomes) may be compounded by differences in decision-making criteria across these bodies. Research suggests that these variations in assessing "value" have led to discrepancies in access to care across jurisdictions.[14] For example, a survey conducted in 2010 across EU member states found, among a sample of 60 orphan drugs assessed for reimbursement, the approval rate ranged from 25% in Greece and 33% in Spain to over 90% in France.[22] Consequently, manufacturers seeking reimbursement for a treatment for a rare disease may have to demonstrate multiple disparate aspects of its value in different territories while simultaneously managing the implications of its high price.

### Ethics and Equity of Access

The challenges in the assessment, and therefore the limited availability, of treatments for rare diseases raises ethical questions about how much a society or healthcare system is prepared to pay for the treatment of people with these conditions. With ICERs for orphan drugs often being above typical willingness-to-pay thresholds, some commentators have expressed concerns that increasing the allocation from a finite healthcare budget to orphan drugs may reduce overall population health.[23] Of note, however, some countries, such as France and Italy, tend to reimburse even highly priced orphan drugs, due to the relatively small patient population involved.[20,24]

To address uncertainties around the cost effectiveness of treatments and give patients access to treatment as early as possible, jurisdictions could grant conditional reimbursement. Under such arrangements, a drug is reimbursed initially for a pre-specified period during which manufacturers can collect and present additional data to inform a final decision on reimbursement. However, critics of such provisions argue that even if the ICER remains unfavourable despite new evidence, the initial positive reimbursement decisions are rarely changed, owing to political considerations.[23]

### Frameworks to Address the Challenges

To address reimbursement challenges for orphan drugs, regulatory and HTA bodies have established assessment frameworks specific to rare diseases or those with a high unmet need. Examples include the Highly Specialised Technology (HST) framework at NICE and the ultra-orphan

medicines pathway of the SMC. Furthermore, international collaborations aim to share experiences regarding clinical trial design and risk-management strategies for long-term safety issues (e.g., EMA and the FDA) or to coordinate access to orphan drugs (e.g., HTA agencies across Europe).

## What's Still Needed?

Despite the long-standing initiatives for orphan drugs, barriers to progress in the development and approval of orphan drugs still exist, and in many conditions, patients' needs are yet to be adequately addressed. Consequently, expert opinion has highlighted various proposals to improve access to care.

First, clinical trial designs need to address the methodological limitations posed by rare, and particularly ultra-rare, diseases. Broader patient population criteria and large, international collaborations could help recruit enough patients to sufficiently power a trial. Although surrogate endpoints are increasingly accepted for regulatory and reimbursement assessments, these should be validated where possible and trial follow-up durations should be extended to also consider hard clinical endpoints or patient-relevant outcomes. This would help ensure that regulatory and reimbursement decisions are based on measures that are relevant to patients.

Second, evaluation frameworks should be further adapted to acknowledge the challenges posed in evidence generation for rare diseases. In the absence of sufficient clinical trial data, real-world evidence should be given more weight in the evaluation process. For example, the FDA launched its Real-World Evidence Program in 2018 to support evidence generation on the safety and effectiveness of medicines, as well as the use of such data in regulatory decisions.[25] In the EU, there have been similar efforts, through establishing standardized patient registries to generate uniform evidence to support benefit-risk evaluations of drugs.[26] There should also be more emphasis on alternative ways of assessing "value" beyond the usual evaluations of clinical effects and cost effectiveness by taking into account patient experience and complex solutions (e.g., multi-component strategies that go beyond pharmacological therapies in isolation). There is also the need to more holistically take quality of life and the impact on family members and caregivers into account given the high burden of rare diseases.[21] While decision makers are increasingly recognizing the importance of incorporating such elements, particularly when robust clinical data are sparse, further changes of assessment processes are required to fully, transparently, and fairly address such "social value judgements."[27]

Third, regulatory and HTA agencies need to increase their collaboration to help ensure they can evaluate and share relevant data, develop clear methodological standards, and establish transparent pathways for the approval and reimbursement of orphan drugs. In addition, changes to reimbursement and funding methods, such as conditional approval and merging healthcare and social care budgets, may be required to increase early access to care.

## Conclusions

With regard to rare diseases, manufacturers and decision makers continue to face major challenges in understanding the conditions, appropriate evidence generation, and adaptation of regulatory and HTA processes to ensure timely approval and availability of treatments. In this context, the needs of patients with such conditions are often inadequately addressed. These therapeutic gaps call for improvements in the design and conduct of clinical trials, the increased use of real-world evidence to inform decision making where there is a lack of high-quality trial evidence, and further efforts to establish value frameworks that go beyond traditional HTA considerations. ■

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# Prevent or Wait and Treat
## Modeling Health Conditions with Preventive and Acute Therapeutic Options in R


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### Introduction

Prevention is broadly understood to refer to measures intended to avoid realization of undesirable outcomes. In the context of healthcare delivery, these outcomes typically consist of injury, disease, and the downstream financial, individual, and societal burdens with which ill health is commonly associated.[1] Prevention types can be categorized in three ways:

- **Primary prevention** activities, such as immunization against infectious diseases or physical activity to manage body mass index (BMI), aim to avoid the development of a disease or condition


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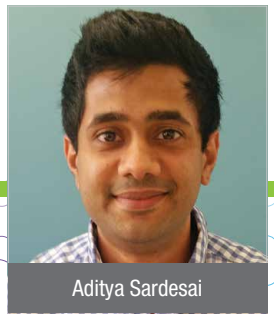
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- **Secondary prevention** activities, such as administration of low-dose aspirin to reduce the risk of a second heart attack or stroke, aim to prevent recurrence of a medical problem that has already manifested
- **Tertiary prevention** seeks to alleviate the long-term effects of an ongoing illness (e.g., rehabilitation or chronic disease management programs)

Health economists and policymakers have long debated whether an ounce of prevention does indeed outweigh a pound of cure. One perspective is that preventive services are worthwhile only when cost-saving. A dissenting view is that such interventions are worthwhile if they offer value for money (i.e., they are cost effective),[2] while still other commentators focus solely on their capacity to save and/or promote the quality of human lives.[3]

This article describes the development of a *de novo* economic model in R designed to study the cost effectiveness of preventive and acute treatments when these are administered concurrently. We first outline the model's structure and discuss the rationale for selecting R as the platform for model implementation. We next demonstrate the model's application with reference to therapies for patients managing migraine in the United States (US). Finally, we discuss the implications of our findings as they relate specifically to the treatment landscape for migraine and more generally to economic modeling of preventive health interventions.

## Model Framework

The modeling framework is equipped to model situations in which an underlying health condition manifests in a series of regularly occurring episodes that contribute to increased medical resource utilization and/or detract from health-related quality of life. Some existing or prospective interventions may be applied when an episode occurs to help manage any detrimental impacts (i.e., acute treatments), while others may be specifically intended to minimize the frequency with which episodes occur (i.e., preventive treatments).

The model has a nested structure consisting of "micro" and "macro" levels (See Figure 1). At the macro level, disease episodes occur periodically over a predefined time span (one year). Preventive treatments serve to reduce the likelihood of experiencing an episode, which translates into fewer episodes.

The micro level simulates in detail the events that follow within an episode, each of which consists of relatively short-lived incidents that result in accrual of direct (medical) losses and reduced patient quality of life. Physicians can administer treatments to manage the duration and severity of symptoms, although these may or may not be effective during any specific episode, necessitating other interventions.

To operationalize this framework, we developed a decision analytic model to study how the selection of acute agents impacts resolution of the average episode. Output from the

Figure 1. Diagrammatic Representation of the Model

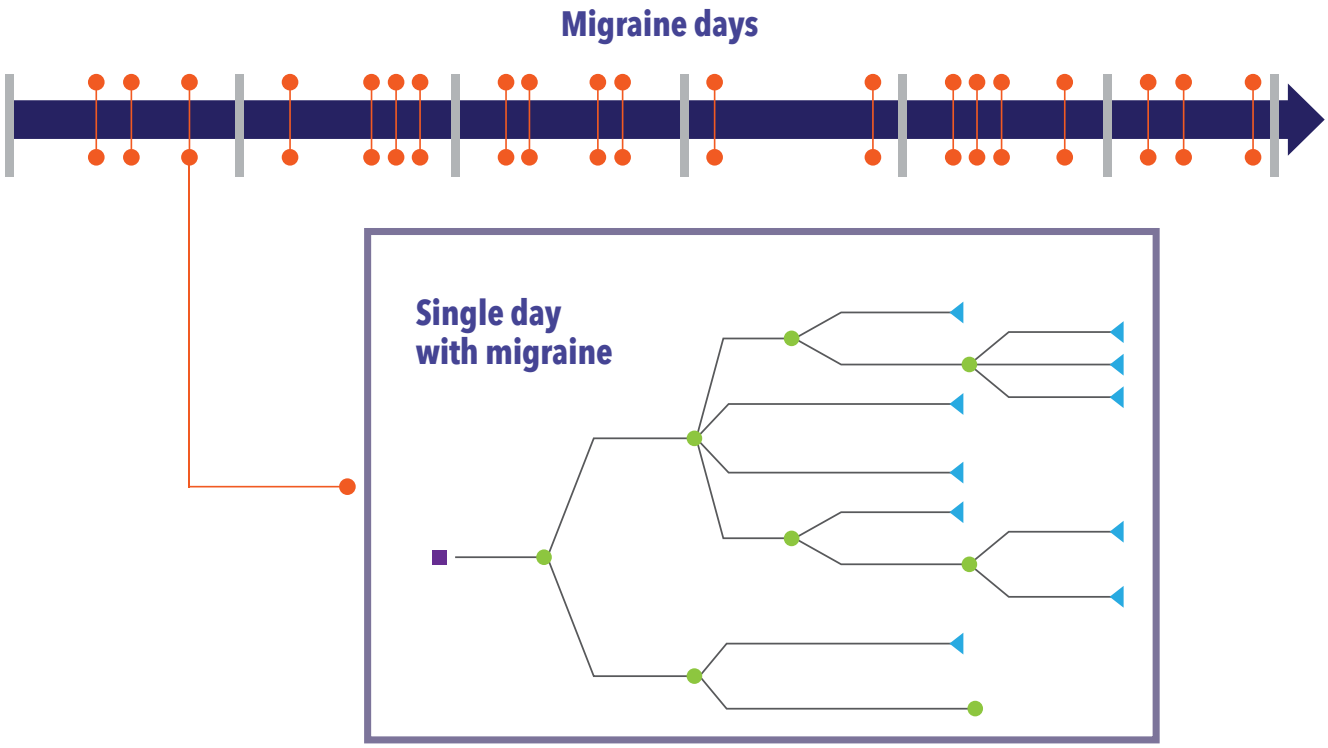
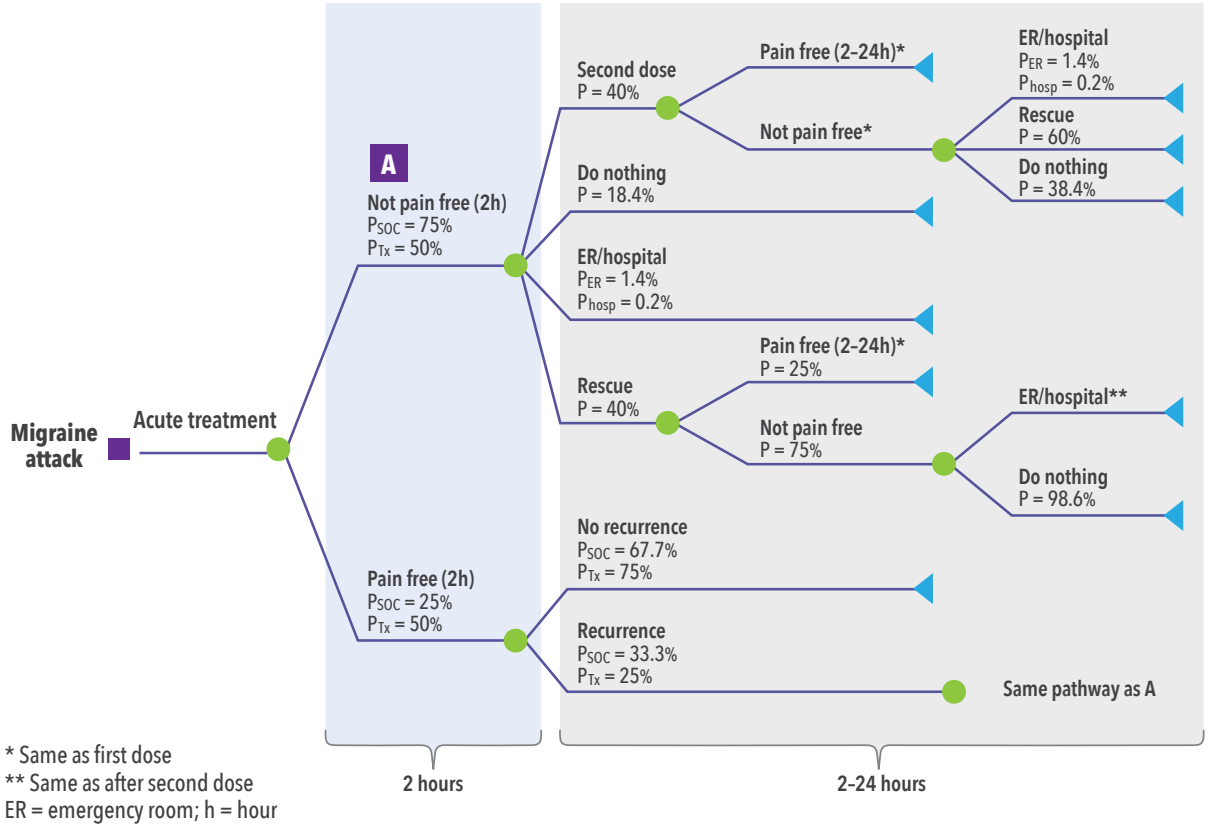


**Figure 2.** Diagrammatic Representation of the Decision Tree




decision model then feeds into a second set of calculations that evaluates the longer-term implications of how the episodes are managed. This macro-level lens further accounts for the impact of preventive treatments.

This modeling framework is suitable for representing a variety of common health conditions, including but not limited to those referenced in the introduction. In the remainder of this article, we demonstrate how the model can be readily applied to examine the cost effectiveness of prospective treatment options for migraine in the US.

## Why Did We Select R?

Microsoft Excel (paired, where appropriate, with Visual Basic for Applications [VBA]) has long been a mainstay of health economics and outcomes research (HEOR) due to its widespread accessibility, perceived transparency, and familiarity to modelers, industry, and regulatory submission bodies alike.[4] Recent years, however, have witnessed expanding utilization of other platforms for implementing some or all components of health economic modeling projects, and R has rapidly grown in popularity due to its low (zero) cost; its capacity to perform analyses or operations that might be difficult or cumbersome to implement in Excel (e.g., model calibration)[5]; seamless integration of statistical analyses and health economic modeling that facilitates validation[5-7]; potential for reductions in model run-time relative to other software[5-7]; access to utilities that allow for automated generation of customizable, high quality graphics[7]; and, integration with the R package Shiny, which facilitates construction of interactive web browser-based user interfaces, allowing users with minimal programming experience to easily navigate sophisticated health economic models.[4,8]

A further advantage of R as a tool for HEOR is the presence of a sizable and dedicated user community that has developed a wide variety of freely available add-ins ("packages") to further extend its functionality.[9] One such group, the Decision Analysis in R for Technologies in Health (DARTH) workgroup, freely disseminates a variety of utilities intended to accelerate update of R within HEOR.[10] We acknowledge our indebtedness to DARTH for two such utilities, the Decision-Analytic Modeling Package (*dampack*) and the Decision Tree Constructor (*dectree*),[9,11-14] which we employ in the analyses summarized below.

## Modeling Migraine Acute and Preventive Treatments as a Case Study

Migraine is a debilitating, recurrent primary headache disorder with severe, incapacitating neurological symptoms that affects approximately 36 million individuals (or 1 in 7 adults) in the US.[15] Migraine patients experiencing 14 or fewer headaches per month are said to suffer from episodic migraines, while those with 15 or more days of headache per month are considered to have chronic migraines.[16]

Within this context, the goals of pharmacotherapy revolve around minimizing the detrimental impact of migraines upon the individual, and the frequency of episodes.[16,17] In particular, administration of acute therapies aims to alleviate symptoms rapidly and consistently and minimize use of rescue medications, while preventive therapies are intended to manage the frequency, severity, and duration of attacks and reliance upon acute treatments.[17] This model considers two acute treatments: standard of care (SOC), mainly consisting of use of simple analgesics and oral triptans, and a second hypothetical agent that is more effective but also more costly than SOC. In addition, it considers the clinical and economic outcomes associated with utilization or non-utilization of preventive agents. It is important to note that the non-SOC acute agent and the preventive agent referenced in this example are hypothetical, in that their cost and efficacy are not intended to reflect the attributes of any existing treatment for migraine.

The core of the model is a decision tree—depicted in Figure 2—which represents key clinical events observed during a typical migraine episode. Patients self-administer acute treatment when a migraine occurs. At two hours, they may or may not experience freedom from pain. If so, they sustain this response or later experience recurrence. If not, or if recurrence takes place, the patient may receive a second dose of the original treatment, or rescue medication; visit the emergency room (ER); be hospitalized; or, do nothing. Patients administered a second dose, or a rescue medication, may or may not subsequently experience relief from symptoms, but if not, they cannot employ the same treatment option for the duration of the episode. In addition to this, patients and their physicians can reduce the frequency with which they experience migraines by adhering to prescribed preventive treatments. A visual representation of the model in its entirety, which encompasses both acute and preventive aspects of treatment, appears in the form of an influence diagram (See Figure 3).

As SOC for acute treatment of migraines is relatively inexpensive, we assume a price of $1/dose, whereas the hypothetical comparator is assumed to cost $30/dose. As noted, however, the latter is more effective, in that it doubles the likelihood of freedom from pain at 2 and 24 hours from 25% to 50% and reduces the risk of recurrence from 33% to 25%. Patients experience an average of 9 headache days per month. Administering a preventive agent can reduce the average number of headache days per month by half. The preventive medication is assumed to cost $450 per month.

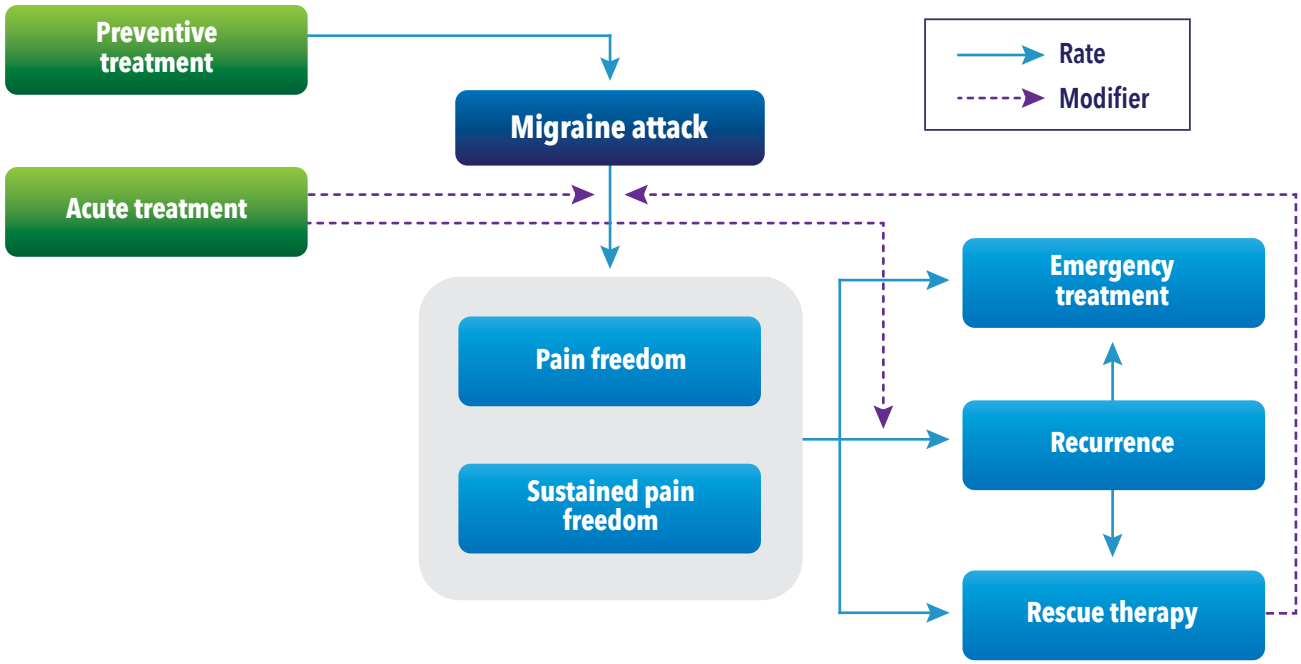
On days without headaches, the model assumes individuals accrue utility of 0.96.[18] Utility accrued during days with headaches—0.605—is the weighted sum of time accrued while free from pain, and time in pain (itself the weighted average of migraine severity and utility corresponding to each "grade" of severity).[18,19]

For simplicity, we assume no cost or utility associated with occurrence of adverse events.

## Results

The model was developed with the flexibility to analyze the cost effectiveness of individual treatments or a complete treatment strategy. To demonstrate this, this study examines market scenarios typical of the introduction of a new acute and/or preventive treatment.

**Figure 3.** Influence Diagram for the Migraine Model



## Cost-Effectiveness Analyses

The first analysis considered the introduction of a hypothetical acute treatment for migraine into a market where an effective standard of care exists. The results of our analysis showed that at an assumed price of $30 per dose, doubling the treatment effect was not enough for the new treatment to be considered cost effective relative to the traditional threshold of $100,000 per quality-adjusted life year (QALY). The presence of a preventive treatment option has no bearing on these results, since the model assumes preventive treatments have no impact on the severity of migraine episodes. Of note, while utilization of a preventive alongside acute treatment does not impact estimated cost-effectiveness, it would likely have significant implications with respect to the budgetary impact of treatment for migraine among plan members. A second analysis considered the cost effectiveness of a preventive treatment supplied alongside either the SOC acute treatment or the hypothetical new treatment described above. The results of this analysis also indicate that prevention would be considered cost effective when administered alongside the hypothetical acute agent (incremental cost-effectiveness ratio [ICER]: $91,083), but not when given with the SOC (ICER: $107,067). These findings speak to the potential for effective preventive options to reduce the overall use of acute agents, albeit at a higher overall expenditure. Results for both analyses are presented in Figure 4.

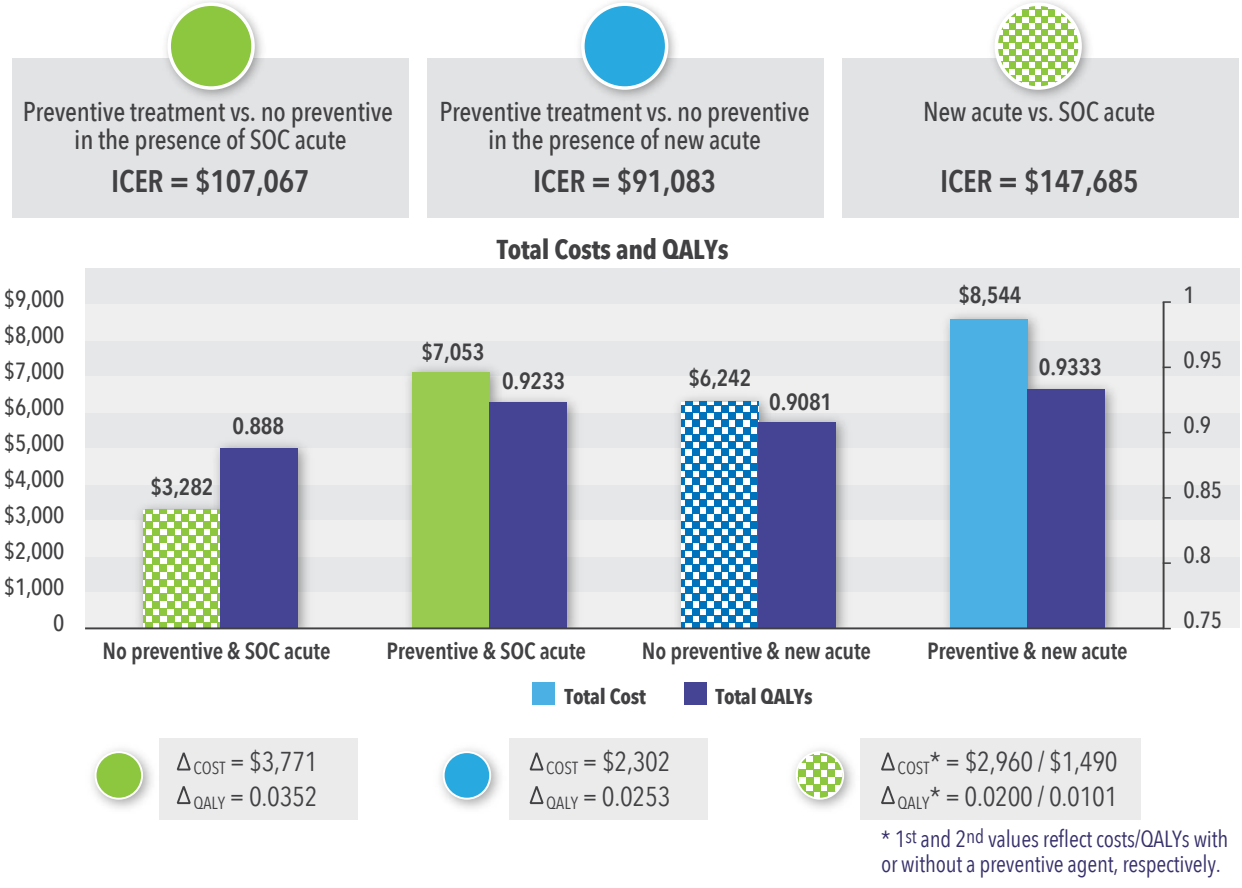
## Economically Justifiable Price

The model calculates the economically justifiable price (EJP) (i.e., the price at which the estimated ICER is equal to a given cost-effectiveness threshold).

The EJP for the hypothetical acute agent is estimated at $22.90 per dose (i.e., 76.3% of the base case value), irrespective of whether a preventive treatment is administered concurrently. This corroborates the earlier finding that the clinical efficacy of the hypothetical agent is not sufficiently superior to achieve cost effectiveness at its original price. The insensitivity of the price of the acute treatment to the presence of a preventive again reflects the intuition that the cost and QALYs accrued as a result of utilization of the acute agent increase and decrease proportionally with changes in the number of episodes a patient experiences.

For preventive agents, the model indicates that given its assumed level of efficacy in reducing monthly episodes of migraine, the preventive agent would be deemed cost-effective at a monthly cost of $429.26 and $468.78 for a threshold of $100,000 per QALY, when paired with the SOC and hypothetical acute agents, respectively. Intuitively, the efficacy of the preventive agent cannot justify its price when it is offered alongside the relatively inexpensive SOC acute agent but sufficient to do so when used with the comparatively costly hypothetical acute agent. This fully

**Figure 4.** Cost-effectiveness Results



corroborates the result that the preventive agent is cost-effective at a price of $450.00 per month when administered in conjunction with the latter but not the former.

Finally, the model calculates the EJP for a preventive when used with an optimally priced hypothetical acute. In this case, when the cost of the hypothetical acute is lowered to its EJP of $22.90, the preventive agent is deemed cost-effective at a monthly cost of $429.00 at a threshold of $100,000 per QALY, which is identical to the EJP for the SOC acute. This reflects the fact that when the hypothetical acute is optimally priced, the net monetary benefit of both acute agents is equalized. EJP calculation results appear in Figure 5.

### Episodes Reduction

To further understand the impact of introducing a preventive treatment into the market, the model calculates the average reduction in monthly migraine episodes required for a preventive to achieve cost effectiveness at its current price and a threshold of $100,000 per QALY.

The results indicate that given its assumed price, the preventive treatment would be considered marginally effective with a reduction in monthly episodes of migraine of 52.0% and 47.6% when used with the SOC and hypothetical acute agents, respectively (as compared to its assumed value of 50.0%).

## Discussion

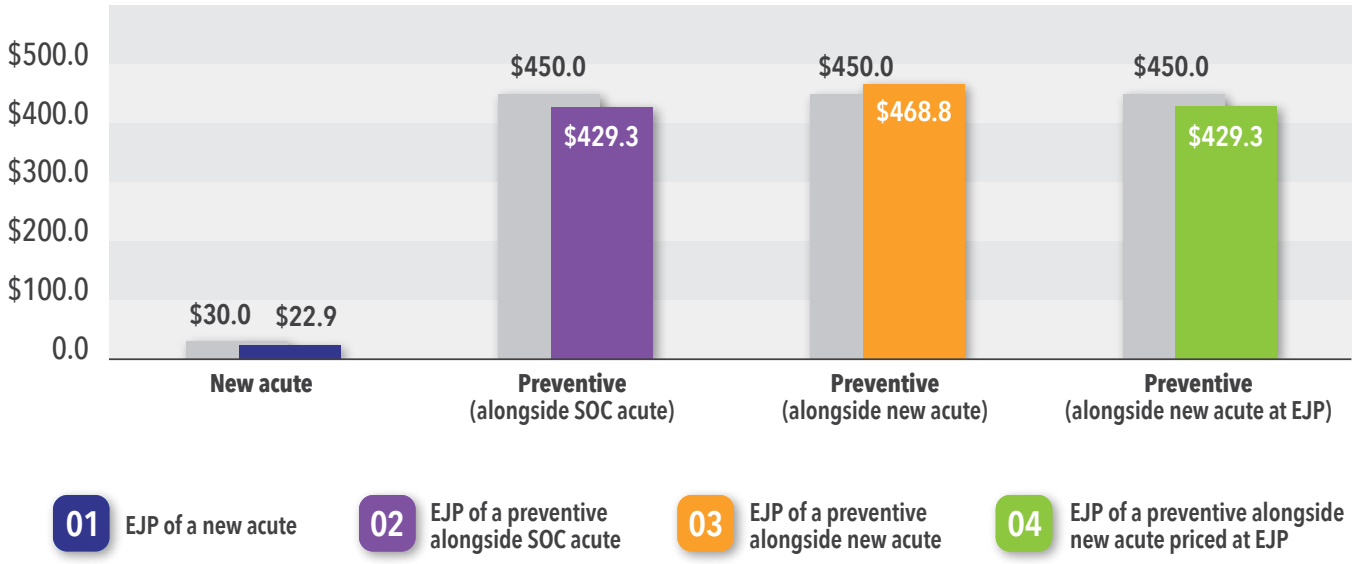
Health economists and policymakers have long been interested in methods for assessing the cost effectiveness of interventions that focus on avoiding or forestalling ill health. We sought to contribute to this active debate through the development of a *de novo* health economic model designed to explore the use of a preventive agent alongside acute treatment. In this study, we demonstrated the application of the model within the context of migraine, although the same concept of the model could be applied to other therapeutic areas with preventive treatments.

In these instances, our analyses suggest preventive and acute treatments should be evaluated jointly to aid decision makers in allocating scarce healthcare resources. Assessments of new acute treatments that do not account for current preventive options—or vice versa—may generate inaccurate conclusions, as they fail to consider contextual factors that can impact how much value for money new health interventions are likely to deliver. Our analysis, for instance, suggests a new preventive for treatment of migraine that fails to meet cost-effectiveness thresholds in the context of a treatment landscape characterized by widespread use of inexpensive SOC acute agents may produce increasingly favorable ICERs if it is assumed to accompany (and to have the potential to reduce utilization of) costlier next-generation acute products.

By implication, the timing of cost-effectiveness analyses is critical. When a new treatment is introduced to the market, available evidence may preclude consideration of all factors that may significantly influence analytical results. Accordingly, we argue that there is potential value in reassessing the cost effectiveness, such as in our case study of preventive interventions whenever the treatment landscape evolves in ways that may overturn conclusions generated by prior evaluations.

This study also demonstrates the utility of compiling and presenting ICERs generated from cost-effectiveness analyses alongside alternative metrics that provide added insight into the value for money associated with new health interventions. Where applicable, measures such as the economically justifiable price or justifiable

Figure 5. EJP Results



reduction in monthly migraine episodes offer new ways of communicating the results of health economic assessments and could be useful in price negotiation discussions with payers.

Finally, this study illustrates the viability and strengths of R as a platform for health economic modeling. This analysis, for example, benefited significantly from our ability to readily extend the functionality of R by exploiting the availability of the Decision-Analytic Modeling Package (*dampack*) and the Decision Tree Constructor (*dectree*) add-ins developed. In addition, validation was facilitated by the fact that the entirety of the model is contained within a single script rather than being distributed across multiple worksheets, named ranges, and VBA modules. Finally, integration with the R package Shiny enabled us to construct an interactive web browser-based user interface, freely accessible to readers (R Migraine Model), that allows users with minimal programming experience to readily reproduce our results or generate their own scenarios without any need to interact with the code underpinning the model. ■

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# Pediatric Drug Development
## Trends and Perspectives in the United States


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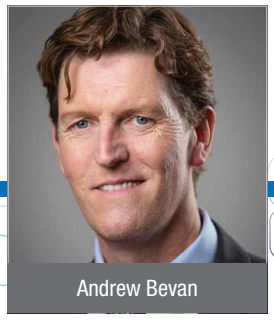
Pediatrics started to emerge as a medical specialty in the United States (US) with the founding of the American Pediatric Society in 1888. However, the field of pediatrics as we know it today originated with the establishment of the American Academy of Pediatrics and American Board of Pediatrics in the 1930s, which were set up to promote excellence in medical care for children and adolescents.

Physiological and psychological development is subject to continuous change from birth through adolescence, which means children should not be considered "small-scale" adults.[1,2] However, as many as 54% of medicines prescribed to children in the US have not been tested for safety and efficacy in this population and are used as "off label" drugs.[3] History has shown that children may be exposed to serious unintended harm if the efficacy and safety of medications is not adequately tested. Examples include gray baby syndrome, a type of circulatory collapse associated with chloramphenicol use in neonates; refractory hypotension and death associated with the use of verapamil for treatment of infants with supraventricular tachycardia; serious extrapyramidal dysfunction and bladder retention leading to hospitalization after treatment with domperidone, and many more.[4-7] This does not mean that the extrapolation of data from studies performed in adult populations has no place in pediatric medicine. It can be beneficial when it is reasonable to assume that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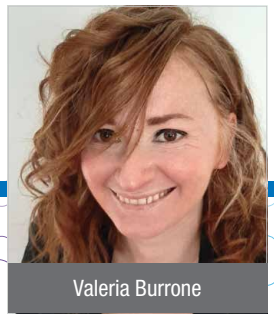
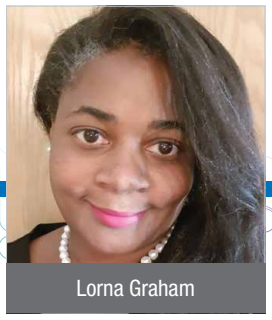

Valeria Burrone


Lorna Graham

the course of disease progression and the response to treatment is similar in children compared to adults, thus minimizing the exposure of children to clinical trials and increasing the speed and efficacy of pediatric drug development giving pediatric patients access to safe and effective medicines more quickly. However, when it is not safe to make these assumptions it's clear that specific pediatric trials are needed.

To facilitate the decision-making process, the U.S. Food and Drug Administration (FDA) developed the FDA Pediatric Study Decision Tree (See Figure 1),[8] a simple assumptions-based framework that can be a helpful starting point in determining the pediatric studies (excluding oncology studies) necessary for labeling based on the ability to extrapolate efficacy from adult populations or other data.

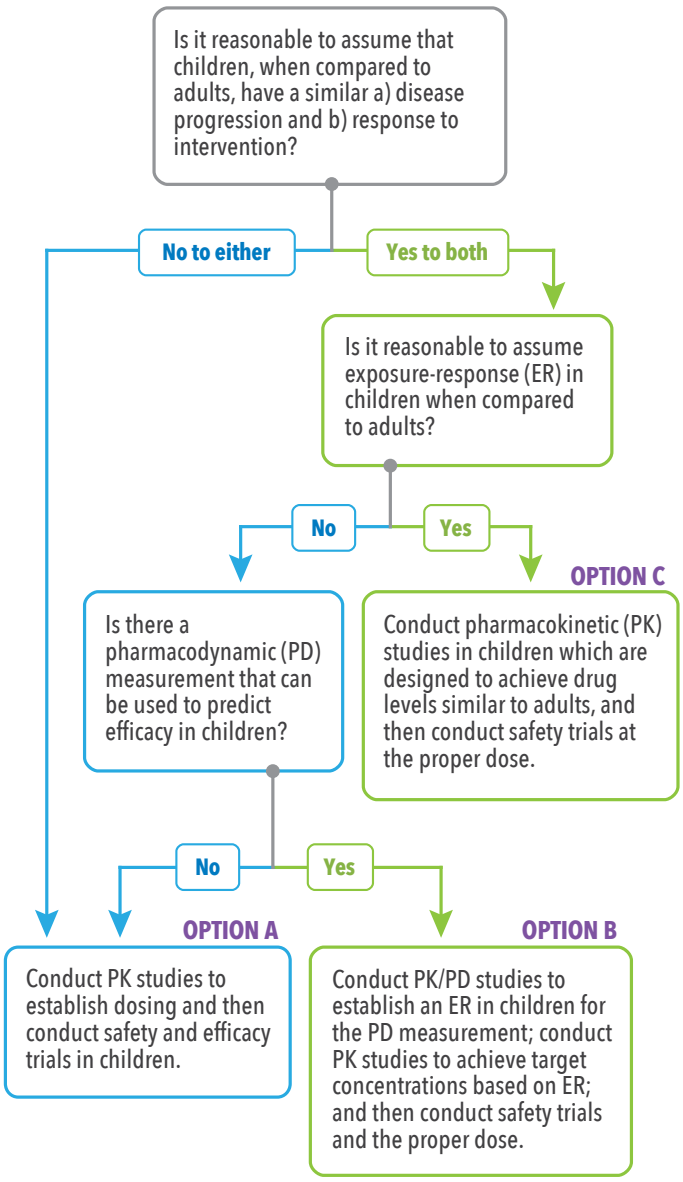
In this article, we discuss the impact of regulatory changes governing pediatric drug development and pediatric drug labeling, some of the challenges of performing clinical trials in pediatric populations, and strategies that may be employed to help address these challenges.

## US Pediatric Drug Legislation and Impact on Pediatric Drug Labeling

The major milestones in US pediatric drug legislation are shown in Figure 2. Legal measures to protect children from harmful medications were introduced in the US in the early part of the 20th century in response to fatalities due to medicinal products.[9,10] However, it wasn't until 1979 that the first notable FDA legal provision relating to pediatric drug labeling appeared. At that time the FDA issued a requirement for sponsors to conduct pediatric clinical trials before including pediatric information in the drug's label. Even so, the FDA did not issue a final Pediatric Labeling Rule until 1994. This labeling rule introduced the extrapolation of adult data to children and required manufacturers of marketed drugs to evaluate whether data existed to support pediatric labeling supplements. However, it did not require companies to conduct pediatric trials, and the legislation proved to be relatively ineffective in improving pediatric use information.[11]

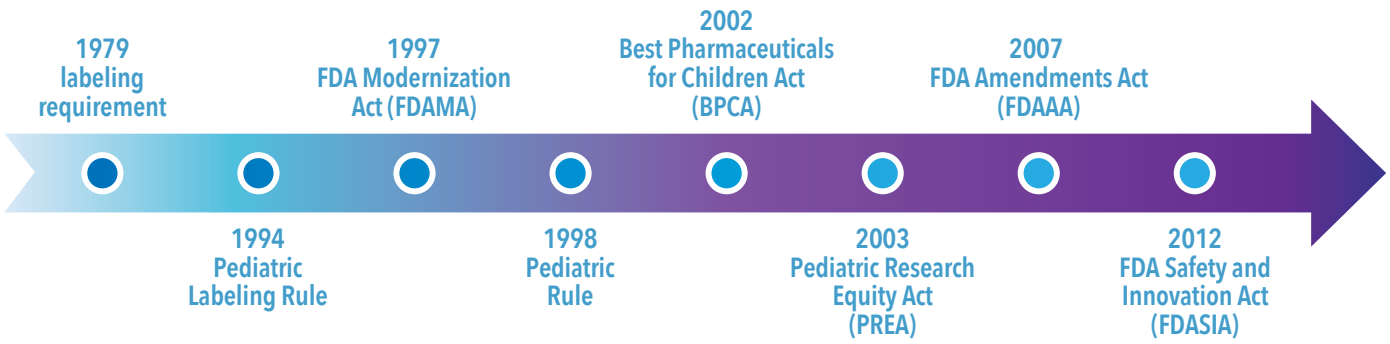
In 1997, the FDA created an incentive for companies to test drugs in pediatric populations with the Food and Drug Administration Modernization Act (FDAMA), which gave manufacturers an additional six months marketing exclusivity if they performed studies in children. This was voluntary. The 1998 Pediatric Rule gave the FDA the power to mandate that companies conduct pediatric studies for marketed new drugs and biologics and established the premise that unapproved products must be studied in pediatric populations. However, manufacturers could request, and be granted, waivers from these requirements if the product 1) did not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and 2) was not likely to be used in a substantial number of pediatric patients. Therefore, the Pediatric Rule did not fundamentally increase the number of products with adequate pediatric labeling.

**Figure 1.** FDA Pediatric Study Decision Tree




The Pediatric Rule was declared invalid by a federal court in 2002 on the basis that Congress had not given authority to the FDA to require extensive testing of drugs for children.[12] In January 2002, the Best Pharmaceuticals for Children Act (BPCA) was passed. It renewed the six months of marketing and patent protection incentive introduced under the FDAMA to sponsors who voluntarily complete pediatric clinical studies outlined in a Written Request (i.e., a formal FDA request that studies be done in pediatric patients). In addition, the BPCA created the Office of Pediatric Therapeutics within the FDA and directed the National Institutes of Health (NIH) to establish a program for pediatric drug development for off-patent drugs. Under the

**Figure 2.** Milestones in US Pediatric Drug Legislation




BPCA, the FDA can issue a Written Request for pediatric studies in any indication and may expand indications for drug use, including orphan indications.

In addition to the voluntary incentives offered by BPCA, the Pediatric Research Equity Act (PREA) of 2003 amended the Federal Food, Drug, and Cosmetic Act. This gave the FDA the power to require companies to perform pediatric studies for products submitted in a new drug application (NDA) if the FDA determined that it is probable the product will be used to treat a sizeable number of pediatric patients, or if it will offer meaningful advancements over current therapies. Unlike the BPCA, the PREA limits the FDA to mandating studies on indication(s) contained in NDA submission(s), and therefore it cannot be used to expand indications. A comparison of the key features of the BPCA and the PREA is presented in Table 1.

In 2007, the BPCA and PREA were reauthorized for another five years under the Food and Drug Administration Amendments Act (FDAAA). The FDAAA also required that Written Requests, pediatric plans, deferrals, and waivers for the performance of studies in pediatric populations be reviewed by the FDA's Pediatric Advisory Committee (PAC) and mandated that the results of pediatric studies be included in the product label even if they are negative or inconclusive. In 2012, the BPCA, PREA and the FDA PAC were made permanent under the Food and Drug Administration Safety and Innovation Act (FDASIA).

We can see the impact of the various legislative instruments (Pediatric Rule, BPCA and PREA) in Figure 3 which shows data from the FDA's New Pediatric Labeling Information Database.[13] The database provides details of 854 FDA pediatric labeling approvals over the last 22 years. This demonstrates that most label approvals—475—have

**Table 1.** Comparison of PREA vs. BPCA
(adapted from *https://www.fda.gov/media/91673/download*)

| BPCA | PREA |
|---|---|
| Covers drugs and biologics | Covers drugs and biologics |
| Studies may expand indications | Studies on indication(s) under review only |
| Studies may be requested for orphan indications | Orphan indications exempt |
| Voluntary studies | Mandatory studies |
| Authorizes FDA to request pediatric studies of approved and/or unapproved indications (Written Requests) and provides a financial incentive (additional six months exclusivity) to companies to submit studies to meet Written Requests | Requires companies to assess safety and effectiveness of new drugs/biologics in pediatric patients (Pediatric Assessment), but allows some or all assessments be deferred until after approval |
| Pediatric studies must be labeled | Pediatric studies must be labeled |

been the result of enforcement under the PREA. Only 199 approvals are the result of incentivization under the BPCA alone, indicating that the stick has been stronger than the carrot in driving pediatric drug development in the US.

## The Challenges of Conducting Pediatric Studies

Pediatric drug development is challenging and the financial incentives for companies to develop treatments for children can be low compared to the research and development (R&D) investment required. This may explain why the voluntary provisions under BPCA have not been more successful in driving pediatric labeling.

The first challenge of pediatric research is to define and identify the needs of the study population. The Center for Drug Evaluation and Research (CDER) generally divides the pediatric population into four groups: neonates (birth up to 1 month), infants (1 month up to 2 years), children (2 to 12 years), and adolescents (12 to 16 years).[14] However, the pediatric population represents an extremely broad maturational range both physiologically and psychologically. As such, the conditions that affect this population and the factors that influence drug pharmacokinetics and pharmacodynamics are highly varied. Therefore, this somewhat arbitrary division is often an oversimplification. For some drugs being developed for pediatric populations it may be necessary to consider further subgroups based on maturity. For example, gastric pH can affect drug absorption. In neonates, gastric pH is close to neutral for the first 1 to 2 weeks of life and gradually declines until age 2 when it approaches adult levels.[15] This means the relatively alkaline environment of the neonate or infant gut can result in ionization of weakly acidic drug molecules such as phenytoin, which is used to treat epilepsy and is best absorbed in its nonionized form. This reduces the bioavailability of the drug and therapeutic effect.

Furthermore, renal excretion of drugs can also be reduced in neonates due to immature glomerular filtration, tubular secretion, and reabsorption leading to higher bioavailability and the potential for adverse reactions.[15]

Other challenges often associated with performing pediatric studies include:

- Smaller disease populations compared to adults (e.g., type 2 diabetes)
- Selection of appropriate dose levels in children
- Blood volume and tissue sampling restrictions
- Availability of validated clinical endpoints in the age groups under study (e.g., lack of validated pediatric patient-reported outcomes (PROs) for indications such as asthma, diabetes, irritable bowel syndrome, oncology)
- Getting accurate adverse event information from infants and young children
- The impact of school and family life on study logistics and visit scheduling
- Obtaining informed consent and assent

These challenges can lead to potential inconsistencies in the types of outcome information contained in the labeling for drugs approved for the same indication.[15] The impact of these complexities on the time, cost, and quality of development programs in pediatrics can be significant in the absence of the appropriate expertise to proactively identify issues and plan mitigation strategies. The issues surrounding these challenges and potential solutions to help address them are summarized in Table 2.

**Figure 3.** Impact of Legislative Instruments on FDA Pediatric Labeling Approvals

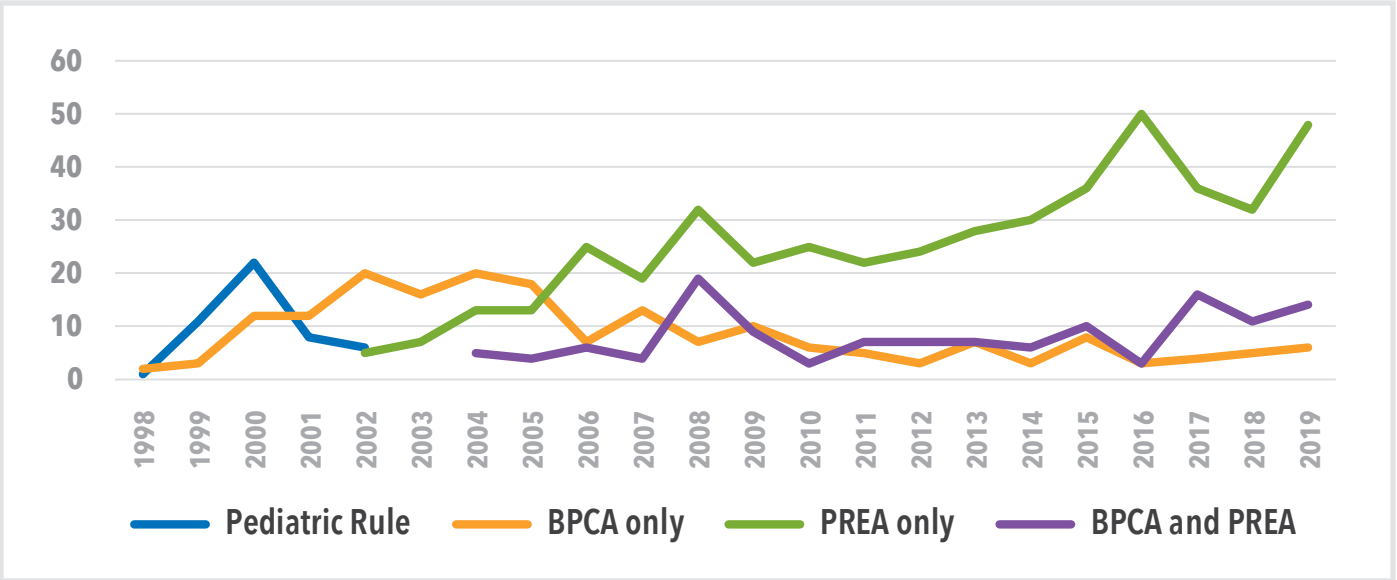


Table 2. Challenges and Solutions for Performing Pediatric Clinical Trials

| Considerations | Issue | Solutions |
|---|---|---|
| Small Patient Populations | Low enrollment leading to risk of study failure | • Adaptive study designs<br>• Bayesian design<br>• Master protocols that allow for collection of data for multiple drug treatments, indications, and/or biomarkers<br>• Modeling and simulation techniques to reduce sample size<br>• Careful site selection and use of Pediatric Research Networks<br>• Decentralized, patient-centric approaches to enable wider access |
| Dose Selection | Appropriate dose selection is required to maximize the likelihood that the studied dose will have a beneficial efficacy and safety profile | • Pharmacokinetic and/or pharmacodynamic modeling and simulation methods can be used to optimize dose selection |
| Blood Volume | Characterizing the pharmacokinetic and pharmacodynamic properties of a drug in the pediatric population can be difficult to perform because of limited blood volume in neonates and infants | • Consider sparse sampling and ultra-low volume bioanalytical assays to facilitate blood testing |
| Selection of Endpoints and Outcomes | Use of adult endpoints and outcome measures may not be appropriate for children, leading to risk of study failure<br>Proxy reporting by caregivers when child is not capable of self-reporting | • Ensure early engagement of KOLs and FDA in study design to define<br>• Ensure use of PROs/COAs that have been validated in children<br>• Use online libraries of validated child-report measures (Ped-PRO-CTCAE, PROMIS)<br>• Ensure patient diaries are specifically designed, and user acceptance tested, with target age groups in mind |
| Adverse Event Reporting | Eliciting adverse event information in children where vocabulary is limited and non-verbal communication with caregivers may be more common can be challenging | • Utilize Ped-PRO-CTCAE to assess adverse events directly in children and adolescents ages 7 to 17 or caregiver-reporting for children younger than age 7 using Ped-PRO-CTCAE[Caregiver] |
| Logistics and Visit Scheduling | Participation may be hindered by school and family schedule | • Use telemedicine to reduce number of clinic visits<br>• Consider direct-to-patient drug supply and home health approaches<br>• Schedule clinic visits after school/work or on weekends |
| Informed Consent | Complex nature of assent, impact of cultural variables and individual life experiences, gaps in local regulations | • Use of staged informed consent<br>• Incorporation of interactive computer technologies to convey complex ideas, and variations in approaches to assent of the child based on multifactorial assessments of competence<br>• Specific training for people involved in pediatric clinical training conduct |

KOLs = key opinion leaders; PROs = patient-reported outcomes; COAs = clinical outcome assessments; Ped-PRO-CTCAE = Pediatric Patient-Reported Outcomes Common Terminology Criteria for Adverse Events; PROMIS = Patient-Reported Outcomes Measurement Information System

## Conclusion

Voluntary incentivization by the FDA in the form of extended exclusivity and patient protection has resulted in an increase in the number of products that are approved for use in pediatrics in the last 20 years. However, the main driver for pediatric label approvals has been the PREA, which authorizes the FDA to impose a requirement on companies to perform pediatric studies. Performing clinical trials in pediatric populations can be challenging, and the additional R&D investment and expertise needed to achieve success can deter sponsors from seeking pediatric labels for their products. Identifying these challenges and the strategies that can be employed to help overcome them is an important step towards achieving success. ■

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# Can Clinical Studies Go Virtual?

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COVID-19 has significantly impacted the way we live, work, and play. It has also had a significant impact on clinical care and real-world research. When the pandemic began, routine clinical care was largely put on hold and then shifted to virtual visits when feasible. The same can be said of clinical research for medical products. While some pharma companies opted to put their studies on hold and others kept studies open, the pandemic's impact has been notable.

According to Global Data,[1] 69.9% of clinical trials were interrupted because of enrollment suspension. Results from a survey of over 5,000 studies and 198,000 study sites globally[2] showed a decline of 59% in new patients entering study sites as of April 2020 compared to 2019 levels, with a decrease in that decline to 20% in August 2020. This same study showed the administration of study drugs has been interrupted due to the inability of patients to access sites and the pandemic's effect on study drug supplies. These interruptions stem from concern for patient safety, lack of staff, and site access for medication administration as some medications must be given in a healthcare facility. Before COVID-19, perceived or actual regulatory or ethics committee hurdles and lack of willingness to try something novel kept the virtual clinical study model from being broadly implemented. However, the desire to continue bringing safe and effective treatments to patients, even during a global pandemic, has led to accelerated adoption


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of virtual study approaches; 67% of the Global Data respondents noted that COVID-19 is the reason for use of a decentralized model for the first time.[1]

## Defining the Virtual or Decentralized Study Model

Virtual clinical studies go by many names, including decentralized and remote, but the concept is the same: bring the study directly to the patient or their caregiver. This often involves leveraging technology such as eConsent, TeleVisit, electronic clinical outcome assessments (eCOA)/ electronic patient-reported outcomes (ePRO), devices and wearables, patient engagement platforms, and virtual study platforms. These virtual or remote strategies can also be supported by home health nurses and phlebotomists or direct-to-patient supplies. This allows the patient to take part in the study from their home, office, or on the go.

Putting these enablement approaches together requires careful deliberation. There are many aspects to consider when assessing the fit of a study to a virtual approach beyond just capability. This includes:

- The geographic areas where the study will be conducted
- Where and how patients will be recruited
- Where follow-up will be performed
- Whether follow-up requires clinical (physician) review
- If the study data is required for registration or regulatory purposes
- Whether electronic informed consent (eConsent) can be used
- Whether the report of measures can be completed by the patient/caregiver and if clinician confirmation is required

Once these questions have been answered, an assessment of the appropriate technology partner and other strategies to support virtualization is undertaken. For technology, it's important to consider:

- Whether the platform complies with regulatory requirements (if required)
- Data protection regulations
- If devices must be provisioned or whether study assessments can use the Bring Your Own Device (BYOD) approach
- Whether the platform supports multiple languages
- If the user interface is intuitive

## Determining a Good Fit for a Virtual Model

Many study types are a good fit for a virtual model. It can be related to the indication or the phase but more specifically about the study approach and types of data that need to be collected. When designing studies to fit the virtual model it is important to build a flexible protocol from the start that will allow for remote capture of study data, where appropriate. There are some things to consider when deciding on a virtual approach:

- Ideally no equipment should be needed, or if required, portable equipment should be available to perform protocol-required assessments
- Geographic footprint includes countries where regulatory, ethics, and cultural norms allow for remote collection of data
- Patient recruitment can be accomplished electronically or is not needed
- Patient population motor and cognitive functions are at the levels that they can enter data digitally via apps or devices
- Drug, if required, is easily administered in a home setting

## Case Study 1

### Long-term, Post Treatment Follow-up

In this long-term follow-up study, patients rolled over from various parent protocols to continue treatment and, finally, long-term follow-up for several years post last dose. All assessments, except vital signs and hematology, were completed per local standard of care (SOC). Data collection for patients in long-term post treatment follow-up was minimal (only every 6 months). The study included patients from sites in the United States (US), Europe, the Middle East, and Asia (See Figure 1). As an open-label rollover study, this seemed to be a good fit for virtualization.

### Virtual Approach Benefits

Virtualization for this study could result in a reduced site footprint with consolidation from multiple sites per country to a single site per country. Further benefits could include reduced burden to the patients by leveraging direct-to-patient data collection.

### Reducing the Site Footprint

Using a virtual approach, only one central site per country may be required. All other sites would transfer the study-related activities to this central investigator for further study follow-up. In assessing the fit of this strategy for this ongoing study, we evaluated all study stakeholders when determining the potential to reduce the number of brick and mortar site locations including the patients, existing investigators, primary care providers, and the sponsor.

From the patient perspective, engaging with a physician they are not familiar with could impact their willingness

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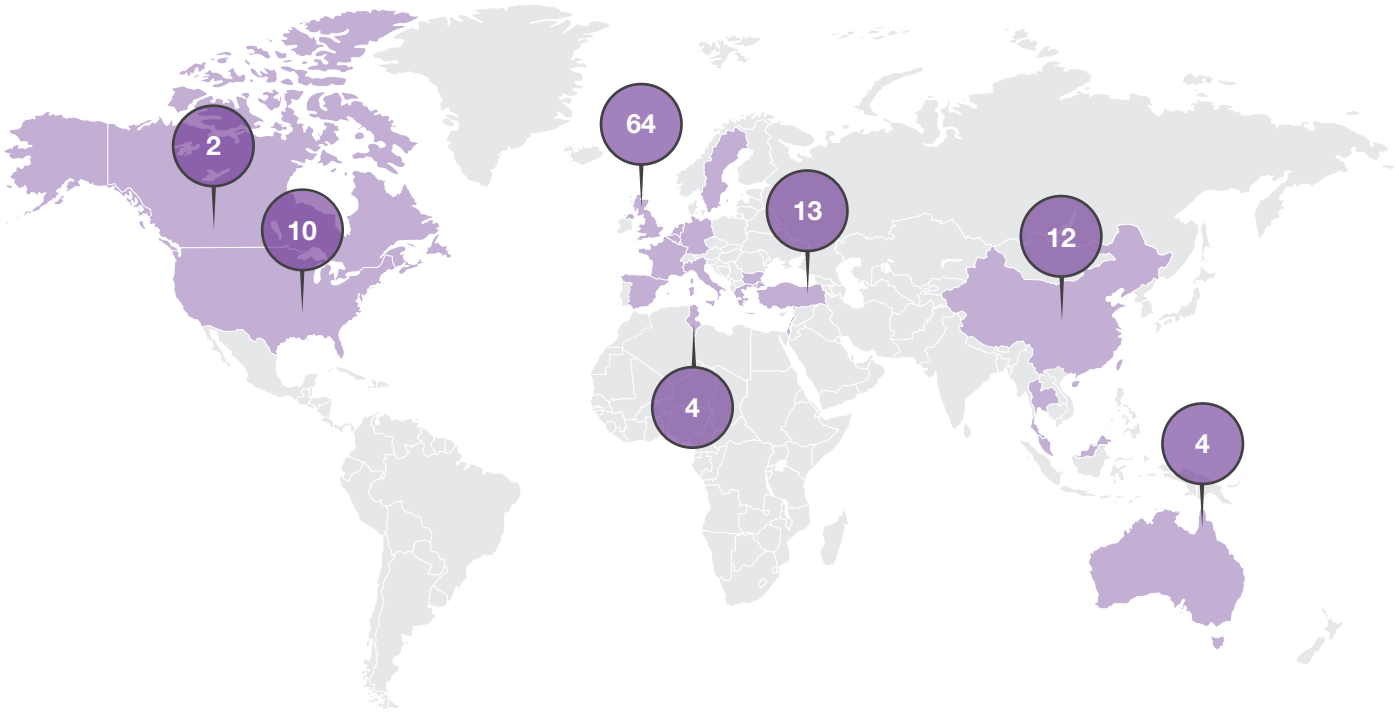
**Figure 1.** Case Study 1 Existing Site Locations




**Case Study 1** CONTINUED FROM PREVIOUS PAGE

to continue with study-specific activities. However, given that most of the data are SOC data collected from the primary care providers by the central site study team, there would be minimal contact with the central site principal investigator (PI), so this challenge is likely minimal.

From an existing study site perspective, closing existing sites and having all patients followed centrally by one site per country may impact the relationship between the sponsor and the PI. Also, in this study part of the patient population is on treatment and patients are transfusion dependent. As a result, on-site visits are still needed as part of SOC and benefits of site consolidation may not be realized.

### Regulatory Acceptability

Given the geographic expanse of this study, there are many regulatory bodies, ethics committees, and cultural norms to consider.

For this study, remote consenting was implemented to allow consenting of long-term follow-up patients without need for an on-site visit. However, only select countries allowed this remote approach due to local regulations. This resulted in the need for a hybrid consenting approach. Using this assessment as a surrogate, it is possible that a virtual approach may not be feasible globally.

### Patient Population

With most of the patient population in some parent studies being more than 80 years of age, there may also be limited capability or willingness for the patients to participate using digital tools. Subjects typically must have a smartphone, a strong internet connection, and fluency in mobile technology. These requirements, coupled with lack of in-person support, may exclude older patients.

### Final Assessment

Considering all factors, this ongoing study, albeit simple in design, is not a good fit for a virtual approach. In assessing the virtual fit for this study, we identified several challenges in application of the virtual approach, including:

- Varied regulatory acceptability of approach in the expansive global footprint
- In-person visits are required for patients receiving the sub-cutaneous investigational product
- The protocol allows for either in-person or phone visits for long-term, post treatment follow-up
- Majority of patients are transfusion-dependent and need to go on-site for in-person visits for those SOC transfusions
- The average patient population is > 80 years of age for some parent studies
- There is a close relationship between patients and the site as investigators are patients' primary specialized provider
- Multiple studies feed into this protocol over time

## Case Study 2

### Early Access Program for Breast Cancer Patients During COVID-19

During the COVID-19 pandemic, an alternative solution to on-site visits for an early access program was required. The solution had to be rapidly deployed to speed access to an investigational treatment for breast cancer patients. This was critically important due to their vulnerable health status and risk factors related to COVID-19. To address this need, the sponsor wanted to bring the study to the patient virtually.

### Assessing Virtual Fit

This study implemented a novel approach to allow patients to continue treatment and ensure patient safety during the pandemic. The goal was to bring the study directly to the patient thereby avoiding risk of exposure to COVID-19 at the treatment clinic. Protocol-defined study procedures were developed to allow assessments to be completed in the patient's home. This included remote sample collection, disease assessment, and study drug administration.

### Enabling a Virtual Approach

In order to operationalize the direct-to-patient approach, the protocol was designed to allow for remote study visits. One of our partners in virtual study execution was selected to perform virtual site services using remote study coordinators and mobile nurses to facilitate in-home patient visits, data collection, direct-to-patient clinical supplies, and study drug administration. A single platform was implemented to digitally enable a variety of study activities including:

- eConsent
- eSource
- Electronic data capture (EDC)
- Electronic patient-reported outcomes (ePRO)
- Video telemedicine

This virtual approach worked well for this study. The study team was able to implement the approach quickly and this solution allowed oncology patients to safely receive access to an investigational product at home during the COVID-19 pandemic while allowing continuity of care. Telemedicine enabled oversight by the patient's treating physician, which assured patient safety and gave comfort to the patients during this new treatment approach. Patients were able to receive treatments as safely as possible through a virtual approach and a well-planned, risk mitigation strategy.

## Conclusion

Adjustments to old approaches and newer, innovative approaches to clinical study data collection have been born out of necessity to address research continuity during COVID-19. Key innovative approaches include digital enablement (using digital technologies to enhance the efficiency or ability to collect data remotely in a study) and virtual/decentralized studies (moving away from the site-based study model to a model where patients are the primary focus). While there are macro considerations to assess fit for these types of innovative approaches, not all studies are the right fit, and each must be assessed by its own merit. In the case studies we assessed an ongoing study for transition to a virtual study, which was not the right fit for the virtual model. We also assessed a new early access study that was a good fit for the virtual study model. When determining whether a digital or virtual model is appropriate, all individuals invested in the success of the strategy should be consulted, especially those well-versed in the right assessments to be made, stakeholders to include, and questions to ask. ■

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# Proactive Management of Study Complexity and Amendment Risks Can Return Millions on the Investment

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## Trends and Problem Statement

Biopharma and biotech companies make significant investments in getting their products to market. Studies are becoming more complex, driven by several factors including eligibility, endpoints, assessments, data collected, and number of sites, etc. This ever-increasing complexity in study design can frequently lead to study cost increases in excess of 25%, in addition to other implications such as difficulty in finding patients, increased effort by sites to conduct a study, more time spent in study start-up, and more costly amendments. For example, in the last two years, 73% of PPD studies have had protocol amendments between receiving the final protocol and reaching first site activated, 83% before first subject screened, and 92% before 50% of sites were activated.

While there is a high level of focus on study costs, and rightly so, the higher cost comes from study delays. One research study[1] looking at lost patent days once a product was launched suggested that the impact on Expected Net


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Present Value (ENPV) of one protocol amendment on a typical oncology program entering Phase II or III ranged from $35 million to $75 million respectively. Given the significant cost of delays, investing the time and effort to design well thought out study protocols in initial planning will benefit companies in the long run.

## What Can be Done to Avoid Lost Revenue?

Companies should assess every study to determine the best options for reducing study complexity, cost, timelines, and amendments while designing the study. Several activities at different times throughout the study design process (See Figure 1) have shown an impact on overall success, including:

- Patient-informed protocol design (PIPD)
- Protocol optimization (PO)
- Finding the right sites (Site ID)
- Protocol de-risking

## Patient Input

PIPD refers to any form of engagement with patients to help inform elements of clinical trial study design. Common approaches include conducting patient focus groups, mock trials, patient surveys, and consulting with representatives from patient advocacy organizations. While there are many benefits of integrating PIPD into standard research practices, one key element is optimizing the study design to meet the needs of a given patient population. This has the potential to improve recruitment, patient enrollment and study outcomes; reduce patient burden and study withdrawal; ensure patients follow the assigned assessment schedules and adhere to therapy; and optimize data quality and capture, to name a few. Furthermore, involving patients during the protocol development stage is crucial to ensure the data on outcomes most relevant to patients are being collected.[2]

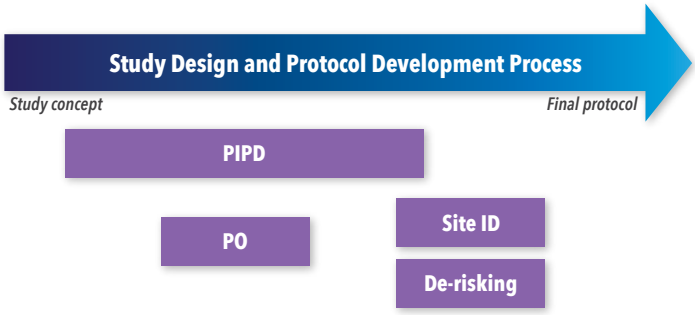
Although the quantitative impact of PIPD is still emerging, previous research has documented a 16% increase in patient enrollment[3] and improved timelines, with recruitment of the first 100 patients reduced by three months.[4,5]

## Protocol Optimization

PO can mean different things to different organizations. Here the term is used to describe a set of protocol-focused assessments meant to uncover areas where study complexity can be reduced.

When a developing protocol reaches synopsis stage, the major components of the overall draft are in place yet are still formative—making it an ideal time to step back and look for areas to optimize. A synopsis typically includes objectives/endpoints, study design/schema, number of participants, intervention groups, duration, statistical

**Figure 1.** Timing of Study Design and Protocol Development Activities




considerations, standard of care (SOC), and inclusion/exclusion (I/E) criteria. It is at this formative point that a protocol optimization assessment may help surface areas where complexity can be reduced, as well as patient burden, study cost, study duration, and likelihood of amendments.

PO requires an expert cross-functional team consisting of product development, clinical science, operational strategy, biostatistics, regulatory, and innovation. Such an expert team should be highly experienced and have access to robust data that allows for the conduct of the following assessments:

- Measure study's **site complexity and patient burden**, compare to competitor studies, and recommend adjustments to the schedule of assessments; quantifying site complexity allows for better management of complexity, and several industry tools exist that allow for measurement of the complexity for a site to conduct the study
- Ensure alignment between **objectives, endpoints, and assessments**
- Analyze the **patient eligibility criteria** and recommend adjustments to increase likelihood of showing response and/or increase ability to recruit
- Evaluate **standards of care**, surface regional differences, and anticipate future changes
- Recommend opportunities to deploy **technology** to improve collection of patient-level data, reduce patient visits, and/or reduce number of sites through **virtualization**
- Analyze **trial design and statistical methodology** to recommend alternative designs or methods
- Surface **alternative strategic options** and the relative impact those options will have on complexity, burden, cost and time

## Example: Complexity, Patient Burden, and Cost Reduction

### Parkinson's Disease Phase III

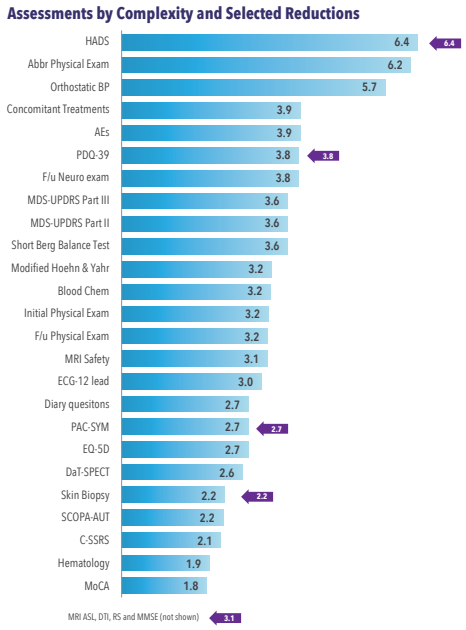
**Findings:**

- Versus benchmarks, protocol above 75th percentile on all key measures (duration, visits, activities, complexity, and burden)
- I/E criteria restricted use of L-dopa (SoC) which exacerbated burden on over 60% of patients*

**Recommendation:** Reduction/removal of six assessments (see chart)

**PO Impact:** Reduction in complexity by 16%, patient burden by 12% and costs by ~$1M

* *TriNetX query for % of patient population treated with L-dopa*




## Example: Biostatistics Study Design

### Lymphoma Phase I/II Study

**PO Recommendation:**

- For Phase I, employ modified toxicity probability interval design instead of 6+6 design
- For Phase II, employ enrichment design following basket trial design instead of Simon 2-stage

**PO Impact:**

- Reduction in sample size[2] and costs ($180K/pt)
- Increased confidence/flexibility in decisions

[2] *Simulations run on Enrichment Design module of FACTS 6.1*

## Example: Patient Population and Standard of Care

### NS NSCLC Phase III

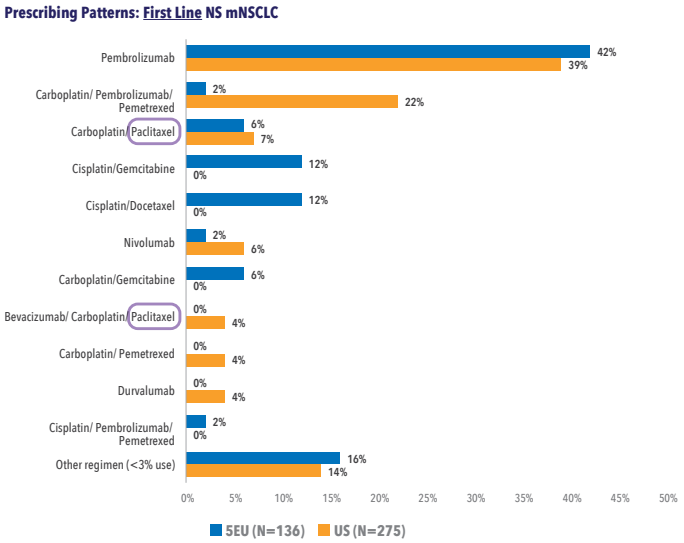
**PO Findings:**

- Exclusion of prior treatment with taxanes will exclude up to 18% (US) and 13% (5EU) after 2L+
- Most all competitors only exclude prior docetaxel

**PO Recommendation:** Exclude prior docetaxel use but allow prior paclitaxel use

**PO Impact:** Avoid excluding approximately 15% of otherwise eligible patients

*NS NSCLC = Nonsquamous Non-Small Cell Lung Cancer*




+ Ipsos Prescribing Data, Q4 2018, Metastatic, nonsquamous NSCLC (EGFR/ALK WT)

## Example: Standard of Care

### Asthma Phase IIb

**PO Findings:**

- Average patient on four respiratory meds++
- Example: ICS/LABA plus LAMA and LTRA
- LTRA often used despite limited efficacy as cheap (generic) and good tolerability**

**PO Recommendation:** Allow more than one additional controller

++ *McDonald Study (2019): Severe Asthma registry from 26 sites across Australia and New Zealand, 434 patients*

** *Comparison to therapies in MENSA and DREAM studies*

*ICS = inhaled corticosteroid; LABA = long-acting beta-agonist; LAMA = long-acting muscarinic antagonists; LTRA = leukotriene receptor antagonists*

The impact of conducting protocol optimization can vary from study to study and each synopsis can yield different areas for optimization. The preceding examples illustrate the types of impact that can be realized.

## Finding the Right Sites

Another key to successful study execution is to identify sites with the highest likelihood of success in the given indication and population. Effective use of data is essential in selecting the sites and validating their experience. There are numerous data sources in existence that can be used and more continue to become available all the time. In assessing possible sites, there is no substitute for real-world experience; therefore, the first step is to query experience data to see how sites have performed previously, in terms of enrollment, quality of data, number of monitoring issues, and speed of activation. Many contract research organizations can "score" the sites based on the parameters above to determine which are historically most successful.

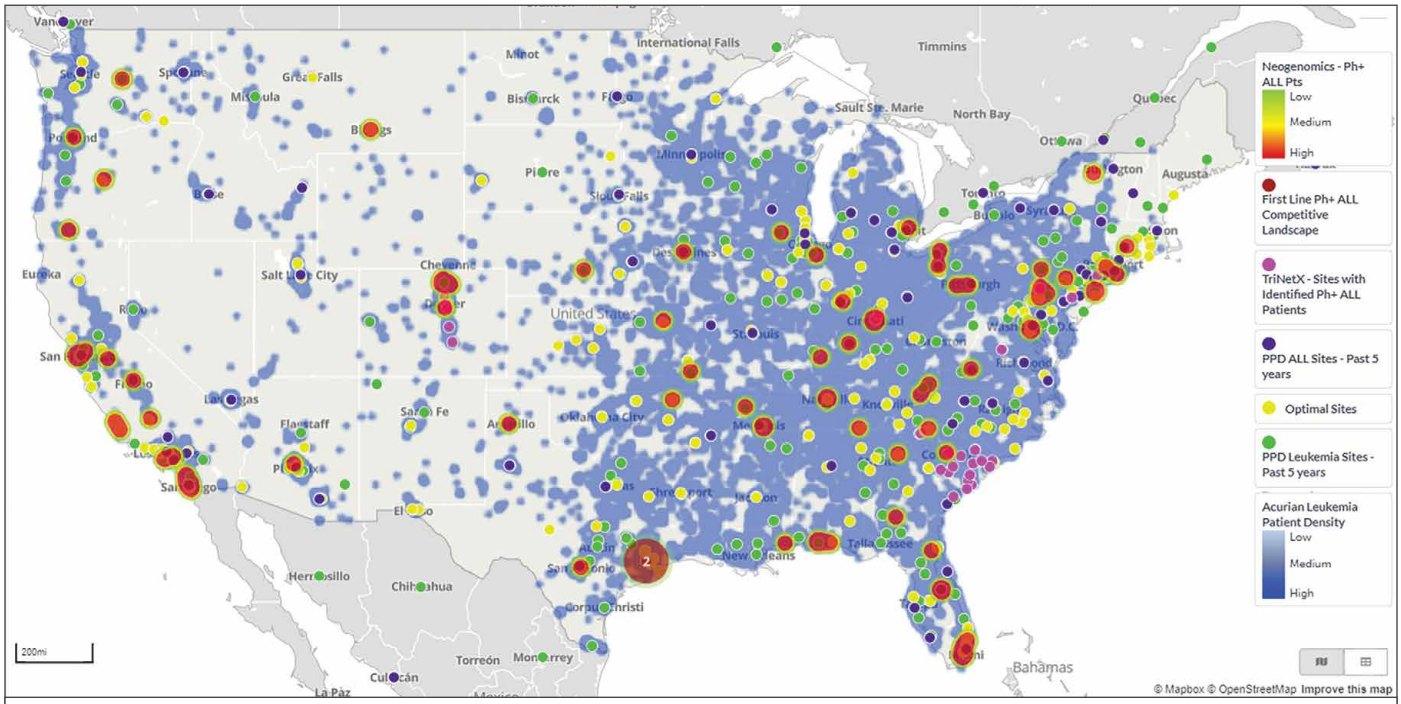
There are, of course, other parameters that should be investigated. Electronic medical records (EMR) data should be examined to determine the actual, demonstrated population for the indication within the practice or institution. One example is TriNetX, a global EMR tool that allows the user to query the data to identify where patients are available. Of course, not all will qualify, but the site totals can be compared to identify which sites have larger potential patient populations. Other sources of data, such as genomics data, can be accessed to identify where patients with the specific genetic trait or marker are located in order to focus on the correct population at the correct sites.

Predictive analytics can also be used to not only show the expected activation of sites and enrollment of patients, but also to do scenario modeling as part of a protocol analysis. This can allow the formulation of alternative, potentially more effective, ways to achieve study objectives.

Once data results are generated from these sources, an analysis should be done to marry results of where patients are located with where the most successful sites are located. PPD, for example, can show this visually using our Site and Patient Visualization Tool (SPVT) that provides information regarding the patient populations by number, location, and source (See Figure 2). Identifying sites with the highest population of available patients also is important to reduce patient burden by limiting travel and inconvenience as much as possible.

In the end, the key to site selection is finding the right sites, with the right patients, at the right location to maximize study success and the ability to deliver new therapies to patients in need.

**Figure 2.** Visual Depiction of Patient Populations and Sites




Enrollment strategies in North America include leveraging Neogenomics data, TriNetX Sites, and Optimal Network in addition to high performing PPD leukemia sites

### Protocol De-risking

Protocol de-risking is another strategy built on conducting a set of protocol-focused assessments; however, its goals, timing, and approach differ from protocol optimization (See Table 1). Protocol de-risking is specifically designed to identify and mitigate areas of avoidable risk within the protocol that are likely to lead to protocol amendments.

> "I just wanted to tell you that having the de-risking team have a look has been really fantastic. The Sponsor was really happy with the de-risking team suggestions and for us [the writing team] it was really nice to get feedback! We REALLY appreciate it."

## Protocol De-risking Case Study

#### OBJECTIVE

Determine the benefits of protocol de-risking review for a Phase II open label oncology trial

#### APPROACH

A broad range of experts within PPD participated in the de-risking review to engage multiple perspectives.

A protocol de-risking tool that focuses on key areas to specifically reduce the number of amendments was used to guide the reviewer.

Timing of review was determined to be at near-final protocol to ensure it mimicked the final protocol yet changes to the protocol were still feasible.

#### RESULTS

Critical findings included: risk to a potential protocol amendment due to lack of clear and/or consistent study treatment instructions, study treatment safety, recruitment challenges, and clear study endpoints. Positive feedback was received by the client and author of the protocol. Positive feedback was also received by the de-risking team regarding the use of a guided tool.

#### CONCLUSION

Implementation of a robust protocol de-risking review by various experts within PPD with the use of a concise tool at the right time helped identify and mitigate avoidable risks that may cause a protocol amendment.

While a protocol, or protocol synopsis/concept sheet, may undergo a de-risking process at any point, the ideal timing is when the protocol is near-final, just prior to regulatory submission. Performing the analysis at this stage addresses the concern that a large percentage of amendments occur before the first patient is enrolled.[6] This timing aims to reduce the probability of receiving competent authority requests for changes, as well as decrease the need for future protocol amendments. As approximately half of amendments are considered avoidable,[6,7] identifying and proactively simplifying and modifying the areas of the protocol, that left unchanged most commonly necessitate a future amendment, reduces overall study timelines and costs related to additional submissions and potential pauses in site activations and/or recruitment of patients.

Similar to protocol optimization, protocol de-risking utilizes a team of operational experts with experience in biostatistics, project and clinical management, feasibility, data management, regulatory, pharmacovigilance, medical writing, and product development. The most common causes of avoidable protocol amendments include **design flaws**, **inconsistencies/errors**, and **recruitment challenges**.[6-8] The cross-functional team concentrates their analysis and associated recommendation in these areas, as well as customizes the review according to project-specific needs. The following critical data, process, and risks are typically assessed, and associated recommendations provided:

- Clear definitions and alignment between **endpoints, objectives, and assessments**, and strategy for monitoring critical data
- **Eligibility criteria** to ensure relevance to study endpoint, clarity, consistency, alignment with applicable guidelines and regional differences, and level of restriction is appropriate for the phase, objectives, and targeted patient population
- **Logistical challenges** in patient recruitment, retention, study supplies/equipment, investigational product/study treatment, and study procedures
- **Study visit assessments** to ensure frequency, length, and complexity are appropriate and as minimal as required to meet objectives
- Clarity and comprehensiveness of **safety reporting and data collection** procedures
- **Randomization, stratification, and blinding** for feasibility and challenges in execution, as well as completeness needed for statistical analysis plan
- End-to-end **consistency review** to identify areas of conflict or confusion

Several pilots were conducted to demonstrate the potential benefits of protocol de-risking.

Table 1. Comparison of Protocol Optimization and Protocol De-risking

| | Protocol Optimization | Protocol De-risking |
|---|---|---|
| **Goal** | Reduce time, cost, site complexity, and/or patient burden | Reduce or mitigate protocol amendments |
| **Emphasis** | Mostly strategic focus with some operational elements | Mostly operational focus with some strategic elements |
| **Input Timing** | Protocol synopsis | Near-final full protocol |
| **Turn-around Time** | ~3 weeks | ~1 week |
| **Data Intensity** | High | Moderate to low |
| **Scope** | Seven optimization areas:<br>• Patient Population<br>• Standard of Care<br>• Protocol Design<br>• Competitive Landscape<br>• Regulatory Review<br>• Statistical Review<br>• Virtualization Assessment | Six de-risking areas:<br>• Entry Criteria<br>• Study Treatment<br>• Study Design<br>• Endpoints<br>• Statistics<br>• Ethics/Safety |

## Conclusion

Lowering study complexity and mitigating amendment risk requires a full complement of activities throughout the design process. Effective strategies include starting with early and ongoing patient-informed protocol design, adding protocol optimization and site identification at the synopsis stage, and concluding with thorough protocol de-risking assessments. The impact of these activities is likely to differ from protocol to protocol, but on average, they have demonstrated significant impacts. Lower complexity and fewer amendments mean faster study enrollment and completion, which equates to patients having earlier access to new therapies and companies seeing significant returns on their investment. ■

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# How Health-Related Social Media Can Complement Traditional Real-World Evidence Approaches to Offer Unique Patient Insights

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Traditional real-world evidence (RWE) is based on data collected in normal clinical practice outside of randomized controlled trials. It is used to complement clinical data in regulatory and health technology assessment submissions. This data is most often generated through retrospective or prospective observational studies using electronic health records, medical claims, disease registries, etc. As more emphasis is placed on the importance of RWE, other sources of useful real-world data have been identified, specifically social media. Online technology platforms have allowed patients to interact with each other and provide unique insight into specific diseases, conditions, and treatments. Mining this health-related social media data provides invaluable real-world data.

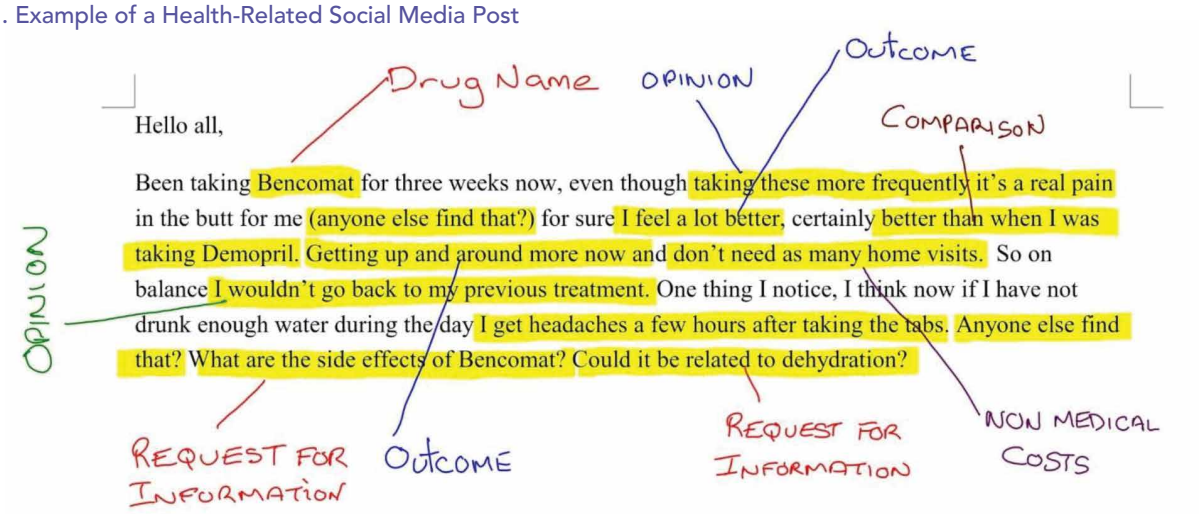
## What is Health-Related Social Media Data?

When we think of social media, we typically think of generic sites like Facebook, Twitter, and Instagram. However, when discussing health-related social media we are referring to forums, blogs, and online communities that are often condition-specific and focus on discussions related to patient experiences such as the American Cancer Society's Cancer Survivors Network, HealthUnlocked, and the Psoriasis Association. There are thousands of similar communities used by both patients and caregivers spanning a broad range of indications, making health-related social media a rich source of real-world evidence.

Posts on these sites contain a vast amount of information ranging from a treatment or drug a patient has received and how long they have received it, information on symptoms

Alison Booth

**Figure 1.** Example of a Health-Related Social Media Post



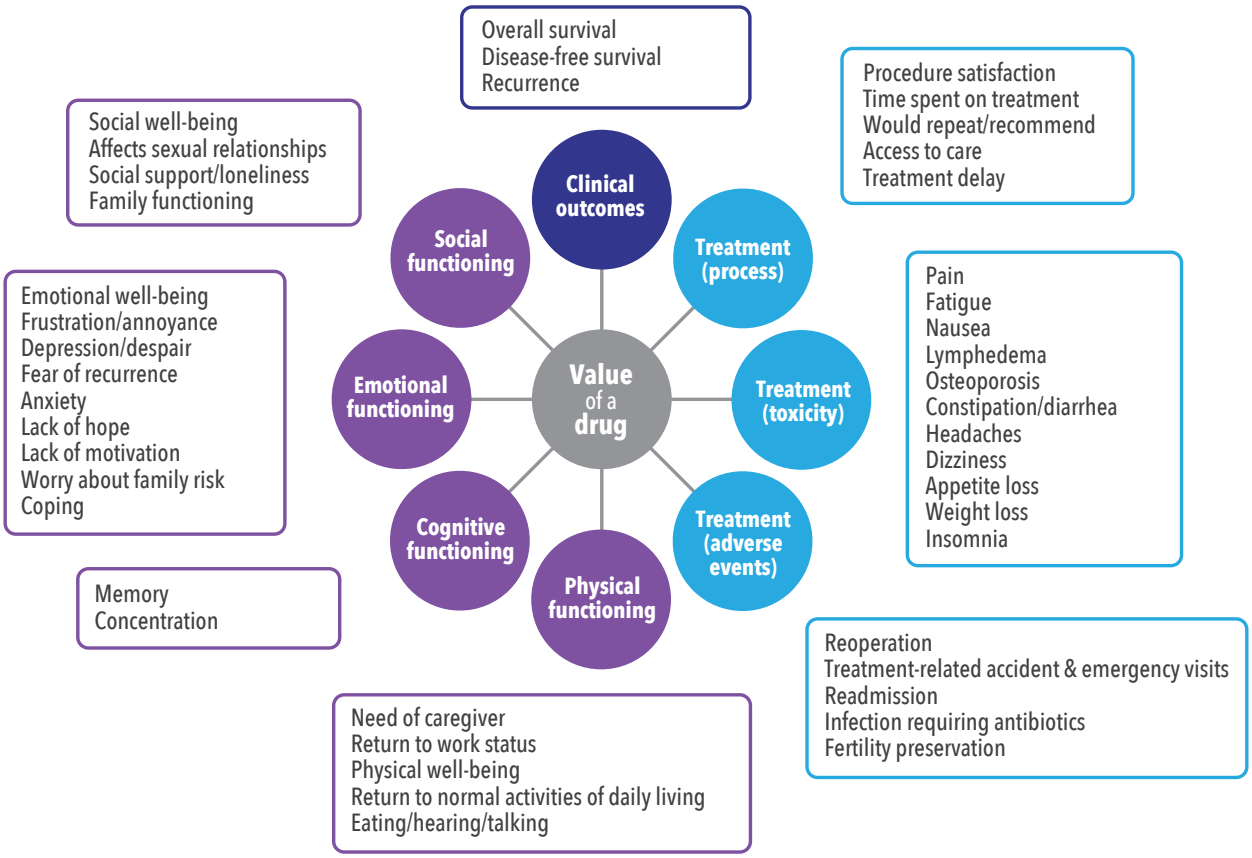

and side effects, and subsequent impacts and questions to other community users. Figure 1 provides an annotated hypothetical post.

## Social Media Listening as a Source of Real-World Data

Health-related social media is constantly growing and gaining momentum as a complementary source of real-world data for both payers and regulators. For example, in June 2018, the United States Food and Drug Administration (FDA) encouraged the use of social media to shed light on the patient's perspective, illustrating the increasing importance being placed on incorporation of the patient experience.[1] In addition, the FDA has its own programs for and perspectives on collecting information about adverse events (AEs) from social media.[2]

Another example illustrating the increasing importance placed on the patient experience is the proposed outcome-based payment model to link the price that the National Health Service (NHS) pays for a cancer drug to patient outcomes[3] (See Figure 2). Certain outcomes evaluated

**Figure 2.** Value of a Drug for Patient vs. Only Efficacy/Safety[3]



are clinical in nature, and can typically be leveraged from traditional sources such as those mentioned earlier; however, many of the other outcomes such as emotions or social functioning can be challenging or even impossible to capture using traditional sources. These represent areas where health-related social media can be used to complement traditional studies to provide a comprehensive picture of patient outcomes and experiences.

### When Should Health-Related Social Media Be Considered?

It is important to think about when it is appropriate and impactful to use health-related social media. These are typically situations when the patient or caregiver perspective and experience are of interest. Health-related social media can be appropriate to gain these insights as the content is driven by patients and caregivers themselves and is therefore more likely to represent topics important to patients that may not have been considered clinically or by the research team. Furthermore, health-related social media can be particularly insightful in the case of emerging conditions where little is known about the patient experience and perspective, such as COVID-19. In the case of rare diseases where large groups of patients can be hard to find, health-related social media forums may be a place where patients from many locations come together. The incorporation of health-related social media should be considered when conducting studies investigating the following:

- **Unmet needs**
  - What elements patients and caregivers struggle with and research can help address
- **Burden of disease**
  - Economic and time impacts, impacts on work, resource utilization, social impacts, and more
- **Wider perspective of caregivers and family**
  - Caregivers often post on disease-specific social media forums, and patients also discuss the impacts of disease on their family
- **Issues important to patients**
  - Content is driven by the topics patients spontaneously mention and wish to discuss
- **Treatment experience**
  - Adverse events, holistic view of impacts on health-related quality of life, understanding of decision drivers for treatment choices, general opinions, perceptions and preferences about treatments
- **Populations and indications hard to find in traditional databases**
  - Rare disease, rapidly progressing conditions, new/emerging diseases (e.g., COVID-19)

Evidera has used health-related social media to inform patient preferences, study treatment patterns, perform sentiment analyses, gather patient and physician perceptions, enhance condition mapping to inform patient-reported outcome study design/instrument selection, analyze treatment decisions, and augment studies looking at safety by capturing adverse events.

## How Do We Use Health-Related Social Media Data?

Once data is extracted from health-related social media sites, it needs to be analyzed in a way that produces useful insights that can be used to inform future clinical studies. There are several techniques that can be used to analyze the data (See Figure 3). **Natural language processing (NLP)** can be used to subset data to populations and discussions of interest, in addition to extracting frequently mentioned terms and topics. For example, Apache cTAKES is a natural language processing tool developed to extract clinical terms, such as disease symptoms or drugs, from text data. Custom lexicons can be derived using NLP to capture lay terms used by patients in addition to clinical terms. **Machine learning (ML)** has many applications but for social media data it can be particularly helpful to filter out noise (text that is not relevant to the study objective). Other applications of machine learning can also be explored based on specific study objectives. **Qualitative data analysis** is also important to social media data. The manual, in-depth analysis helps pull the full potential out of the data, allowing for deeper understanding of concepts and topics being discussed by patients.

### General Aspects of Social Media Analyses

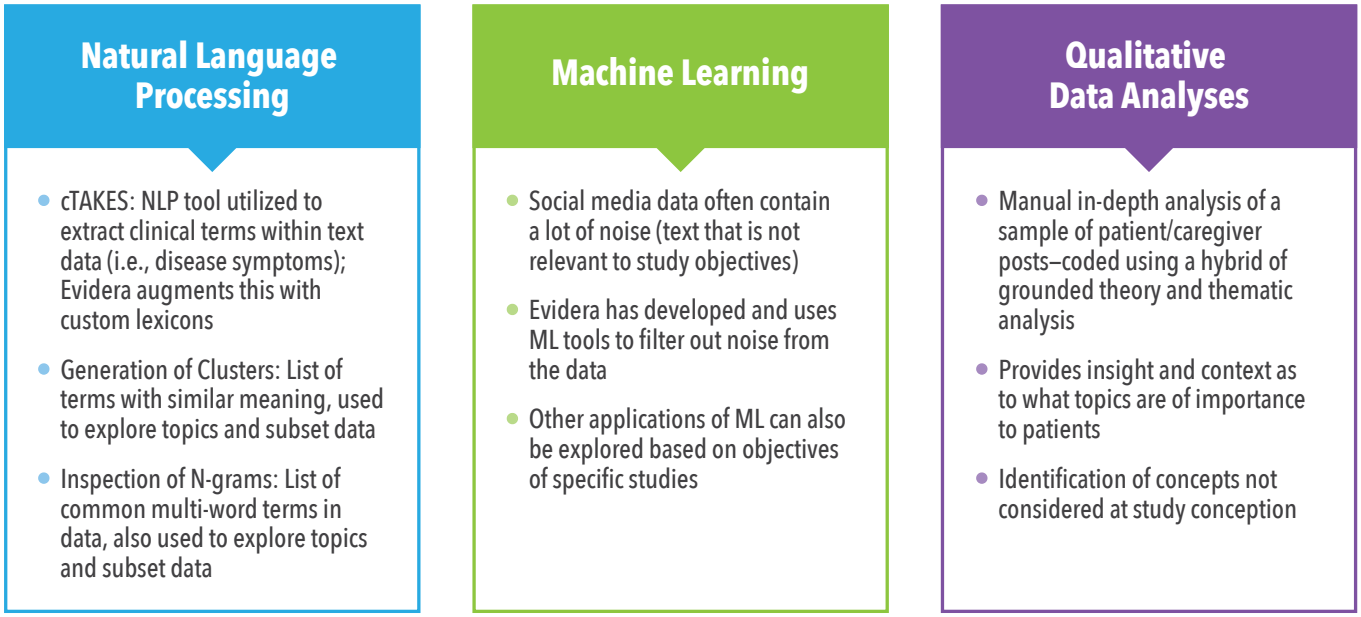
We use posts from publicly available, condition-specific, social media forums to conduct studies. One consideration with health-related social media data is that the topics that may arise are not possible to specify a priori. Therefore, every social media study uses a scaled feasibility approach to mitigate risks and determine the appropriate sources and methods to use based on the specific research question.

Health-related social media posts can contain a large quantity of noise that is challenging to remove. Evidera has developed supervised machine learning algorithms to predict whether posts contain a true patient experience, and those posts are carried forward for analysis. A mixed-methods approach, combining quantitative and qualitative analyses, is often used to extract the most value out of the data as possible.

### Health-Related Social Media and Ethics

Ethical considerations are extremely important when using any data, especially patient privacy and appropriate use of the data. While there are no specific guidelines on the use of health-related social media data, we believe it is important to follow specific rules to protect the privacy of patients and caregivers. For example, it is important to read

Figure 3. Common Types of Analyses




the terms and conditions for each site and check whether there are any restrictions around extracting the content. We also look at the robot files, which may indicate whether elements of text can be programmatically retrieved. Any forum where text elements cannot be retrieved would not be extracted for a study. Additionally, only public, open-access forums should be used, as opposed to a closed forum that requires a login to view content, and researchers should not post to sites. This passive role is important for the integrity of the study and respect of patient privacy.

When using social media websites, seeking informed consent is often not feasible since it is not possible or practical to directly contact users. Per the ethics framework developed by the University of Sheffield,[4] steps should be taken to protect patient privacy and retain anonymity. All data should be de-identified and anonymized and posts or post content should not be reproduced verbatim or in a manner that allows the original post to be identified from study outputs.

## Example Social Media Studies

The following section provides examples of how to utilize health-related social media to address different research needs.

### EMERGING DISEASES

#### COVID-19

**Population:** Patients with breast cancer

**Challenge:** COVID-19 emerged in late 2019 and was declared a global pandemic by the World Health Organization in March 2020. To date there have been over 40 million cases and over 1 million deaths related to COVID-19 globally (as of October 20, 2020).[5] The aim was to understand the impact of COVID-19 on patients with other diseases, as well as their perceptions of COVID-19.

**Approach:** Extracted posts relating to COVID-19 from a large global breast cancer community and derived key themes and topics within the data using qualitative analyses.

**Key Findings:** The results of this study will be disseminated in late 2020, but we have already seen the prevalence of COVID-19 in health-related social media discussions. Real-time information and speed of access make social media a useful tool when information from other sources are lacking, such as with newly emerging diseases.

### RARE DISEASES

#### Using Social Media and Advanced Analytics to Inform Study Design in AML and MDS[6]

**Population:** Patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) ineligible for intensive chemotherapy

**Challenge:** The population is difficult to capture due to the rapidly progressing nature of the disease. The challenge was to understand patient preferences regarding end-of-life treatment and to attempt to uncover unmet needs.

**Approach:** Posts from three AML/MDS-specific forums were extracted, and NLP was used to obtain posts from patients who were ineligible for intensive chemotherapy. We then conducted a targeted qualitative review to extract the patient and caregiver insights.

**Findings:** Findings from this study were presented at the American Society of Hematology 2018 annual conference and have been published in a manuscript.[6] The study

**Figure 4.** Word Cloud AEs for Chemotherapy, Hormone Therapy and Targeted Therapy[8]


identified the desire of patients to be treated at home, suggested considerations for communicating information on treatment options, and highlighted the humanistic burden placed on patients and their caregivers.

## TREATMENT PATTERNS

### Extraction of Treatment Patterns from Health-Related Social Media Data

**Population:** Patients with metastatic renal cell carcinoma (RCC)

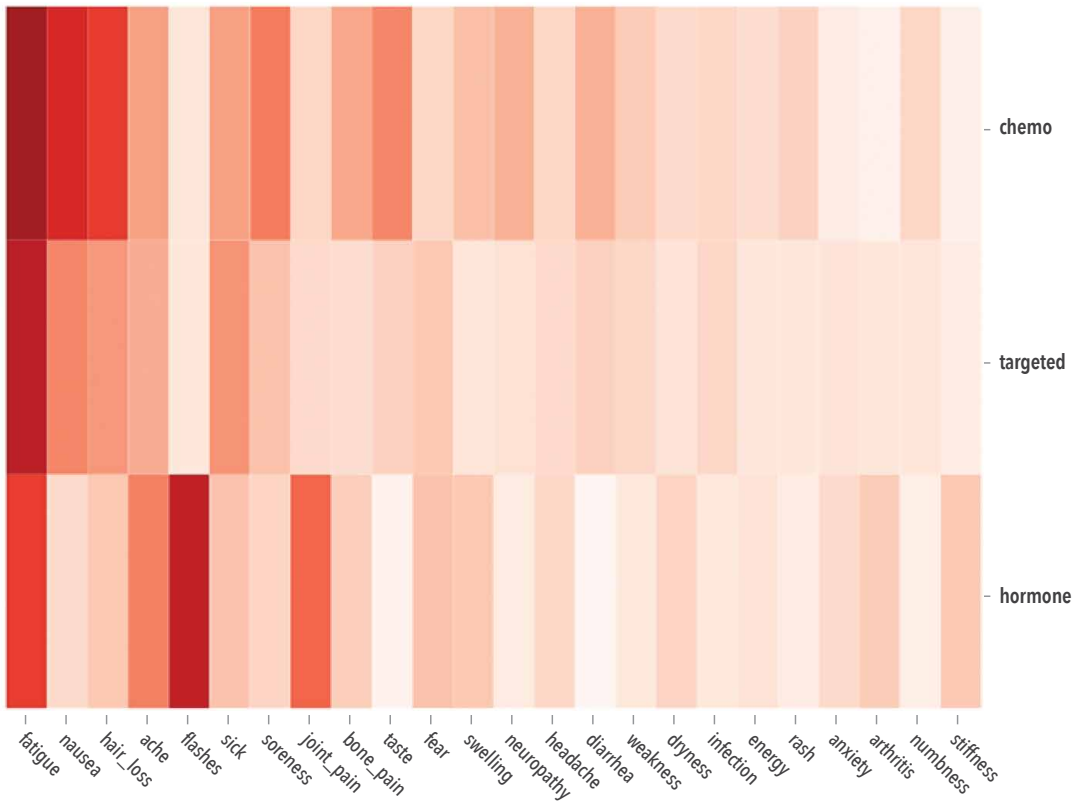
**Challenge:** To understand whether it is possible to accurately extract treatment patterns of patients with RCC in an automated manner from health-related social media data using natural language processing, rule-based decisions, and machine learning.

**Approach:** Posts from metastatic RCC patients were extracted through a machine learning algorithm. Receipt of treatments of interest was identified using NLP and line of therapy was defined as the order in which the therapies of interest were administered.

**Findings:** While this work was exploratory, it showed that the patterns derived from the social media sources were within the range of estimates from the published studies for the majority of the treatments investigated. Findings from this study have been published in a manuscript.[7]

**Figure 5.** Heatmap of Top 25 Events Across Treatment Groups[8]

The most common AEs are shown on the horizontal axis and the treatment classes on the vertical axis. The frequency of associated mentions in posts are illustrated by the darkness of color, deep red having a high frequency of mentions and pale pink or white with fewest mentions. Overall, fatigue was the most commonly reported AE across chemotherapy and targeted treatment groups. Targeted therapies appeared to have a lower AE profile than either chemo or hormone-based therapies. Hormone therapy was strongly associated with flashes.



## CAPTURING ADVERSE EVENTS
### Adverse Event Profiling of Treatments for Breast Cancer

**Population:** Patients with breast cancer receiving chemotherapy, targeted therapy, or hormone therapy

**Challenge:** To identify symptoms and AEs from a large amount of unstructured text extracted from health-related social media forums to determine if this approach could provide novel information.

**Approach:** Posts were programmatically extracted from a large breast cancer community. After data cleaning and deidentification, AEs and symptom mentions were extracted using a lexical NLP approach, accounting for clinical and lay terms. Co-occurrences of treatment mentions, and symptom/AE mentions, were calculated for each treatment group (See Figures 4 and 5).

**Findings:** In addition to commonly reported symptoms and AEs, the study also uncovered less severe, or new and otherwise less frequently reported, symptoms/AEs that may have a significant impact on patients' quality of life. Supplementing traditional approaches through analysis of social media can generate additional insights and can enhance current approaches toward incorporating the patient perspective into healthcare research. Findings from this study will be presented at the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) Europe conference in November 2020.

## Conclusion

Health-related social media is a novel, growing, and constantly updated source of real-world data that has great value in uncovering patient experiences and perspectives. Outputs from health-related social media data can inform future research questions and its use can help provide a comprehensive understanding of treatment and disease outcomes, including outcomes not possible to capture in traditional sources of real-world data. ■

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# Value is in the Eye of the Beholder


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Therapeutics must demonstrate efficacy and safety to relevant regulatory authorities before they are approved for use in clinical practice. This is a relatively straightforward process, assuming the treatment positively impacts the relevant therapeutic area (e.g., ability to prevent major adverse coronary events [MACE] in coronary heart disease, ability to maintain/improve lung function in respiratory disease). While necessary, efficacy and safety alone are insufficient for a successful launch, as decision makers who safeguard access to therapies must have evidence of the value-for-money associated with new therapies before they allow for widespread use.

Unlike regulatory hurdles of efficacy and safety, demonstrating value is more challenging. Why is this the case? One reason is "value" can mean different things to different stakeholders. For example, patients likely perceive value primarily in terms of effectiveness and safety (and potentially convenience). Conversely, payers may be more focused on economic implications, especially if less expensive and well-known alternatives exist. Physicians likely fall in the middle, wanting to provide optimal patient care while thinking about pricing/profit.


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To maximize uptake, manufacturers must demonstrate value that resonates with each relevant stakeholder. However, it has been our experience that manufacturers tend to focus primarily on payers, risking optimal market access after regulatory approval because such evidence, while important, may not resonate with all relevant decision makers.

We will look at how value is perceived by different stakeholders, using case studies to illustrate differences. We will also provide suggestions to guide evidence generation efforts that incorporate multiple perspectives. Our recommendations are intended to help manufacturers generate evidence to inform discussions on value, both internally and externally, from early in the development process through loss of exclusivity.

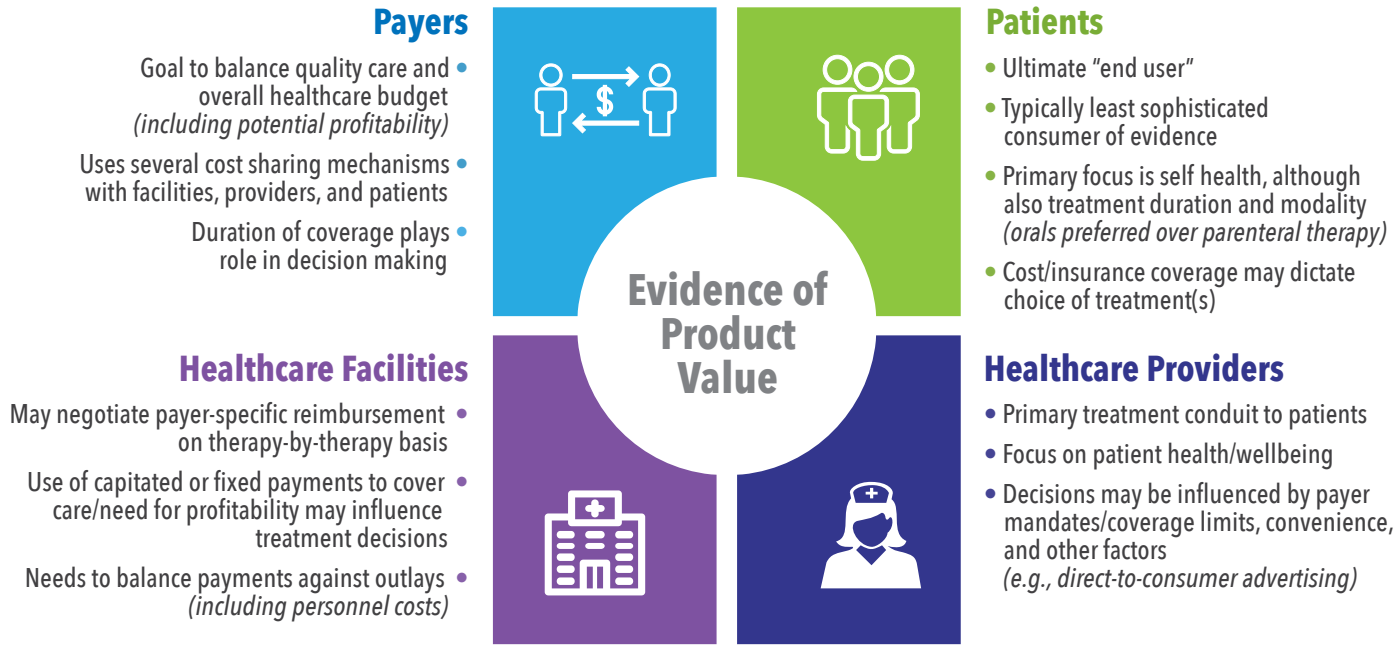
## Efficacy and Safety … and Value?

The road to regulatory approval for a new drug can be challenging. Only about one in nine drugs that reach clinical testing will ultimately receive regulatory approval; moreover, the process often takes between six to seven years.[1] By the time clinical testing is complete, overall development cost before submission for regulatory approval may have already exceeded $1 billion.[1] Many manufacturers dedicate substantial time and resources to generating evidence of efficacy and safety during the early phases of development. Companies often wait until the peri-approval period to consider evidence of potential value; however, the peri-approval period is relatively short. By not treating value as an equally pressing need alongside clinical development, products may launch without the necessary information in place to demonstrate value to all stakeholders. This can negatively impact acceptability of, and access to, the product.

Several stakeholders sit at the "value table" (See Figure 1). Each stakeholder has specific needs that must be met before they will approve or facilitate access to a product. Sometimes these needs align and sometimes they differ substantially. For example, both healthcare payers (including for-profit commercial insurers as well as government entities) and healthcare facilities tend to focus on budget management and are therefore more receptive to value demonstrations focused on cost. This generalization is not always true, as some services are capitated. This means that while the payer will not need to worry about the use of a new product (assuming it does not impact an existing contract), the facility receiving the capitated payment will need to be concerned with the prospect of losing money.

Similarly, both physicians and patients tend to prioritize potential health benefits (versus risks) associated with a new therapy. However, physicians tend to consider costs (especially if under capitated payments) and the perceived burden of getting approval from payers to treat while minimizing risk (including malpractice lawsuits), while patients will typically focus on quantity and quality of life (i.e., a quick cure with the least chance of recurrence).

**Figure 1.** Key Stakeholders for Demonstration of Product Value



Why generate evidence that a therapy is "admission-sparing" if current standard of care results in profit to hospitals? For example, certain musculoskeletal procedures (e.g., knee or hip replacement; spinal fusion; treatment of dislocation/fracture of hip, femur, or other lower extremity; and amputation of lower extremity) make up 17% of operating room procedures, yet account for over 25% of hospital revenue.[2] Therefore, hospitals have an incentive to perform more of these procedures, not less.

Assuming a "one size fits all" approach to generating a value proposition, as opposed to tailoring the message to each relevant stakeholder, therefore may result in regulatory approval without widespread use. This could, in turn, keep potentially life-changing therapies from the patients who need them the most.

**CASE STUDY 1**

## Stem Cell Transplant

### Is the Ounce of Prevention Preferable to the Pound of Cure?

Use of hematopoietic stem-cell transplantation (HSCT) in the United States (US) has increased steadily, with nearly 25,000 procedures performed in 2018.[3,4] This has led to increased healthcare costs due to the rise in total hospital stays and post-HSCT complications.[5,6] To help manage this issue, payers offer a "bundled" reimbursement to HSCT centers based on expected average costs. If the center exceeds this amount, they are not reimbursed and must absorb the financial loss.[7]

Several studies have indicated that unwanted, and potentially avoidable, complications post-HSCT (e.g., graft versus host disease and infections) are major cost drivers.[5,8-10] Antifungal prophylaxis has been shown to reduce the incidence of invasive fungal infections, which are a leading cause of morbidity, infection-related mortality, and costs among HSCT recipients.[11,12] Thus, there is value to both the patient and the center in preventing these complications. However, studies have shown that antifungal prophylaxis is underutilized in high-risk patients.[13] It is possible that the risk versus value calculation for prophylaxis varies by institution and/or provider,[14] since the cost variation by case mix can make the situation complex. Providers and institutions need to balance the cost of antifungal prophylaxis (which varies based on agent, dosage, route of administration, and duration of treatment)[15] with the risk of the patient developing a fungal infection. This means the financial benefit of prophylaxis depends on whether it will offset the "downstream" costs of an infection.

**CASE STUDY 2**

## Dialysis

### Do Better Outcomes and Lower Costs Matter?

Barring kidney transplant, end-stage renal disease requires dialysis using either hemodialysis (HD), which is often administered in a dialysis center (in-center hemodialysis [ICHD]), or with peritoneal dialysis (PD), which is a portable system that allows the patient more freedom. Home-based HD is also a potential solution. Dialysis is expensive, albeit less costly in the short term than a kidney transplant, which is preferred when the organ is available and when the patient is a good transplant candidate.

Several studies have shown that PD is associated with lower risk of mortality (at least in the year following initiation of dialysis) and lower healthcare costs. Several countries, including the US, have established a "Home Dialysis-First" policy to incentivize patients to these preferred modalities.[16,17] However, only about 10% of dialysis patients in the US received PD in 2017, despite the Centers for Medicare & Medicaid Services (CMS) enacting a prospective payment system that bundles most dialysis services.[18] While there are many reasons for this, one may be a lack of compelling evidence geared toward healthcare providers. Physicians, who play a large role in a patient's decision-making process, are likely incentivized to suggest ICHD. In the US, most physicians lack training in other dialysis modalities. During training, physicians are exposed mainly to ICHD; only 5% of a nephrologist fellow's time (median value) is spent managing PD patients (it is 10% in Canada).[19] There are also several financial incentives associated with HD, including owning a dialysis clinic and reimbursement mechanisms for anti-anemia therapy,[20] as well as corresponding disincentives for PD. For example, in the US, Medicare and other payers generally do not cover PD-related educational sessions. These upfront costs are shifted to hospitals/institutions, which may pass them on to patients.[21]

## Framework for Establishing Value from Different Perspectives

In both case studies, we believe if manufacturers had built a value framework early in the development process, they may have been able to quantify various stakeholder concerns and create relevant evidence of value necessary to improve treatment uptake.

Creating a rudimentary economic model early in the development process can help manufacturers test and assess the potential value of their product with multiple stakeholders. Such a model, assuming it can evolve as new information becomes available, allows manufacturers to evaluate and update potential value arguments alongside estimates of efficacy and safety throughout the pre- and peri-approval process. Each assessment can be shared with relevant stakeholders who can provide feedback that will help shape future evidence generation efforts, including:

- Potential design modifications to clinical studies
- Health economics and outcomes research (HEOR) efforts
- Internal (and potentially external) pricing discussions

These results can inform future updates and reruns of the model, thereby allowing the manufacturer to develop and evolve pharmacoeconomic arguments that are supported by clinical and HEOR studies and tailored to meet the potential objections and needs of different stakeholder groups.

Cost effectiveness analyses (CEA) are used for informing value to payers when cost effectiveness is part of the requirements for submissions for new treatments, particularly in countries with health technology assessment bodies. For that reason, manufacturers often build early models to evaluate cost effectiveness and expected incremental cost-effectiveness ratios from payer and/or societal perspectives and adapt that model to multiple geographies. However, a key outcome is the traditional cost per quality-adjusted life-year. Although these models are often equipped to estimate other clinical outcomes (e.g., cost per life-year gained or cost per event avoided), they are not well positioned to answer questions associated with how other stakeholders (e.g., healthcare facilities, providers, patients) perceive value.

Budget impact analysis (BIA) models are another helpful tool for multiple stakeholders, including payers and facilities, by forecasting expected costs associated with a new treatment. However, their role is limited as they typically only capture short-term affordability such as the financial impact the new treatment might have on formulary or institutional budget. These models typically ignore other definitions of value.

Cost consequences analysis (CCA) is another method of economic evaluation that has not been widely used. CCA is a form of economic evaluation that allows for the presentation of disaggregated costs and a wide range of outcomes, thereby allowing stakeholders to form their own opinion based on perceived value that matters to them.[22,23] Unlike CEAs where costs and outcomes are aggregated to a single estimate, CCA outcomes are not restricted and can include other measures of value, such as:

- Estimates of infections avoided
- Number of unscheduled outpatient visits
- Number of hospital readmissions reduced
- Days without symptoms
- Patient satisfaction

Unlike BIAs, CCAs are not restricted to differences between "new scenario with intervention" and "old scenario without intervention," and can include other measures such as profitability for institution (or physician) or the cost to a patient.

CCAs are particularly useful early in the development lifecycle when it may not yet be clear which costs and outcomes will be most relevant to various stakeholders.

> … a failure to identify relevant stakeholders and the evidence that will resonate with each may decrease the likelihood of a successful product launch.

This type of analyses is easily approachable and understandable with CCA since each stakeholder can select the component(s) most relevant to their own perspective.[24] With that noted, CCA should be viewed only as a complement to, and not a substitute for, CEA and budget impact assessment (BIA). In fact, early CCAs can evolve to incorporate BIA and/or CEA.

Given that funding for value propositions is often limited early in the development process, and that the asset-specific information required to conduct robust CEAs is often immature (or unavailable),[25] CCA provides manufacturers with the ability to examine the potential value of a development asset side-by-side with corresponding assessments of efficacy and safety. This allows for comprehensive and repeatable assessments throughout the pre- and peri-approval process, including fully informing early discussions on potential asset pricing and "go/no go" decisions for subsequent clinical development (See Table 1).

## Plan Early, Revisit Often

In our opinion, it is vital that some attention be paid during the early development phase to establishing value. As we have stressed throughout this discussion, perceptions of value differ by stakeholder. Similarly, a failure to identify relevant stakeholders and the evidence that will resonate with each may decrease the likelihood of a successful product launch.

In addition to the CCA, we recommend developing a plan that describes the evidence necessary for each relevant stakeholder and corresponding efforts required to generate that evidence. The plan should be developed early in the product's lifecycle and have frequent checkpoints based on when new information (e.g., results of early evidence generation efforts, results from clinical studies, output from a CCA) become available. It should also have a predetermined plan to evaluate evidence generation efforts, how to support key differentiators between the development asset and currently marketed products, and, as applicable, information from competing manufacturers. As part of this plan, we recommend developing a cost-consequence model that can estimate outcomes specific to each stakeholder and then be updated when new information becomes available. While the plan and the model should be developed relatively early, both should be sufficiently robust to support evidence-generation efforts throughout the pre- and peri-approval process.

Table 1. Modeling Framework for CCA from Multiple Perspectives

| | Payer | Healthcare Facilities | Healthcare Provider | Patient |
|---|---|---|---|---|
| **Broad Health Outcomes** | • Efficacy and safety<br>• Quality of life | • Efficacy and safety<br>• Quality of life | • Efficacy and safety<br>• Quality of life | • Efficacy and safety<br>• Quality of life |
| **Disaggregated Health Outcomes** | • Cases<br>• Cure<br>• Symptom-free<br>• Complications (unless within bundled payment)<br>• Adverse events<br>• Admissions<br>• Readmissions | • Cases<br>• Cure<br>• Complications<br>• Adverse events<br>• Admissions<br>• Readmissions<br>• Pains or symptom days | • Cases<br>• Cure<br>• Complications<br>• Adverse events<br>• Admissions<br>• Readmissions<br>• Pains or symptom days | • Cure<br>• Complications<br>• Adverse events<br>• Admissions<br>• Readmissions<br>• Pains or symptom days |
| **Other Health Outcomes** | • Health system efficiencies<br>• Episode length in bundled agreement<br>• Productivity losses | • Health system efficiencies<br>• Patient satisfaction<br>• Healing time<br>• Real time to discharge vs. episode length in bundled agreement | • Patient satisfaction<br>• Healing time<br>• Real time to discharge | • Patient satisfaction<br>• Caregiver outcomes<br>• Healing time<br>• Real time to discharge<br>• Activity restrictions<br>• Productivity losses<br>• Convenience |
| **Broad Cost Outcomes** | • Total treatment cost | • Total treatment cost | • Total treatment cost | • Total treatment cost |
| **Disaggregated Cost Outcomes** | • Drug cost<br>• Administration cost<br>• Medical resource use cost | • Drug cost<br>• Administration cost<br>• Medical resource use cost<br>• Inpatient<br>• Outpatient | • Drug cost<br>• Administration cost<br>• Medical resource use cost<br>• Inpatient<br>• Outpatient | • Drug cost<br>• Administration cost<br>• Medical resource use cost<br>• Inpatient<br>• Outpatient |
| **Other Cost Outcomes** | • Cost per patient<br>• Cost per member per month | • Cost per patient<br>• Cost per "episode"<br>• Costs to render care vs. paid amounts from diagnosis-related group<br>• Cost vs charge ratio<br>• Innovation<br>• Training investment<br>• Infrastructure<br>• Personnel cost | • Cost per patient<br>• Cost per "episode"<br>• Training investments | • Out of pocket expenses<br>• Transportation costs<br>• Paid caregiving |

Most crucial is the ability to evolve to incorporate new inputs and/or outputs as the relevant knowledge base grows through early evidence generation efforts and the clinical development program.

## Conclusion

While necessary, regulatory approval does not guarantee a product will be added to formulary and/or reimbursed at the manufacturer's requested price. Similarly, being added to formulary and reimbursed does not guarantee broad access and use. Once regulatory approval has been granted, the key to reimbursement and access is in the ability to demonstrate value that is both relevant to key stakeholders and enough to inform their decision making. It is important to proactively conceptualize how product availability will impact each relevant stakeholder group (e.g., payers, healthcare facilities, healthcare providers, and patients) and the evidence that each will need to change how they approach treating their condition. This is not an easy task. Stakeholders have different wants and needs, and what is a benefit to one may be perceived as a detriment to another. Accordingly, manufacturers should incorporate value demonstration early in the development lifecycle to fully inform internal discussions.

The need for robust value propositions that speak to different stakeholders will only become more important as new treatments, especially disruptive and transformative therapies, are developed and brought to market. ■

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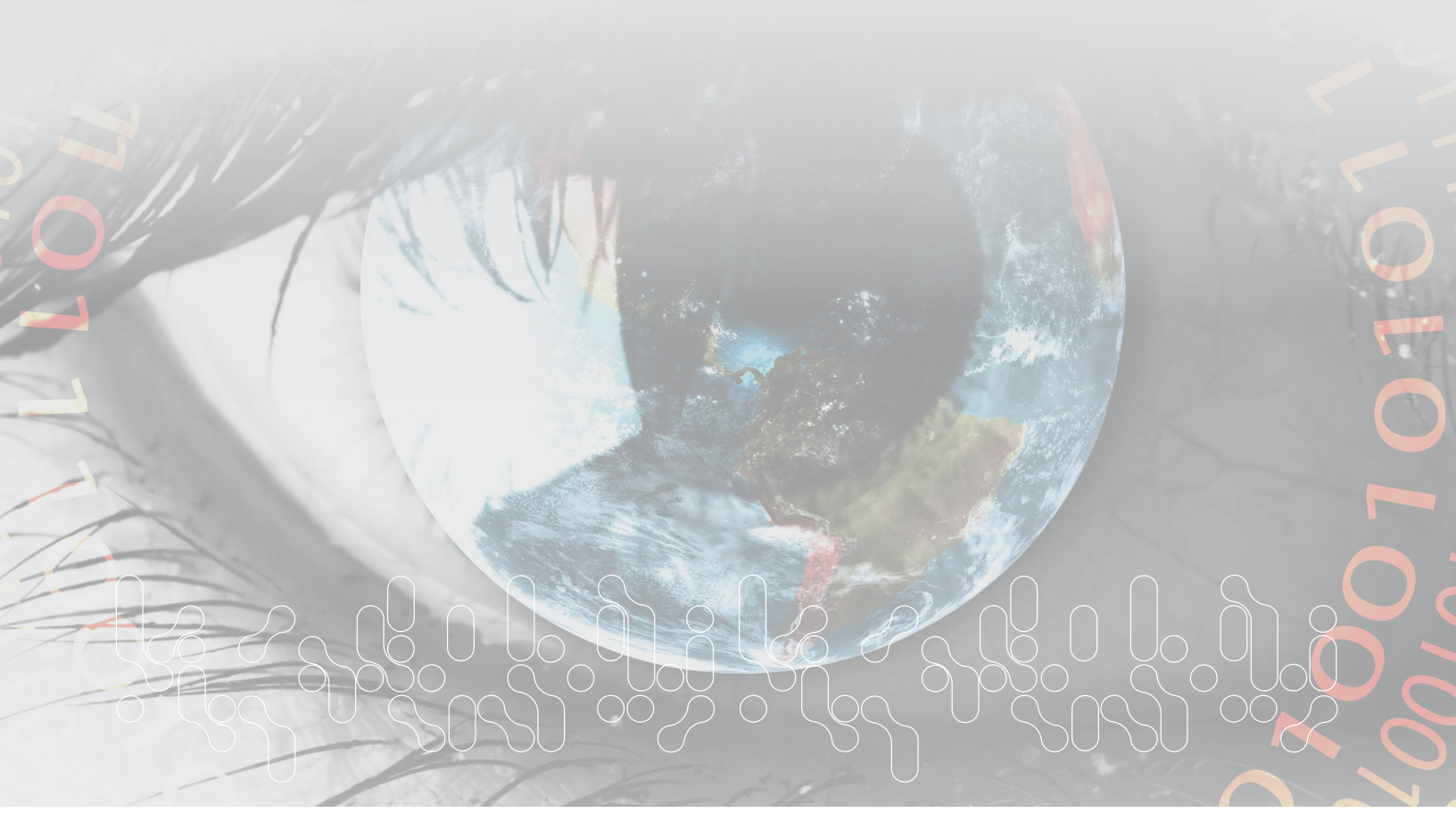

# Supporting Clinical Trial Site Selection During the COVID-19 Pandemic Using WAVE, a Custom Hybrid Epidemiologic Model

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## Introduction

COVID-19 has posed major challenges to healthcare on a global scale, affecting everything from access to care, management of medical facilities, and effective recruitment for clinical studies. Drug developers have had to incorporate new approaches to site selection as they strive to accelerate timelines for SARS-COV-2 vaccines and COVID-19 therapeutic trials, as well as minimize interference of COVID-19 for site selection in non-COVID trials. For potential vaccines or COVID-19 treatments, sponsors need to find study sites in areas that are expected to see many cases during the patient enrollment period (in the case of treatments) or shortly thereafter (for vaccines). This is crucial for efficient trial execution. Conversely, studies in other therapeutic areas face challenges with patient recruitment due to sites being affected by COVID-19 and need to identify sites in locations with expected low incidence of COVID-19 cases over the study period.

Planning and site selection can be aided by an adaptable epidemiologic model that can produce accurate predictions

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customized to the specific locales of potential sites. Such a model, the **W**ave **A**ssessment of co**V**id **E**pidemiology (WAVE), was developed to help inform site selection by considering the expected trajectory of the pandemic. WAVE is a process of deriving actionable forecasts for very specific local areas where potential sites are located. Using granular data, the observed caseloads are regularly updated for each small area of interest. These data are fit using a set of differential equations specifying ongoing sequences of exponential growth and decay. This hybrid model is then incorporated into a predictive simulation implemented in the Discretely Integrated Condition Event (DICE) framework. The forecasts for the time periods of interest are examined and interpreted considering each trial's particulars.

Use of WAVE extends beyond site selection to inform hospital resource planning. The model can also help prepare for health technology assessment (HTA) submissions. In this whitepaper, we detail some of the use cases for the WAVE model.

## Granular Data Obtained for WAVE

Observed case data for one potential site in the United State (US) are plotted in Figure 1. The blue dots represent local daily COVID-19 case counts from early March 2020 through the beginning of July 2020. The red and orange dashed lines indicate some potential fits of that site's data. Given the variation in the data, one challenge is fitting in some detail without overfitting the short-term fluctuations due to data reporting practices and other factors. The final model blends ongoing growth (red lines) and decay (orange lines) portions to reflect the patterns without trying to replicate every up and down.

## Beyond Just Site Selection

The full simulation consists of three modules. **Module 1** is the epidemiologic module that uses the fitted equations to project the case load in each site's catchment area. Users can examine the impact of starting nonpharmaceutical interventions (NPIs), when NPIs stop, and look at various scenarios. For example, a forecast might be needed to predict what happens if a locality institutes business closures for the second time. Information from Module 1 feeds into Module 2, which focuses on in-hospital management of patients. **Module 2** takes a case from admission through to discharge or death. **Module 3** addresses the longer term, including adverse consequences and their management. All of this is achieved within the DICE framework.

Figure 1. COVID-19 Cases Observed in the Catchment for a Particular Site from March to July 2020

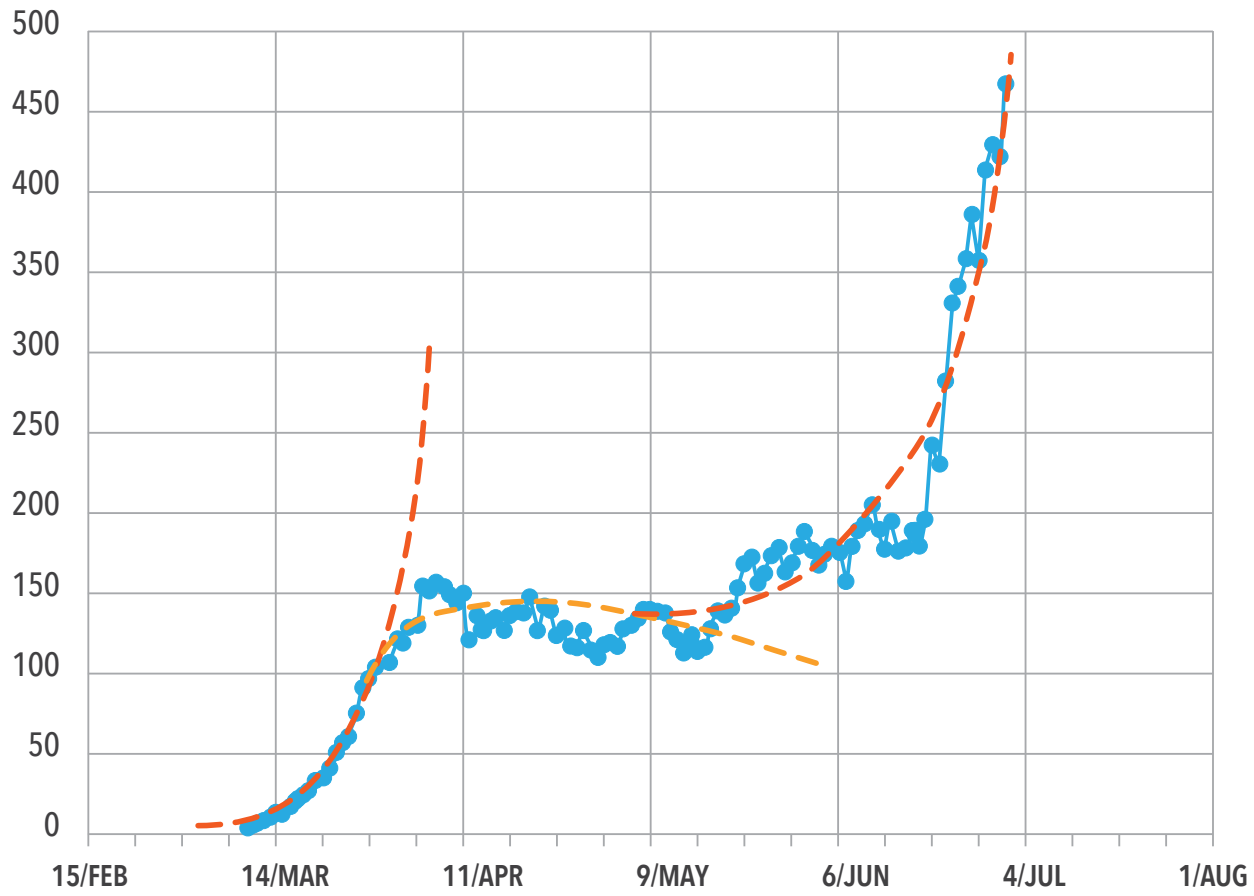
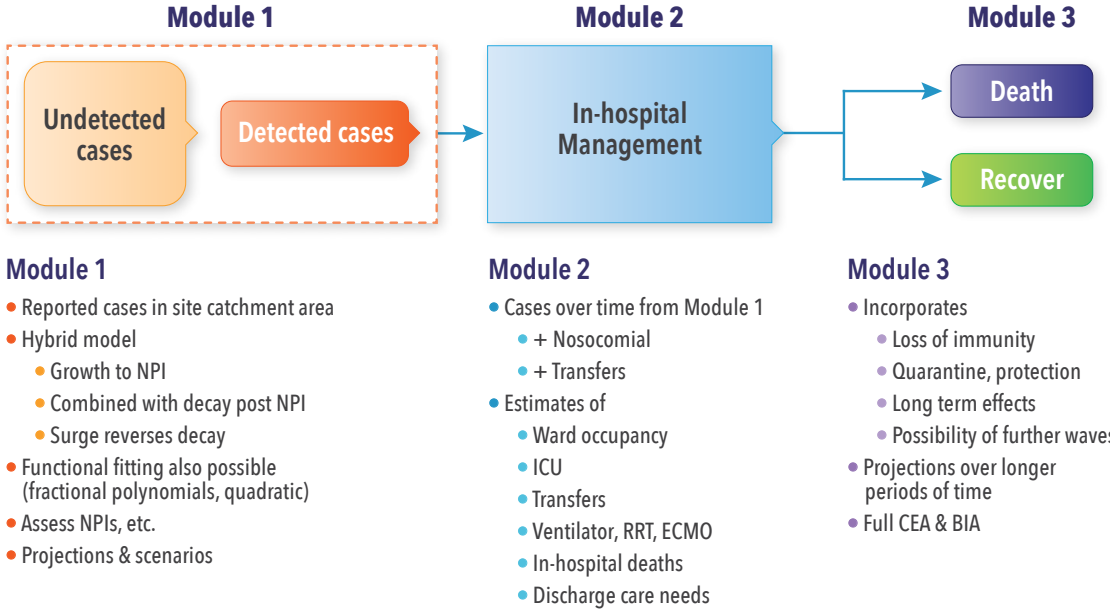


Figure 2. WAVE Model Schematic




RRT = Renal replacement therapy; ECMO = Extracorporeal membrane oxygenation; CEA = Cost-effectiveness analysis; BIA = Budget impact analysis

## DICE Simulation

Developed and tested in 2016, the DICE approach conceptualizes the course of an illness in terms of the information (conditions) and the events when some of those conditions change. DICE simulations are specified entirely in a set of Excel tables which are very easy to read and understand; there's no programming or special software needed.

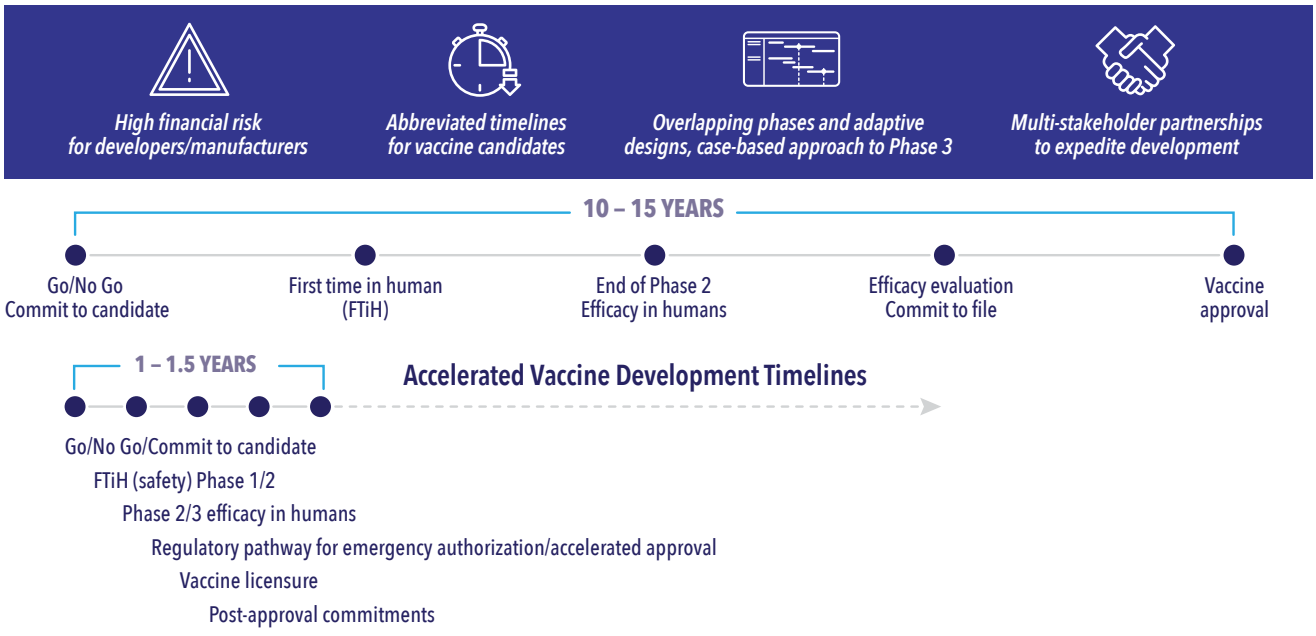
DICE allows users to make forecasts, test different scenarios, and conduct sensitivity analyses. Users can select a site and use its fitted equations or input custom dates for when NPIs might be started or stopped. This information is used to select the transmission parameters that will control the growth and delay curves.

## Real-World Applications for the WAVE Model

### WAVE Model Enables Rapid Vaccine Development

The vaccine development landscape for SARS-COV-2 is unique in history with its highly abbreviated timelines (See Figure 3). Where a traditional vaccine development program might take anywhere from 10 to 15 years, COVID-19 timelines are in the range of 1 to 1-1/2 years.

Figure 3. SARS-COV-2 Vaccine Development Landscape



This requires overlapping phases and adaptive designs. Most of the later phase vaccine programs are using an event-based approach (based on number of incident cases occurring post-vaccination) to power their Phase 3 studies.

There is high financial risk for developers and manufacturers to try to meet these timelines and be successful. Strong multi-stakeholder partnerships are expediting the development of these vaccine programs. While this is very positive, it poses additional challenges in terms of ensuring alignment across stakeholders in the trial design and implementation.

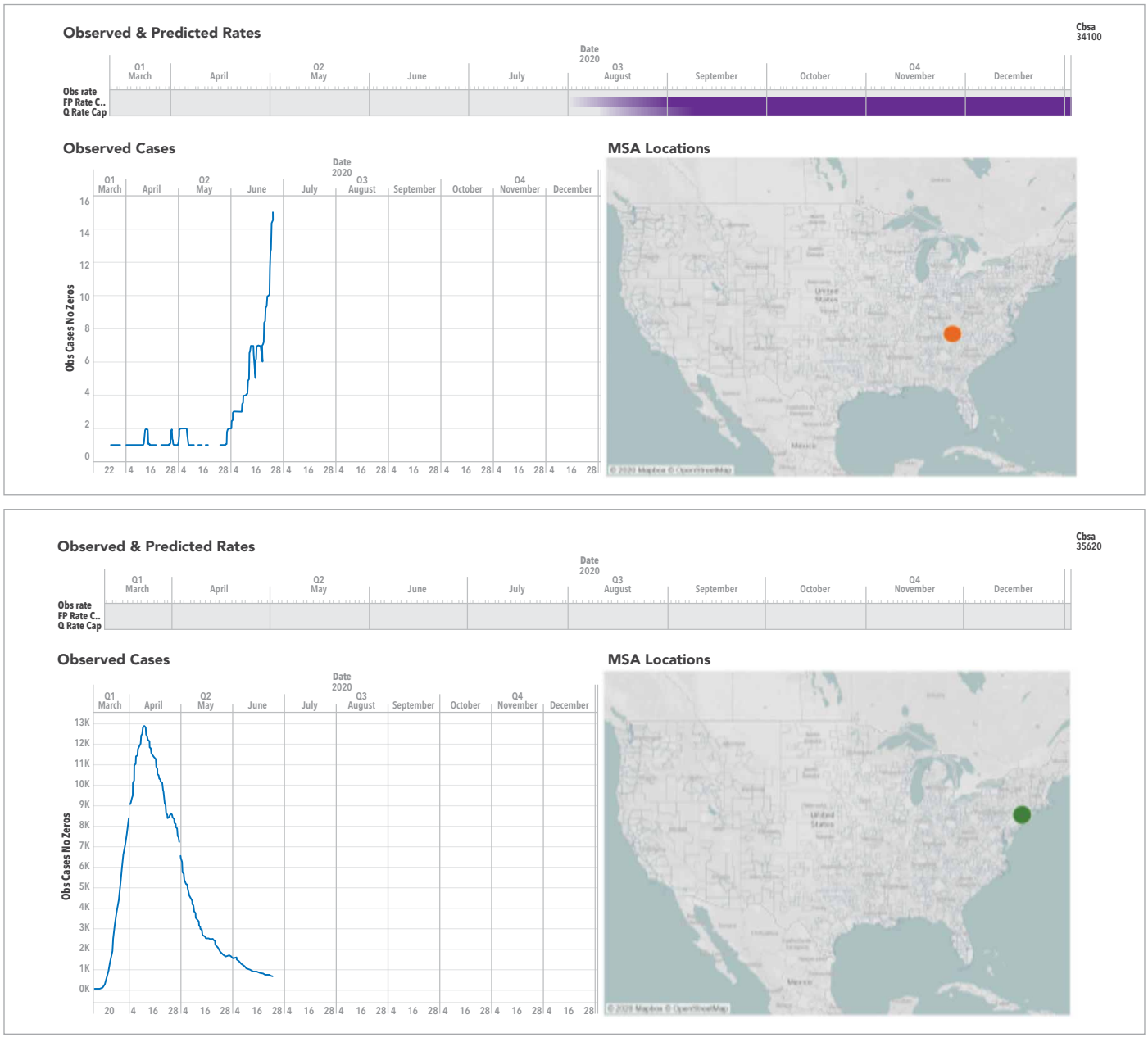
## Module 1 Applications

### CASE STUDY
### Site Selection

In the face of highly accelerated timelines, a company needed an enhanced, evidence-driven site selection approach for a large footprint SARS-COV-2 vaccine development program with many sites across the US. They were interested in selecting sites that had a large susceptible catchment population and a predicted rise in COVID-19 cases diagnosed over the trial period, but not too soon after the first dose was administered.

**Figure 4.** WAVE Dashboards: Observed and Predicted Rates

*The WAVE model predictions can be displayed by selecting locations on an interactive map (See Figure 4). For the selected site, color heat charts indicate the expected intensity of cases over time. Gray indicates a low number of cases while deepening purple indicates higher anticipated accumulation of cases in that site catchment area.*



A traditional site-based feasibility study was used to identify a large list of possible target sites. Using the WAVE model, the expected case numbers over time for each site's catchment area were forecast for the time period of interest. Use of the WAVE model improved site selection—actionable predictions were instrumental in facilitating multi-stakeholder agreement for which sites would be selected and which sites would be eliminated. The WAVE model successfully predicted a surge in cases for many sites prior to the observed surge. In addition, the WAVE model predicted sites where the first wave was already closing, enabling the client to avoid these sites.

CASE 2

### Modeling the Impact of Public Health Interventions

The WAVE model can also be used to predict the impact of public health interventions. Figure 5 shows a location that is doing a good job controlling the pandemic. Their R number (indicated in blue) is the reproduction number read off the right-hand axis. It drops below 1 approximately 42 days after they first saw 25 or more cases. In Figure 6, the model is used to determine what would happen if NPIs were only left in place for three weeks. The model shows the drop in R-number stalls and then starts to go back up, and predicted caseloads skyrocket.

## Conclusion

The COVID-19 pandemic has challenged the life sciences community. It has prompted highly accelerated development programs in both vaccines and treatments and has had a major impact on non-COVID-19 clinical development programs. The WAVE model is a hybrid dynamic transmission model that leverages granular local data to forecast case numbers, accounting for the impact of NPIs and other interventions. It has supported enhanced site feasibility and ongoing monitoring of predicted case numbers for clinical development programs in both COVID-19 vaccines and treatments with the aim of increasing trial efficiency and reducing timelines to expedite the availability of these innovations. ■

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Figure 5. Location Where Pandemic is Well Controlled

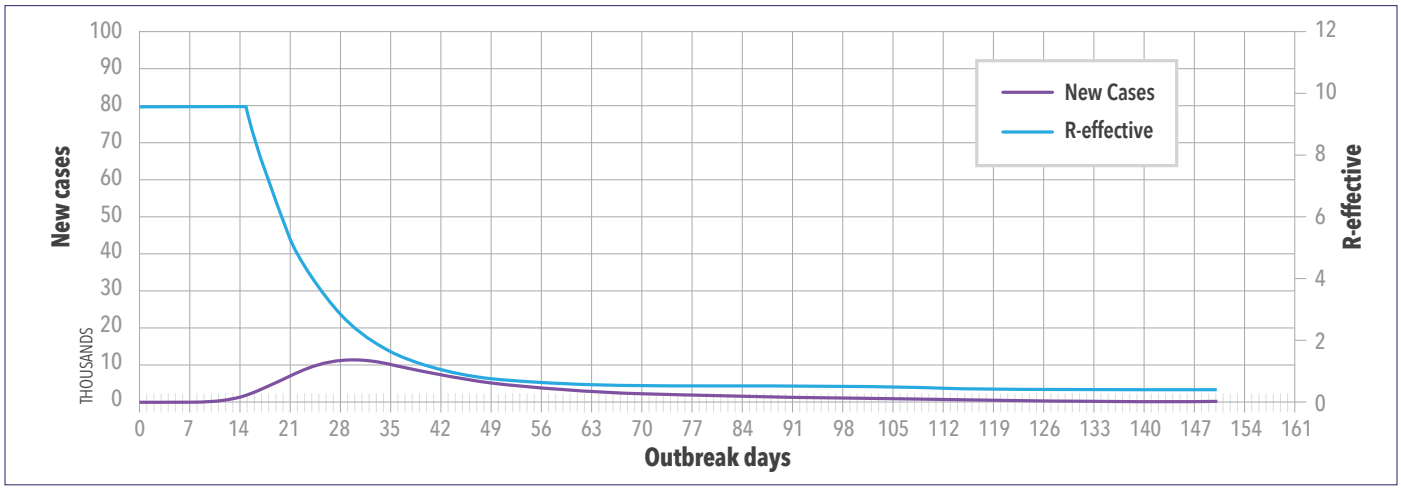
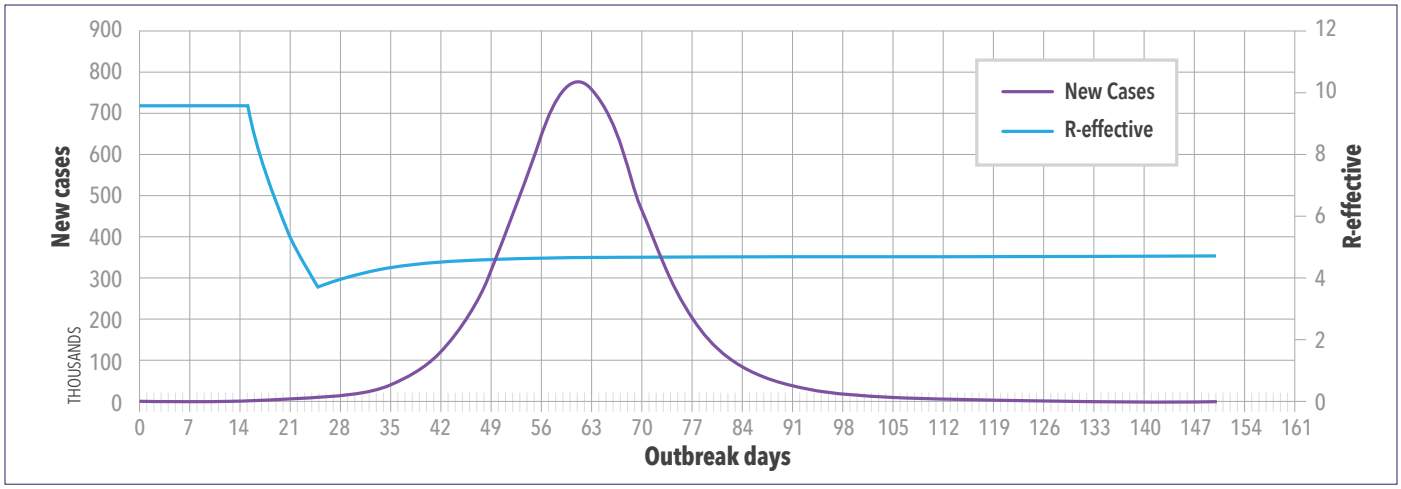
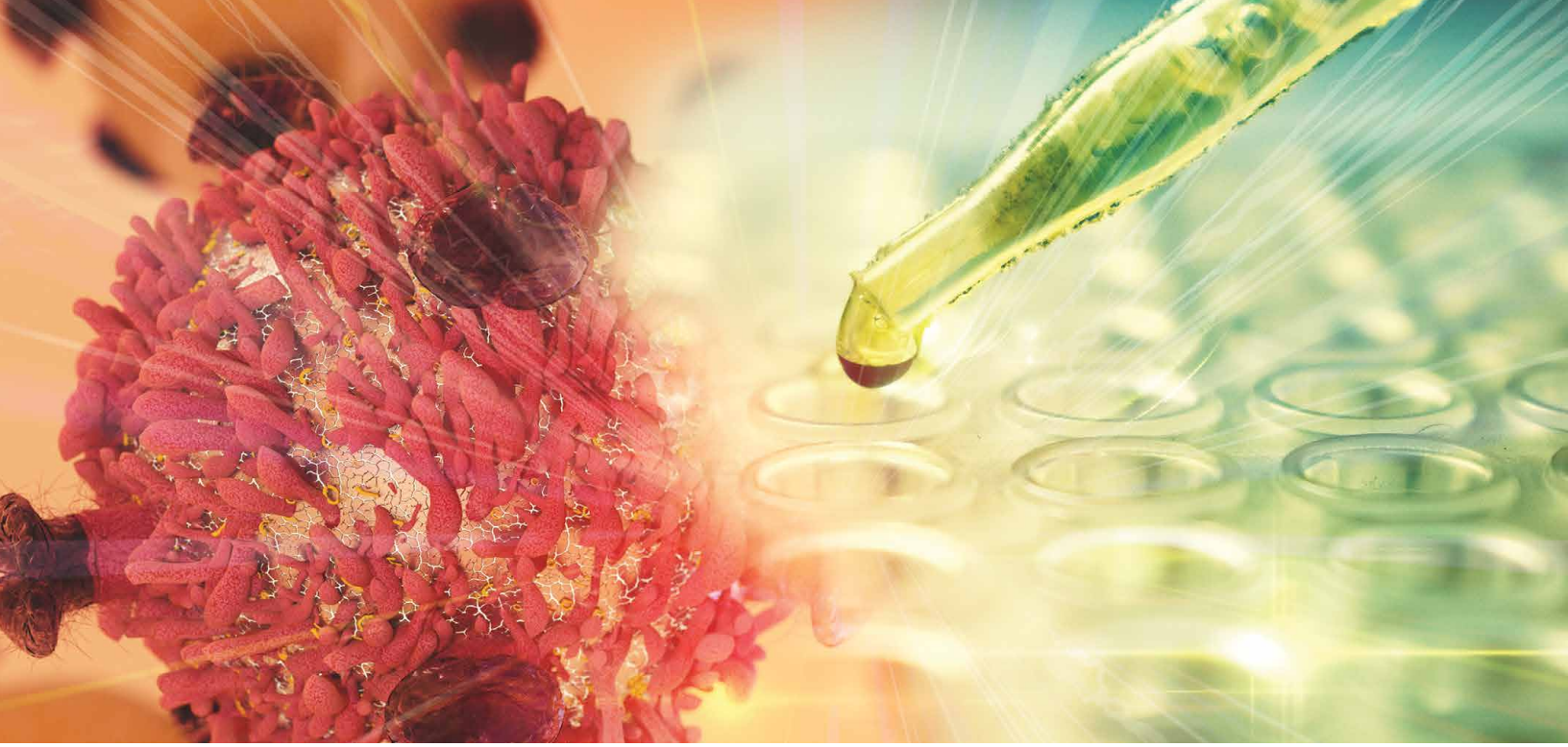



Figure 6. Location with NPIs Removed After Three Weeks





# Advancing Early Stage Oncology Research with Adaptive Designs and Master Protocols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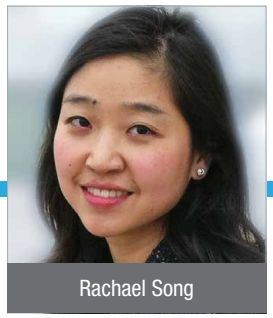
Oncology trials make up over a third of today's pharmaceutical research pipeline, but conventional oncology drug development programs are often inefficient, expensive, and suffer from high failure rates.[1] Of the oncology agents that enter Phase I trials, only about 3% eventually receive approval from the United States Food and Drug Administration (FDA).[2]

Just as other industries have moved toward more flexible methodologies that foster continual improvement and operational efficiencies, clinical development is slowly ramping up adoption of innovative designs after being encouraged by regulatory agencies to speed progress, reduce inefficiencies, and improve success rates.

This article focuses on the early stage of oncology trials where important decisions about dose selection and target indications that may have far-reaching consequences are made. We explore potential scientific and operational implications for two different well-established designs:


Jürgen Hummel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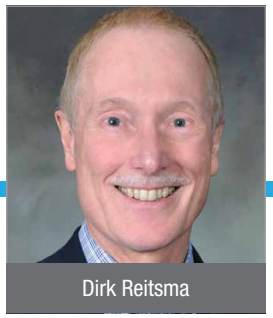
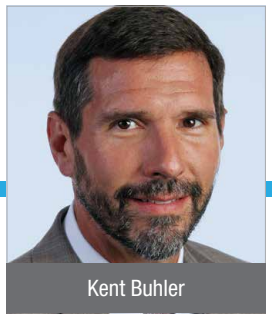

Dirk Reitsma


Kent Buhler


Song Wang

1. The continual reassessment method (CRM), an adaptive design that identifies the target dose
2. Basket and umbrella trial designs, types of master protocols that may address multiple research questions under one protocol to identify target indications and patient populations

## Adaptive vs. Traditional Designs

Traditional designs contribute to high failure rates and escalating costs. Traditionally, each trial is designed to answer only one narrow scientific question at a time in sequence. Moreover, answers to pivotal research questions are often obtained only at the end of the trial. In contrast, adaptive designs potentially allow a trial to answer multiple questions at once, leveraging accumulating data so early findings can inform decisions in an ongoing process.

Adaptive designs allow for prospectively planned modifications to one or more aspects of the design based on accumulating data from patients in the trial. Modifying trials as they progress can accelerate timelines, reduce costs, and generate more knowledge, thereby improving the overall quality and efficiency of decision making.

The adaptation process is typically prescribed in the trial protocol. Modifications may include dosage, sample size, patient selection criteria, and novel drug combinations, as well as specific indications as more information becomes available. The trial protocol is designed before the trial begins; the protocol pre-specifies the adaptation schedule and processes.

Surprisingly, innovative designs are not used as often as one would expect given that the methods are well established, more efficient, and regulators encourage their use. The largest untapped opportunities are arguably in the early phases of clinical development where adoption of innovative designs may, in fact, lead to an accelerated approval.

## Regulatory Support and Buy-in

In 2007, the European Medicines Agency (EMA) began introducing frameworks for adaptive designs and encouraged their use.[3] The FDA provided draft guidance in 2010, which was then refined and finalized in 2019.[4,5] The FDA also drafted *Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics* in 2018.[6] European Clinical Trial Facilitation Group (CTFG) perspectives on complex clinical trials with master protocols were presented in 2019.[7] The International Council for Harmonisation (ICH) issued a final concept paper on adaptive clinical trials in 2019 with final guidance expected in three years.[8]

Our experience in submitting protocols with adaptive designs in early stage oncology trials to United States and European regulators is that they not only accept these designs, they actively encourage them. Investigators have a growing understanding of the many benefits of these approaches and the world is now onboard with these study designs. Regulatory agencies not only promote usage, they welcome dialogue with sponsors pursuing these models. Early engagement with regulatory agencies is key. The FDA, for example, also strongly encourages sponsors to discuss plans to develop drugs under a master protocol with the clinical review division early in the program to obtain feedback.

## Adaptive Design in Current Practice: Defining the Maximum Tolerated Dose

Accurately defining the optimal dose in oncology clinical trials is a common challenge. The correct maximum tolerated dose (MTD) estimation rate is only about 40%,[9] which may result in patients being treated at subtherapeutic doses or doses that are too toxic. Selection of the wrong dose can not only disrupt the outcomes of all subsequent phases, it can, without a correction, ultimately lead to the development program's failure. Most trials identify MTD using the 3+3 design, a rule-based design which offers simplicity, convenience, and familiarity. However, the 3+3 design method has limitations, including:

- It is defined based only on data from last dose
- The method ignores uncertainty
- There is no ability to re-escalate
- Cohort sizes are fixed

Because 3+3 offers a poor ability to determine the correct MTD, we do not recommend it. Several improved, rule-based, dose escalation designs are available, including the Modified Toxicity Probability Interval (mTPI) design and Bayesian Optimal INterval (BOIN) design. These designs offer more accuracy and flexibility than 3+3; however, they are not able to match the accuracy of a model-based design, therefore, we only recommend using these designs if the number of dose levels to be tested is fewer than five.

In most situations, the CRM design is the best choice for dose escalation studies. CRM is an adaptive, Bayesian, model-based approach that is superior to the 3+3 design. The CRM uses simulation software to efficiently evaluate a larger number of doses to estimate the MTD more precisely compared to 3+3, mTPI, and BOIN.[10] CRM uses all data to update the estimation of the MTD and to allocate the next patients, either in cohorts or continuously. The model is frequently updated and thus is improved as data accrues, allowing researchers to make better, more efficient use of data. The model is typically updated within one working day.

The CRM provides an increased chance of treating study patients around the MTD and a decreased chance of exposing patients to dose levels greater than MTD.[10] Also, in many cases the CRM can determine MTD from a smaller number of patients, which may lead to cost savings and a

shortened timeline. CRM also provides more flexibility than a rule-based model, both scientifically and operationally. Rules are tailored for each study and expected toxicity profile, and priority can be given to MTD accuracy or study timelines.

Because of their flexibility, adaptive designs can overcome inherent limitations in the fixed structure of traditional designs. For example, CRM can adapt to accommodate late toxicities because it builds on previous knowledge, allowing it to generate predictions and directional guidance that can steer determination of the doses to investigate in combination trials. Borrowing of information also makes subsequent trials (e.g., defining other populations) more efficient.

Although the scientific methodology can be more difficult to understand, operational considerations for a CRM design resemble those of a 3+3 design. While a CRM design does require more front-end time, overall, it may save time by requiring fewer patients and by allowing for more rapid progression through early dosing levels depending on the operating characteristics and rules that are established in the design.

Looking at the big picture, from a cost perspective, a CRM design carries a much lower risk of overestimating or underestimating the MTD. In fact, considering the potential costs of taking a suboptimal dose into the next phase, it becomes clear that identifying the right MTD in the dose escalation phase could arguably generate the greatest cost savings, and advantage, that a program could gain.

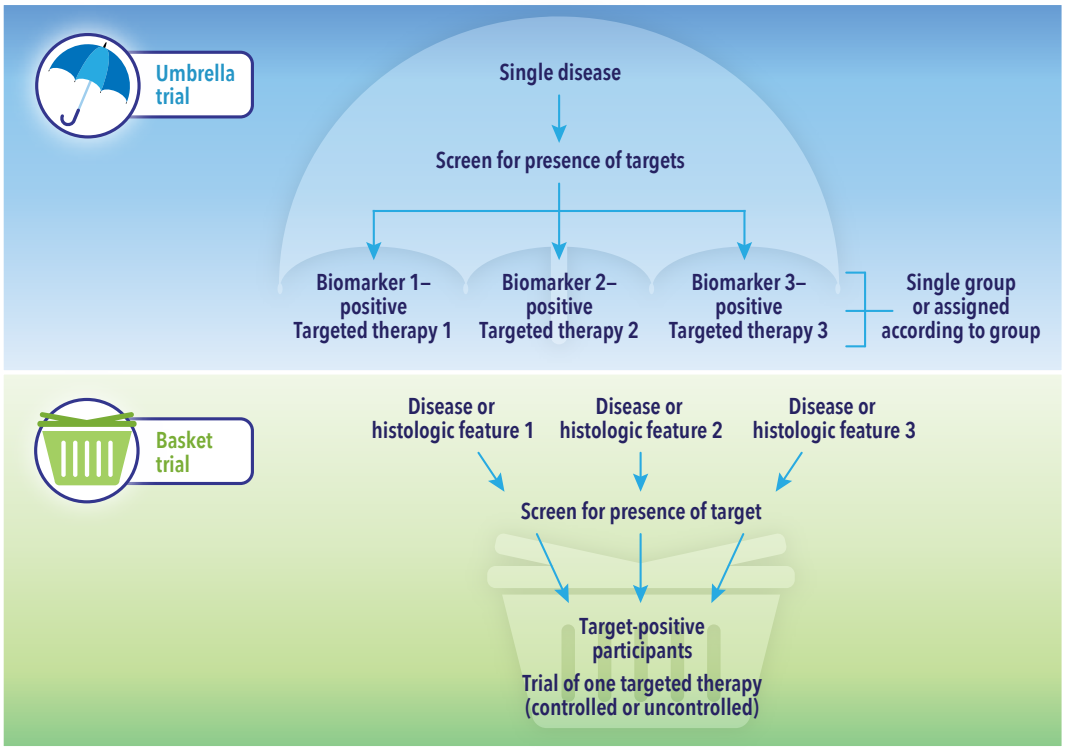
## Master Protocols: Efficient and Accelerated Development That Can Improve the Probability of Success

Master protocols employed in the early stages of a trial can help answer multiple questions simultaneously using a single infrastructure, design, and protocol, not only adding speed and efficiencies but rapid learning and data-driven, improved decision making (See Figure 1). Study teams can flex midstream, for example, to add or remove indication cohorts, drug combinations, and conduct other investigations in response to early findings without having to go back to the drawing board to write a new protocol and set up additional studies.

Master protocols may be used for exploratory purposes or in support of a marketing application. Many designs can be made adaptive, making them both more efficient and better able to answer questions accurately, and several innovations can be applied within a master protocol to improve trial efficiency. In an umbrella trial, for example, a common control arm can be used to reduce sample size. In a basket trial, a Bayesian hierarchical model could allow for information borrowing across patient cohorts and detect signals earlier with high efficiency.

In both umbrella and basket trials, investigators may be able to save resources and treat more patients with more promising drugs by adding or stopping indication cohorts and/or treatment arms, or they can adjust the randomization ratio among treatment arms based on interim analysis results. Bayesian decision rules based on posterior probability of meaningful treatment effect or

**Figure 1.** Two Types of Master Protocols: Umbrella and Basket Trials[11]




**Umbrella**
To study multiple targeted therapies in the context of a single disease

**Basket**
To study a single targeted therapy in the context of multiple diseases or disease subtypes

success in future trials would provide flexibility in decision making and interim data monitoring, making it easier to detect efficacy signals earlier and reduce sample size.

Leveraging master protocols in the early stages of a trial can be particularly impactful to develop, amend, and answer hypotheses. Master protocols can provide multiple benefits:

- Increase speed and quality of decisions: de-risk by accelerating successful investigations and failing faster
- Reduce costs: shared trial infrastructure, design, and protocol deliver cost efficiencies; Deloitte estimates master protocols reduce costs by an estimated 13-18%[12]
- Shorten timeline: efficiencies accelerate effective therapies to market; Deloitte estimates master protocols reduce timelines by 12-15%[12]
- Benefit patients: patients are screened and allocated to the appropriate sub-study with the applicable treatments

Master protocol trials offer very practical operational benefits. For example, the use of a common protocol allows amendments to be developed, reviewed, and approved more quickly. Other efficiencies include site contracts and budget negotiations, streamlined site communications, and increased enrollment momentum. In balance, our experiences show the efficiencies and benefits far outweigh the complexities.

Trials that address many questions simultaneously using a master protocol can be operationally complicated. However, these complexities can be managed, even, for example, in complex global studies used to support a marketing application. Operational activities will not be linear, but instead are likely to run concurrently. Study teams must be poised to manage near-constant change, but with proper diligence and operational excellence, great advantages can be realized with these innovative designs. ■

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# Transformation of Clinical Trial Design and Operations

## Interviews with **Science 37**, **Medable** and **Takeda**

Recently, Brittany Erana, MPM, Vice President of PPD® Digital; and Niklas Morton, MSc, Senior Vice President of PPD® Digital, spoke with leaders of Science 37, Medable, and Takeda in an online forum about how the industry is shifting to focus on decentralized trials. They then took questions from attendees regarding their experiences and best practices with decentralized studies.

### PART 1
### INDUSTRY PANEL DISCUSSION

***Why do you believe the industry is just now focusing their attention on decentralized trials?***

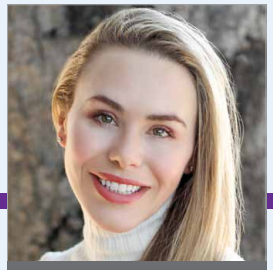
*David Coman, Science 37*
The benefit of decentralization has always been there, but sponsors have been nervous to take the leap. In today's environment, with limited access to sites, sponsors can't afford not to move in that direction. The decentralized environment has more continuity throughout the patient journey because it's not dependent on sites being open.

*Michelle Longmire, Medable*
Necessity is the mother of invention and adoption. When COVID-19 hit and sites started closing worldwide, we launched a partnership to keep ongoing trials moving. There's a drive and interest to deliver trials directly to patients. I think we're going to continue to see rapid adoption.

***What does a decentralized strategy offer that a traditional model doesn't?***

*Trinette Mitchell, Takeda*
I think a decentralized trial strategy really helps us recognize some of the long-term goals that we've had as sponsors in the industry, which is to extend the reach to patients regardless of their geography. Many sites are far from our patient populations. Our vision for decentralized trials is to expand that reach. From the viewpoint of a sponsor, we can also deploy devices or different types of wearables and that gives us continuous access to data. Maybe there's something in the patient care that's happening off-site that


David Coman
Science 37


Michelle Longmire
Medable


Trinette Mitchell
Takeda Pharmaceuticals


Brittany Erana
PPD


Niklas Morton
PPD

we wouldn't have previously had access to. By looking at that data, we might get more information about the disease state or even identify a digital biomarker that we want to measure. That could propel treatment forward for the solution to that disease state.

*David Coman, Science 37*
If you look at a world where there's no geographic limits, you essentially get access to any patient anywhere. I think that's the first huge benefit. The second would be enrolling patients faster in a decentralized environment relative to a typical site-based environment. Then it's about being able to keep those patients throughout the trial and the ability to access a more representative and diverse patient population. It's really democratizing clinical research to bring it to everybody. If you look at the current environment, being able to access patients anywhere is particularly important.

> Ultimately, everything goes back to the patient. Instead of thinking about a site as the center of the universe, you start thinking about the patient as the center of the universe and think about how everything extends out from the patient.

### *Are there specific synergies created by pivoting to decentralized trials?*

*Trinette Mitchell, Takeda*
Telehealth has been an easy thing that we've been able to deploy. And, of course, the change in regulations because of COVID-19 has supported us being able to pivot the way we work. There are more things we need to think about and consider, like removing the brick and mortar site, that we're not ready for yet. But we know everything that we do today is taking us closer to that goal. One thing we do on a regular basis is stay in contact with our patient populations. What's the patient looking for? What is the true burden to a patient in a clinical trial? It may not be what comes to mind for all of us and we're learning that it's different depending on the patient population. We're laying the foundation now to deploy a fully decentralized trial with eConsent and telehealth and supporting our trials with wearable devices.

### *Is there an increase in data collection or quality that is attributable to running a decentralized trial?*

*Trinette Mitchell, Takeda*
We hope so. As a sponsor, this is always what we're looking for—increased data collection and better quality. We're trying to answer that question by thinking about journey mapping and the patient perspective. Can we understand when they stop entering data? We're also looking at different touch points and incrementally removing pain points that, in turn, will help us have better data collection. Having good technology partners and thinking about how we can streamline the interaction between the patient, the site, and the technology.

### *Are there other related strategies that contribute to the success of a decentralized trial?*

*Michelle Longmire, Medable*
Clinical trials are a very complex process, but at a fundamental level you have a patient who is looking to receive healthcare from a physician. Sometimes we lose sight of this, but this is the essence of what the patient's expectations are, in addition to participating in an important research endeavor. The key to any clinical trial is delivering the best that healthcare has to offer. Decentralized trials offer convenience and improve access, but patients still want a relationship with the provider and to feel that they're receiving high quality healthcare. It's important to generate that patient-physician relationship and deliver high quality healthcare when using new modalities and methodologies. What we've seen is that telemedicine, and decentralization in general, can facilitate better and more patient-physician interaction, but you must keep communication channels open and provide enough education.

*David Coman, Science 37*
You've got a whole industry that's spent decades on the site-based model—doing it and always trying to improve. When you think about a decentralized model, you need to look at everything differently. You need to think about the protocol, data integrity, and how to collect the same kind of data that you'd get at a brick and mortar site. You need to think through logistics like direct shipment, nurse coordination, and standard operating procedures. Repetition is important to success, just like in the old model.

### *Who are the stakeholders that need to be considered in a decentralized trial design?*

*David Coman, Science 37*
We're an industry that, historically, focused on sites as the primary stakeholders. You need to pick the right sites; you need to make sure you have enough sites and think about all the logistics. That paradigm is changing. Ultimately, everything goes back to the patient. Instead of thinking about a site as the center of the universe, you start thinking about the patient as the center of the universe and think about how everything extends out from the patient. It creates a different dynamic where we can work with the patient from the comfort of their own home and make it as easy as possible for them from the very beginning.

*Michelle Longmire, Medable*
Ultimately, we're delivering healthcare to patients who are part of a clinical trial. Part of that equation is the investigator or the physician, as well as the clinical team delivering care. This new model requires a tremendous amount of consideration for how we deliver care in the patient's

home. How do we collect high quality data and how do we ensure that the providers are well trained? The patient is the primary stakeholder, but you have several additional stakeholders from the clinical team, the sponsor, and the contract research organization (CRO) who are also involved in the study.

***Do you see decentralized trials as a short-term solution? Or, as a sustainable, long-term strategy?***

*Michelle Longmire, Medable*

There's been a shift in the way we conduct clinical research. A lot of the conversations around COVID-19 and life sciences and clinical trials have focused on the shift in sponsor adoption, which has been momentous largely out of necessity. But, if you look to the broader trends in healthcare delivery that this has facilitated, it's more of a consumer mindset around technology that's been available for a while even if we haven't adopted it. Look at telehealth and remote healthcare. People are seeing how care can be delivered directly to them conveniently and efficiently. Not only is this a long-term shift born from necessity, it's created an important behavior shift for patients as consumers trying to understand the accessibility and benefits of remote healthcare delivery. I think this is going to lead to a dramatic shift for decentralized trials and patient healthcare delivery in general.

***Will the adoption of decentralized trials continue to increase? Do you think this is due to sponsor preference, patient demand, both, or something else entirely?***

*Trinette Mitchell, Takeda*

If we can demonstrate value to both the patient and the sites, that will help increase adoption. I think there is willingness to use technology, so the promise of what that can bring to data collection, and the opportunity to identify digital biomarkers, are reasons why sponsors are interested. I really think it comes down to value and being able to demonstrate it.

***Looking ahead, how do you see decentralized trials continuing to evolve? What are other predictions you have and what should we be looking out for as an industry?***

*Trinette Mitchell, Takeda*

At Takeda, our evolution must be holistic. Our internal procedures need to radically change, and we need to look at how we're reaching some of our goals. We all know that we need to collect data, and technology can change how we do that, but we don't need to use the same processes and procedures. How can we reimagine interacting with a patient? How do we change the data flow and still meet all our obligations?

*David Coman, Science 37*

I think most trials will have some form of decentralization in the future. It's about democratizing clinical research. Studies can't wait for the pandemic to end and patients certainly can't wait. We're in the process of going virtual today.

*Michelle Longmire, Medable*

As a physician, I think the standard healthcare delivery model leaves a lot to be desired. People want better treatment options. If we collectively execute our vision for decentralized trials, we could make this healthcare delivery model better and more desirable for patients. I see the future of clinical trials as a care option, largely enabled through a decentralized trial approach, where we can deliver new therapies directly to patients.

**PART 2**

## PPD EXPERTS ANSWER YOUR QUESTIONS

***What evidence or benchmarks of operational success can you share?***

*Niklas Morton, PPD*

We are continually focused on understanding the metrics of operational success and the value that these types of trials can bring. No two studies are alike, but we're seeing positive trends. The key measures of operational success are patient recruitment and patient retention. In that regard, we've seen the decentralized trial model deliver enrollment rates that are three to five times the enrollment witnessed in the traditional setting. We're also seeing high retention rates, around 90%, which could be 20% to 30% higher than the traditional setting.

***There seems to be a lot of considerations and moving parts. How do we get started in developing a decentralized strategy?***

*Brittany Erana, PPD*

There's a lot to think about, but if you identify an internal team to engage with external experts, they can review your protocols and work through simple changes to the schedule to reduce the number of on-site visits and allow others to be conducted at home. As an initial step, you can ask about technology and resources available to support remote visits, considering what it would look like from the patient's perspective. This can help you and your team see where decentralized trial design can bring the most benefit to your organization, indication, and therapeutic area. Getting into the space, workshopping a few protocols, and seeing what questions and ideas surface is key.

***How far in advance should we be thinking about or planning for digital trials? Are there situations where it's too late to make the transition?***

*Niklas Morton, PPD*

I don't think it's ever too late, as COVID-19 has shown. When planning for the incorporation of decentralized trial options, earlier is always better. By doing so, it allows you to engage all stakeholders and get their buy-in so you can properly educate and inform patients. For the sponsor who's in the midst of developing a protocol, it's a matter of getting ahead of any obstacles that would impact timelines. With digital enablement, we are seeing data capture happen earlier. Overall, by laying this sort of

groundwork there's an opportunity to have it easily woven into subsequent protocols.

### *Are there limitations for certain phases of development or therapeutic areas?*

*Niklas Morton, PPD*
This is a really common question circulating in the industry. There are some theories about where these approaches are more established or might be more accepted by stakeholders, like post-approval and observational trials or long-term follow-up studies. However, as a sponsor, it's less about the indication and more about the study design itself and whether or not the center of the trial could be shifted from the site to the patient. If you design clinical trials to mimic the approach that physicians and patients are used to, it's an easier lift.

### *Is there any difference between the different terms floating around in the industry—telemedicine, TeleVisits, telehealth, remote visits, virtual care, Metasites, etc.?*

*Brittany Erana (PPD)*
Yes, there are some differences and nuances to terms such as "telehealth" and "televisits," but if you're getting started in this space don't worry about the technicalities. You're going to get the point across when you're using these terms in the context of clinical research. They all convey the concept of remote engagement between a physician and patient using fit-for-purpose, video-enabled communication tools.

### *My organization is evaluating a handful of technology vendors. What criteria is the most important to measure them against?*

*Brittany Erana (PPD)*
Two criteria come to mind. First, look for an integrated platform that offers a seamless experience for patients and site users. Secondly, if you don't currently have in-house digital implementation subject matter experts, or a CRO partner that can support the design and operations, be on the lookout for a tech vendor that demonstrates a strong understanding of your protocol and can explain in detail how their platform will be designed to support it.

### *How can we assure quality and adherence to regulations when things are changing every day?*

*Niklas Morton (PPD)*
Regulations are certainly changing—or rather, adapting—as the industry evolves in its approach to trials. For instance, we've witnessed regulatory bodies providing updated and timely guidance on decentralized trial conduct. Today, most companies have a process to stay up-to-date with regulations and disseminate information across their organization while ensuring that the processes and study deployments meet those expectations. I know that within PPD, our digital and regulatory teams are aligned and work together to keep our internal knowledge management system up-to-date on elements of a decentralized trial, including regulations on a country-by-country basis.

### *Are there any incremental steps we can take to help promote hybrid or decentralized trials across our portfolio?*

*Brittany Erana (PPD)*
It seems simple, but one of the initial steps is moving away from paper and increasing electronic options such as eCOA and remote eConsent. These types of options have been around for decades, yet patients are routinely sent home with paper diaries or asked to digitally sign paperwork in an office. Capturing this data both remotely and electronically is one of the easiest places to start. Think about it—whether or not the patient is at the site completing eConsent or hundreds of miles away, a digital signature is a digital signature in both cases. Many of these platforms are 21 CFR Part 11 compliant and adhere to strict data and privacy principles.

Setting a goal for your organization can help shift the mindset from "this is how it's always been done" to "how can we do it differently?" This creates an environment that's more open to the innovation that's required with decentralized trials.

### *How do I balance the risk associated with the ongoing pandemic (including impacts to traditional models) versus taking on a new, decentralized trial model?*

*Niklas Morton (PPD)*
There's always a chance by remaining unchanged and maintaining your current, traditional protocol, you end up seeing lower recruitment rates across sites as more and more patients become more hesitant to visit sites. This is an incredible risk as it would put research timelines in jeopardy. Historically, teams have been hesitant to "risk swap" and go with a new or novel solution. However, during these times, sponsors have started to see hybrid and decentralized trials as a positive way to reduce risk. At the core of this decision is opportunity cost.

### *With digital and decentralized trials gaining momentum, does this mean we won't need investigator sites? What does their new role look like?*

*Niklas Morton (PPD)*
At this point, I don't think digital or decentralized trials make investigator sites redundant. Investigators and coordinators are still needed to conduct research and support patients—whether near or far. The reality is that there's no one-size-fits all answer. At this time, we are seeing more hybrid or digitally enabled studies where there still might be some in-person visits needed for key milestones. We are just starting to see the beginning of this evolution, and we are seeing it with healthcare providers as well. So, while more visits may become virtual in nature, investigators, like physicians, will still be needed. Their role is evolving and we will need to see where that goes over time.

> We've seen the most success when all stakeholders are engaged, asking questions and being proactive early on. This helps lay the foundation for success.

***How can we make sure patients and caregivers are adequately trained on any new technology and equipped with the right devices? Have you seen a significant learning curve?***

*Brittany Erana (PPD)*

Training a patient or caregiver on the proper way to wear a smartwatch or how to navigate an app is crucial. As with anything new or different, there's a learning curve, so it's necessary to have an education strategy that takes the patient experience into account. There's also a nuance between training and education when it comes to compliance and data quality. For example, we can train a patient how to navigate an app to log a migraine, but it's just as important to educate them on the value of logging that migraine in real time and answering all the questions in their diary, particularly the ones about pain or discomfort.

How you train and educate patients depends on the technology and the patient population. Some patients will do fine with a train-the-trainer approach. Some will benefit from interactive videos or an illustrated guide. It's important to find a partner that can design the education and training program with the patient experience in mind.

***My organization has set goals to increase patient diversity for the clinical trials we are recruiting for in the United States. Could decentralized trials help address that?***

*Brittany Erana (PPD)*

Decentralized trials in the United States typically recruit anywhere from 30% to 60% of patients from Black and Hispanic communities, compared to the 2% to 10% that we see in traditional studies. Certain obstacles like access to transportation, the financial impact of taking time off work during standard business hours, and childcare needs can hinder efforts to increase minority participation in traditional trials. A model where some visits can be conducted remotely allows patients to participate from home during non-working hours or on weekends, and this model is certainly a key component of a broader strategy to increase patient diversity in trials.

***What recommendations do you have for sponsors looking to engage in design and implementation of such trials for the first time?***

*Niklas Morton (PPD)*

We've seen the most success when all stakeholders are engaged, asking questions and being proactive early on. This helps lay the foundation for success. Identify internal experts and partners to help with the design, operational execution, and technology so you can confidently demonstrate the processes and get people on board.

***Are sponsors designing these studies on their own and asking CROs like PPD to implement, or are you designing the studies for sponsors?***

*Brittany Erana (PPD)*

Sometimes we see protocols come in with a "pre-baked" hybrid or decentralized approach and other times we're asked to layer a digital or decentralized strategy on top of a traditional strategy. In the second scenario, a team of consultants will do a deep dive and suggest changes to the protocol to reduce patient and site burden, which technology or device will work best for the patient population, the assessment schedule, study objectives, and recruitment strategies. We've also had sponsors do their own assessment and look to us to validate their approach and optimize the protocol to further reduce patient burden.

***How do you incorporate hybrid in oncology trials where some of the visits occur on site with IP delivery? What are your thoughts?***

*Niklas Morton (PPD)*

This is certainly a common question. It really depends on the Investigational Product (IP) itself, the route of administration and the other protocol requirements, such as the need for scans which might require a site visit. In most cases, it's uncommon for sites to need to administer IP at each visit. Patient burden can be reduced using a hybrid model where visits outside those requiring IP administration are conducted remotely. In fact, the most frequently administered oncology drugs tend to be oral. When that's the case there is an opportunity for the patient to participate from the safety of their home through a combination of direct-to-patient (DTP) logistics and remote support from the site. ■

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*For more information, please contact godigital@ppd.com.*

**David Coman, MBA,** is the chief executive officer at Science 37 and is focused on furthering the company's mission to accelerate biomedical research by putting patients first. In pursuit of its mission, Science 37 makes it easier to participate by connecting patients with doctors and nurses through telemedicine visits and home health screenings, then managing trial logistics from an integrated, comprehensive platform. In an era when 85% of all traditional trials experience delays and capital costs have more than doubled over a 10-year period, Science 37's decentralized model is reimagining biomedical research to get more life-enhancing medicines to patients faster. Prior to joining Science 37, Mr. Coman led the data and analytics business at ERT after serving as the company's chief strategy officer. He also previously worked for Quintiles (now IQVIA) as chief marketing officer and founder of its Digital Patient business. Mr. Coman earned his BA in advertising from Michigan State University and his MBA in marketing, entrepreneurship, and finance from the Kellogg Graduate School of Management at Northwestern University.

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**Michelle Longmire, MD,** is the founder and chief executive officer of Medable. Dr. Longmire is mission driven to accelerate the development of new therapies for disease. As a Stanford-trained physician-scientist, Dr. Longmire identified critical barriers to drug development and founded Medable to pioneer a new category of clinical trial technologies that remove traditional roadblocks to participation and radically accelerate the research process. Medable is now the industry leader in decentralized and direct-to-patient research, serving patients in clinical trials in over 30 languages, 40 countries, and across all therapeutic areas. In addition to having raised over 40 million dollars in venture capital and driving Medable to an industry-leading position, Dr. Longmire has received recognition as a leading innovator and businesswoman, including being named as one of the 100 most creative people in business by Fast Company.

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**Trinette Mitchell** is head of clinical trial innovation at Takeda Pharmaceuticals where she leads a team focused on eClinical trial tools for decentralized trials. With a background in clinical data solutions and partnership management, Ms. Mitchell has a talent for transforming the business process through the implementation of innovative technology.

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**Brittany Erana, MPM,** is responsible for setting the vision and designing the operational infrastructure and capabilities necessary to successfully deliver decentralized and digitally enabled clinical trials while upholding quality. Ms. Erana brings more than 15 years of broad industry experience in global research operations and strategy and digital implementation project and program delivery. She holds a bachelor of arts in psychology from East Carolina University, a master's degree in project management from Western Carolina University, and a certificate in international business from University College Dublin Smurfit Business School.

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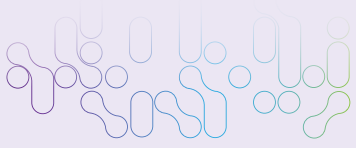
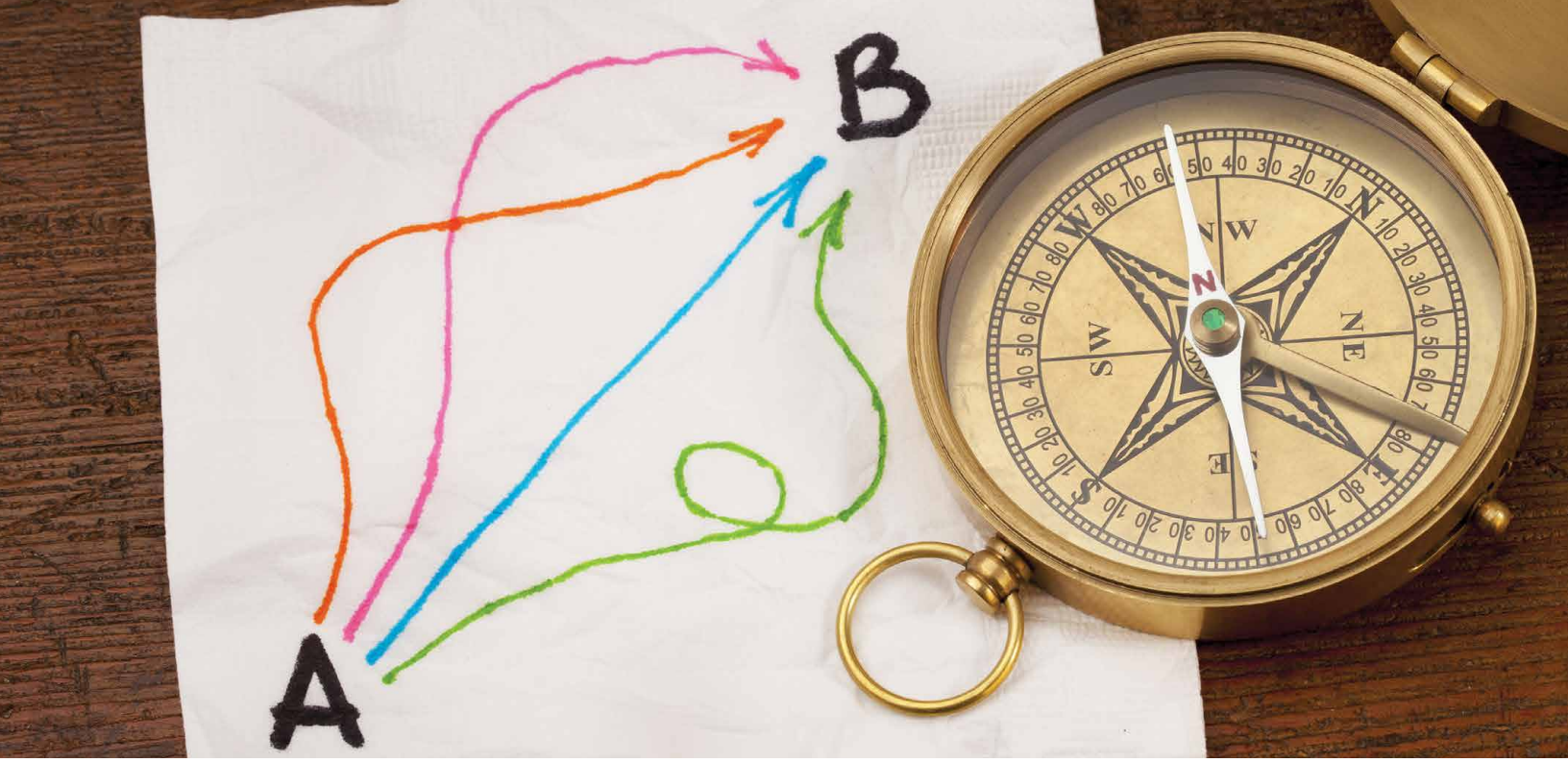
**Niklas Morton, MSc,** oversees the operations and delivery of digitally enabled and decentralized/ virtual studies, along with PPD's robotic automation capabilities. Prior to his most recent appointment, Mr. Morton was senior vice president of site and patient access, overseeing the site intelligence and activation, strategic feasibility, strategic site collaboration and clinical innovation teams. Since joining PPD in 1998 as a biostatistics manager, Mr. Morton has advanced through various roles of increasing leadership and responsibility within the company. He earned a master's degree in medical statistics from the University of Leicester and a bachelor's degree in statistics from the University of Glasgow, both in the United Kingdom.






# Incorporating Innovation into the 505(b)(2) Development Pathway

Brendt Stier, MS
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Value & Development Consulting
Evidera, a PPD business

## Introduction

It is very common for a biotech or biopharma company to change or improve existing drugs by creating a new formulation or dosage. In these cases, a new drug application (NDA) can often use the wealth of existing data, with a focus on specific new required studies.

Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act[1] gives the United States Food and Drug Administration (FDA) express permission to rely on data not developed by the NDA applicant, such as full reports of safety and effectiveness. It may also rely on FDA findings of safety and effectiveness to the extent that the proposed drug product shares characteristics with the listed drug. This makes the 505(b)(2) pathway appealing as it helps avoid unnecessary duplication of studies already performed on a previously approved drug and can result in a less expensive and faster approval compared to traditional development paths such as 505(b)(1). One caveat is the applicant must demonstrate that the bridge between the proposed drug product and the listed drug is scientifically justified, which is where challenges can occur.

In this whitepaper we discuss how innovation can help develop the bridge needed for 505(b)(2) approval, compare traditional and streamlined approaches to clinical development, and discuss how to save money and time with hybrid protocol designs. We also use a case study as a real-world example of how innovative solutions to development strategies can reduce costs and timelines.

## Pathways to New Drug Approval and Typical Development Studies

There are three possible pathways for NDAs, and each requires different development studies (See Figure 1).


Brendt Stier

**505(b)(1)**: this is the traditional pathway for an NDA. Studies used in this pathway include first time in human trial, clinical pharmacology package, Phase IIa/IIb studies, and Phase III studies. A traditional program under the 505(b)(1) pathway could take five years and cost several hundred million dollars.

**505(b)(2)**: this is an abbreviated pathway and the typical development studies are much smaller. By referencing available safety and clinical data from an approved product, a pharmacokinetic (PK) bridging study can investigate either the new formulation or new route of administration compared to the approved product and establish bioequivalence. In some cases, clinical pharmacology studies or food-effect studies will be needed. For example, an orally administered drug might need an alcohol dose-dumping study. FDA approval hinges on the pivotal bioequivalence study.

**505(j)**: this pathway is used for drugs that are identical to a referenced listed drug (RLD). Studies employed in this pathway include a fasted bioequivalence study, fed bioequivalence, adhesion studies, and specific dermatological studies.

## Bringing Innovation to 505(b)(2)

Receiving approval through 505(b)(2) requires not just a detailed process but a 30,000-foot view of the landscape. Drug manufacturers tend to focus solely on the approval process and don't see what other studies may be needed for their development pathway and how they can differentiate their product from what is already approved. This is where a comprehensive strategy that looks at what data is available and how to obtain the most robust data from the outset can play an effective role in achieving approval while reducing timelines and costs.

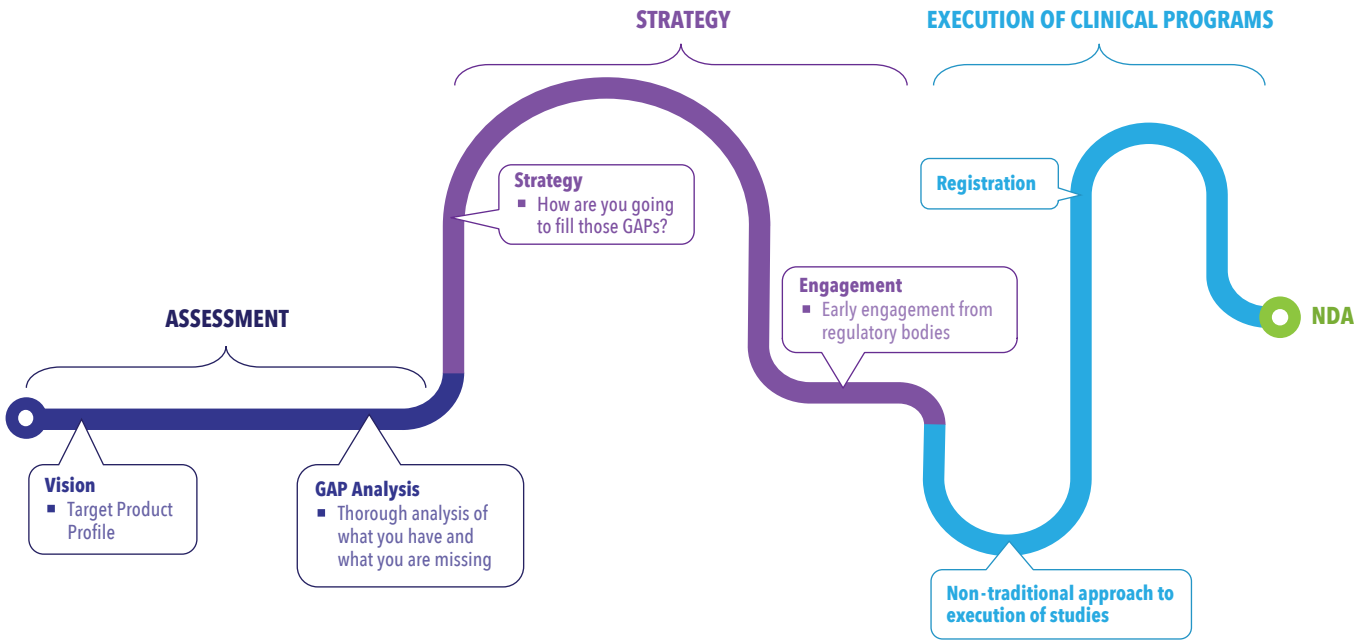
In reviewing the 505(b)(2) NDA approvals for 2019, 64 drugs were approved, 45% of which were new formulations or new manufacturers, and 25% involved a new dosage form.[2] The balance are new combinations (8%), new molecular entities (8%), new active ingredients (6%), unknown (6%), or already marketed (2%). The challenge for drug developers is referencing the right existing studies and conducting the new studies needed to show bioequivalence with the already approved drug.

Changing a formulation or dosage can create some challenges to the 505(b)(2) pathway. A five-year retrospective analysis of drugs approved via the 505(b)(2) pathway showed over 80% of new dosage forms or new formulations included a bioavailability/bioequivalence (BA/BE) study and nearly 100% included food-effect (FE) studies.[3] Alcohol dose-dumping studies were included in 72% of extended-release formulation NDAs.[3] Older drugs that are repurposed or changed may not have had proper clinical pharmacology (i.e., drug-drug interaction (DDI) or FE) studies at the time of approval; therefore, FE or DDI studies may need to be completed. While the clinical-pharmaceutical packages may still be relevant, trials

Figure 1. Summary of Approved Pathways

| Application Type | Typical Development Studies |
|---|---|
| 505(b)(1) | • First Time in Human (FTIH) study<br>• Clinical pharmacology package<br>• Phase IIa/IIb study<br>• Phase III study (can be multiple depending on endpoints and therapeutic area) |
| Typical 505(b)(2) | • Reference available safety and clinical trial data<br>• Perform a PK bridging study to investigate new formulation or route of administration compared to approved product<br>• May include food effect study if orally administered<br>• Pivotal bioequivalence study |
| 505(j) | • Fasted bioequivalence<br>• Fed bioequivalence<br>• Adhesion PK study<br>• Specialty dermatology studies |

**Figure 2.** Integration of Innovation Throughout the NDA Process




will need to be performed if they are not referenced in literature. The biggest challenge is going back and finding the information in the literature; if the information cannot be found, and therefore referenced, it needs to be created. That is where innovation comes into play.

Looking at the process of NDAs from start to finish, integrating innovative thinking into the assessment process early, and continuing that perspective through the strategy and execution stages, can have a direct impact on your program from the beginning to the end. (See Figure 2).

## Assessment

Due diligence in the assessment stage will pay off in the long run. In this stage, a vision for the product is established through the creation of a target product profile (TPP). The patient population for the drug is identified as well as how it will be differentiated from other drugs on the market. Differentiation is not only key to marketing the drug but to developing the drug. In the assessment stage, it is important to identify how to fill the gaps that are missing from what is available on the market. A robust gap analysis established early on provides a roadmap for moving forward with development of the drug. Without this step, companies can become focused on getting the drug into clinical trials without recognizing they need to augment the available referenced data with new data that may be needed to fill in the development gaps of the program.

## Strategy

Forming a comprehensive strategy utilizing available information, new information, and innovative study designs can help expedite development timelines. The strategy phase is used to determine how the gaps identified in the assessment phase will be filled. This might be through bridging toxicology, PK studies, or clinical studies. Pulling all this information together in a very comprehensive strategy early on is key to success in the 505(b)(2) pathway.

One step in the strategy phase that many companies miss is taking advantage of engagement with the FDA. A pre-investigational new drug (Pre-IND) meeting is a way to engage with the FDA early and mitigate risk. Regulatory bodies are open to innovative approaches as long the rationale in the development plans can be justified. The Pre-IND meeting should be used to lay out the strategy and seek agency agreement of the plan to help mitigate risk. Through this process manufacturers are able to get a better understanding of what regulatory bodies are looking for in the approach. This can help drug developers avoid spending money on research that would ultimately be rejected.

## Execution of Clinical Programs

In the execution phase, an innovative, streamlined approach can save money and time compared to a traditional approach. The traditional approach for clinical development is less risk averse, following a sequential path and waiting for results to be available before moving on to the next study. It is a longer development pathway, and costs tend to be higher due to the cost of each study and the fact that during wait time no revenue is generated. In essence, it is development "white space." The more time spent developing a compound, the less time that compound is on the market generating profit.

A streamlined approach is one that can be especially advantageous for smaller companies and companies looking to get on the market quicker because the

development time is shorter. In a hybrid trial, multiple studies are combined under one protocol. There is some potential for higher risk, but it can be mitigated by implementing go/no-go criteria through adaptive design and other tools.

The FDA has shown they are willing to move forward with these hybrid trials, as long as risk mitigation is well defined in the protocol. A hybrid trial is going to be less expensive than several larger trials and will take less time. By decreasing timelines in development, white space is decreased, resulting in long-term savings.

## Five Elements for Streamlined Hybrid Protocol Designs

Having a well-planned protocol can help mitigate concerns among regulatory bodies and institutional review boards when executing hybrid protocols. These five elements should be included in most designs:

1. **Safety Review Committee**: responsible for reviewing the data and making key safety decisions
2. **Dose escalation criteria**: details if certain criteria occur, the product dose is deemed safe by a medical monitor and the medical criteria in the Safety Review Committee and the dose can be escalated
3. **Stopping criteria**: outlines the conditions that will determine when the study will be stopped or the dosage lowered based on safety and pharmacokinetic data
4. **Decision tree**: shows how decisions will be made
5. **Data analysis plan**: establishes when and how the data will be reviewed and by whom, if the review will be blinded, how to maintain the blind, etc.

## Timeline Comparison: Traditional vs. Streamlined 505(b)(2) Development

If we compare the timeline of a traditional approach with a streamlined approach for a 505(b)(2) study, the traditional approach takes approximately 30 months while the streamlined approach takes 15 months (See Figure 3). The traditional approach includes a PK bridging study that will be stopped and started, an FE study, and a pivotal BE study. In this approach, the company waits for each study to be completed before moving on to the next study. It is clearly a longer pathway.

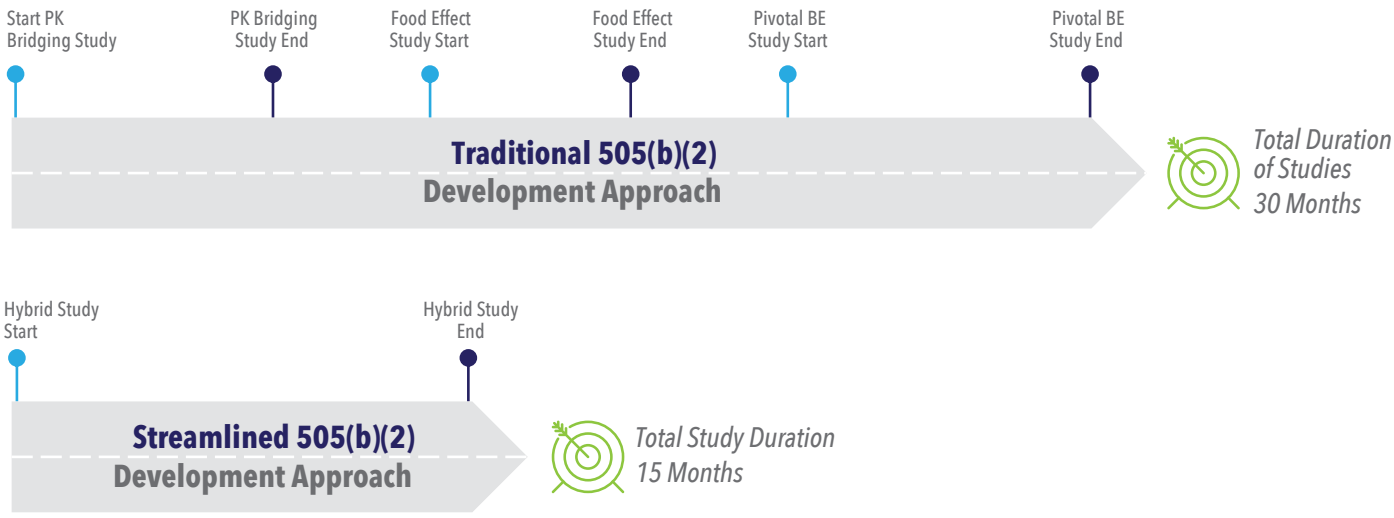
The streamlined pathway utilizing a hybrid study combines several parts into one protocol. For example, hybrid studies can include PK bridging, FE, and pivotal BE studies simultaneously, cutting the timeline in half. This streamlined pathway has been used successfully with several clients. By running the hybrid study at one time, subjects can begin very quickly and each segment of these studies can be turned around rapidly with the analysis and interim analysis. There is no time spent waiting for separate reports and separate protocols for each study. The development timeline is shorter and costs less because it is done as one study.

**CASE STUDY**

## A Streamlined Approach for 505(b)(2) Development

One example to demonstrate streamlined development focuses on testing of a new formulation for a drug with better taste tolerability. Drug A was the only drug on the market for a specific disease, but the taste was awful and patients did not like taking the drug. The client was considering doing three studies:  a taste assessment study with four formations to see which tasted better, a PK study

Figure 3. Traditional Versus Streamlined Development Timelines



to determine which formulation had the best PK profile, and a pivotal BE study to see how it compares to what was on the market.

We proposed a hybrid study instead where Part A of the study was taste assessment with a small-run PK study to see if the formulation changes the PK. If they are all the same, then Part B would take the best formulation from Part A and conduct the pivotal BE study. By utilizing a streamlined protocol, we were able to demonstrate bioequivalence and this data was used in our client's submission to the FDA.

This approach saved the client a significant amount of time and resulted in cost savings. They were able to go to the FDA quickly, and the FDA appreciated that they were able to see each of the steps, how well they were defined, and that the criteria to move from Part A to Part B was very clear. If our client had gone with the traditional approach, they would have done three separate studies, taken at least twice as long to conduct the study, and there would have been greater costs.

## Conclusion

A traditional approach is not the only way to achieve NDA approval using the 505(b)(2) pathway. Bringing innovation to all stages of the development strategy can streamline the process in the assessment stage when determining what is needed, in the strategy phase as you decide how to demonstrate the bridge between the proposed drug product and the listed drug, and in the execution of the trial. By going to the FDA early on with your plan, risk can be mitigated and the agency has shown it is willing to accept hybrid studies as long as the protocol is clearly defined, and all the components are there. In considering a 505(b)(2) pathway, taking a step back to consider all available options, including thinking outside the box, can open up novel solutions to development, ultimately leading to expedited timelines, increased time on market, and overall greater success for both patients and companies. ■

*For more information, please contact Brendt.Stier@ppd.com.*

## REFERENCES

1. US Food and Drug Administration. Guidance Document: Applications Covered by Section 505(b)(2). December 1999. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/applications-covered-section-505b2. Accessed October 6, 2020.
2. Camargo Blog. 2019 505(b)2 NDA Approvals in Review. Available at: https://camargopharma.com/resources/blog/2019-505-b-2-nda-approvals-in-review/. Accessed September 8, 2020.
3. Freije I, Lamouche S, Tanguay M. Review of Drugs Approved via the 505(b)(2) Pathway: Uncovering Drug Development Trends and Regulatory Requirements. *Ther Innov Regul Sci.* 2020 Jan;54(1):128-138. doi: 10.1007/s43441-019-00036-y. Epub 2020 Jan 6.

# Evidera's Presentations at ISPOR 2020 Europe Virtual

## WORKSHOPS

Cost-Effectiveness Modelling of Complex Pathways

Faria R, Fenwick E, **Tosh J**, Albrow R

Is Population Adjustment Enough to Reduce Bias in Unanchored Comparisons of Progression-Free Survival in Oncology? The Importance of Dealing with Progression Assessment Time Differences

**Kapetanakis V**, Bharmal M, **Ishak KJ**

## ISSUE PANELS

**IP3:** The Meaning of Cure - The Search for What?

**Ishak KJ**, Latimer NR, Ryll B, **Benedict A**

**IP8:** Integrating Patient Preference into Health Technology Assessment: Can Patient Preferences be Incorporated into the ICER?

de Bekker-Grob E, Bouvy J, Dzingina M, **Marsh K**

## PODIUM PRESENTATION

**CV2:** Patients' Preferences for Once-Daily Oral Versus Once-Weekly Injectable Diabetes Medications: The REVISE Study

Boye K, **Ross M**, Mody R, Konig M, **Gelhorn H**

## POSTERS

### PBI: BIOLOGICS/BIOSIMILARS/ REGENERATIVE MEDICINE

**PBI5:** An Indirect Comparison of Sustained Remission and FLARE Rates in Responders with NON-Radiographic Axial Spondyloarthritis (NR-AXSPA)

Kiri S, Kim M, **Betts MB, Chitnis MK, Turner M, Fahrbach K, Tarpey J**

**PBI56:** Psychometric Validation of the P-SIM, a NOVEL Patient-Reported Outcome Instrument for Patients with Plaque Psoriasis

Warren RB, Gottlieb AB, Merola JF, Garcia L, Cioffi C, Peterson L, **Pelligra C**, Ciaravino V

### PCN: CANCER

**PCN65:** Economic Impact of First-Line (1L) Immunotherapies in Advanced/Metastatic Non-Small Cell Lung Cancer (NSCLC): A Systematic Literature Review (SLR)

Sarri G, **Freitag A, Kazmierska P**, Lin B, Pawar V, Zhang X

**PCN66:** The Health Economic IMPACT of Number of Cancer Types Detectable by a MULTI-Cancer EARLY Detection (MCED) Test

**Tafazzoli A**, Quon P, **Shaul A, Chavan A**, Chung KC, Kansal A, Fendrick AM, Ramsey SD

**PCN71:** Cost-Effectiveness of Brentuximab Vedotin for the Frontline Treatment of Peripheral T-Cell Lymphomas in Canada

**Zou D**, Lee J, Kansal A, Ma W, **Harris M**, Lisano J, Fenton K, Yu-Isenberg K

**PCN79:** Modeling Approaches in Cost-Effectiveness Analysis (CEA) of First-Line (1L) Immuno-Oncology (IO) Therapies in Non-Small Cell Lung Cancer (NSCLC): A Systematic Literature Review (SLR).

**Kongnakorn T**, Walker A, Sarri G, **Freitag A, Marczell K, Kazmierska P**, Masters E, Pawar V, Zhang X

**PCN107:** Considerations and Challenges for Economic Modeling in NON-Metastatic NON-SMALL CELL LUNG Cancer (NMNSCLC)

**Milev S, Harris M**, Quon P, Vo L, McKenna M, **Sun A**, Chaudhary MA, Penrod JR, **Sorensen S**

**PCN154:** Budget Impact Analysis of Subcutaneous Daratumumab for the Treatment of Patients with Multiple Myeloma in Sweden

**Toro-Diaz H, Li S**, Morano R, Tambour M, Dansk V, Lam A, Slavcev M

**PCN182:** Estimating the Number of US Patients with Multiple Myeloma (MM) at 5 or More Lines of Treatment (LOT)

**Nikolaou A**, Maiese EM, Samyshkin Y, Sansbury L, **Oguz M, Cid Ruzafa J**, Sapra S, **Kapoor R**, Wang F

**PCN187:** Design Innovation for Efficient Post-Approval Drug Utilization and Effectiveness Studies

**Saragoussi D, Rouleau A, Capart P, Deveras CC, Brett N,** Ognar R, **Gazay H, Payne K**

**PCN293:** Understanding Real-World Experiences and Impacts of COVID-19 on Patients with Breast Cancer: A Social MEDIA Listening Analysis

**Halhol S, Raluy-Callado M, Oguz M, Booth A**

**PCN302:** Using Health Related Social MEDIA to Understand Experiences of Adults with LUNG Cancer in the Era of Immune-Oncology and Targeted Therapies

**Booth A,** Manson S, **Halhol S,** Merinopoulou E, **Raluy-Callado M, Hareendran A,** Knoll S

**PCN319:** A Systematic Review of Discrete Choice Experiments in Oncology: Status-Quo and Implications

**Collacott H,** Soekhai V, **Thomas C, Brooks A, Brookes E,** Lo R, Mulnick S, **Heidenreich S**

## PDB: DIABETES/ENDOCRINE/METABOLIC DISORDERS

**PDB68:** Maximum-Likelihood Estimation of Transition Probabilities between Fibrosis Stages in Nonalcoholic Steatohepatitis (NASH)

**Gal P, Rakonczai P**

**PDB74:** Unmet Needs of Patients with Type 2 Diabetes and the Value of Achieving Near Normoglycemia: A Qualitative Study

**Gelhorn H, Balantac ZL**, Shinde S, Thieu VT, Boye KS

**PDB79:** Patient and Caregiver Preference Ranking of Glucagon Treatment for Severe Hypoglycaemia from Spain- Initial Results from a Discrete Choice Experiment

Artime E, Mitchell B, **Shaffer S Chua GN, Rentz A**

## PIH: INDIVIDUAL'S HEALTH

**PIH19:** Success Factors for a Nice HTA Experience in Paediatrics

**James S, Gruber P, Vilu HL, Martin M**

## PIN: INFECTIOUS DISEASES

**PIN11:** A Generic Simple Model to Assess Candidate Vaccines in Development

**Roiz J, Sutton K, Chapman R**

**PIN34:** COVID 19 - What Is the Health-Economic Economically Justifiable Price of Lockdown?

**Gani R, Brown L, Kapoor R**

## PMU: MULTIPLE DISEASES

**PMU37:** Towards Joint Decision Making- The Need for a Framework to Address Asymmetrical VALUE

**Parkinson M, Olid Gonzalez A**

**PMU38:** Considerations for Companies and Healthcare Systems for Managed Entry Agreements: A Review of the Recent Trends across Italy, Spain and the UK in Oncology

**Vanoni C, Parkinson M, Olid Gonzalez A, Iliadi Alexiou A**

**PMU44:** Can Price-Prevalence Trends be Used to Guide the Pricing and Reimbursement Strategy for New Orphan Drugs? A Two-Country Case Study

**Vanoni C, Laughlin W, Rakonczai P, Katsoulis IA, Bending MW**

**PMU55:** Methods and Acceptability of Comparator Arms for CAR-T HTA Submission

**Chapman R, Kovacs V, Sorensen S**

**PMU90:** Exploring Symptoms, Impacts, and Patient-Reported Outcome (PRO) Measures in Prurigo Nodularis: A Review of the Literature

**Chanis R, Dias Barbosa C, Wilson R**, Jabbar-Lopez Z, Puelles J, Gabriel S

**PMU91:** Heterogeneity of Patient Preferences for Low-Dose Aspirin Treatment - Evidence from a Discrete Choice Experiment in Italy

**Tervonen T**, Vora P, **Seo J, Krucien N, Marsh K**, Wissinger U, Soriano-Gabarro M

**PMU105:** Patient Preferences for Systemic Atopic Dermatitis Treatments in the UK, France and Spain: A Discrete Choice Experiment

**Thomas C**, Raibouaa A, Wollenberg A, Capron J, **Krucien N, Karn H, Tervonen T**

## PND: NEUROLOGICAL DISORDERS

**PND57:** Cost-Effectiveness Analysis of a Hypothetical Disease Modifying Therapy for Parkinson's Disease

**Chandler C, Gal P, Folse H, Chavan A, Ward A**

**PND103:** Patient Preferences for Multiple Sclerosis Treatment during a Phase 3 Trial

**Chua GN,** Beyer A, Hennessy B, **Brooks A, Tervonen T**

## PNS: NO SPECIFIC DISEASE

**PNS10:** Research in the COVID-19 Era: Accelerating the Shift in the Research Paradigm from Traditional Towards Digital/ Virtual Solutions

**Stein D, Baltezegar M**

**PNS156:** Are Surrogate Outcomes Enough for the Reimbursement of Health Technologies? An Umbrella Literature Review.

**Freitag A**, Sarri G

**PNS162:** An Initial Framework to Describe and Classify Integrated Scientific Advice Procedures: Trends and Developments

**Boss J, Griffiths J, Laughlin W, Vanoni C, Olid Gonzalez A, Bending M**

**PNS170:** An Analysis of NICE Approval Prospects for Drugs with ICERs >£30,000 per QALY Gained

**Thomas H, Mitchell C, Papaleontiou L, Sharif S, Rawson K**

**PNS176:** Is the Door for RWE Acceptance in the German HTA Now Open?

**Emich H, Schmetz A, Prawitz T, Raluy M**

**PNS201:** A Simple Method of Sampling Ordered Bounded Parameters in Probabilistic Sensitivity Analysis

**Litkiewicz M, Nikolaou A**

**PNS216:** Beyond the Statistical Methods-Design Strategies Impacting the Method to Compare Cohorts in Prospective Observational Studies

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

**PNS221:** Healthcare Decision-Making Using Real-World Evidence- Many Opportunities, Little Guidance. Results from a Systematic Review of Guidance

Sarri G, Abrams KR, Muszbek N, Debray T

**PNS229:** Using MIXED Methods to Explore the Content Validity and Importance of Various SLEEP Parameters in a SLEEP Diary Questionnaire

Beyer A, **Mannix S, Kleinman L**

## PRO: RARE & ORPHAN DISEASES

**PRO9:** What's Clear About Assessing Airway Clearance Techniques in Cystic Fibrosis? A Systematic Literature Review

Milenkovic D, Gomez Espinosa E, **Iheanacho I**

**PRO67:** Does Society Support the Prioritisation of High-cost Treatments for Rare Diseases? A Systematic Literature Review

**Dodman S, Iheanacho I**, Koufopoulou M

**PRO100:** Analysis of Expert Opinion Informing Model Parameters in NICE Appraisals of Highly Specialised Technologies for Rare Conditions

**Tosh J, Masclet A**

**PRO110:** A Framework for Developing a MODEL of Chronic Acid Sphingomyelinase Deficiency

**Folse H, Ward A, Chandler C,** Fournier M, **Sardesai A,** Pulikottil-Jacob R

## PRS: RESPIRATORY-RELATED DISORDERS

**PRS64:** Lung Function and Asthma Control in Patients on Medium-to-High-Dose ICS-LABA- A Systematic Review of the Observational Literature

Czira A, Meeraus W, **Martin A, Turner M**, Birch H, Zhang S

**PRS66:** The Economic Burden of Adult Asthma That Is Uncontrolled on Medium-to-High-Dose ICS-LABA- A Systematic Literature Review

Czira A, **Martin A, Turner M**, Meeraus W, Birch H, Zhang S

**PRS75:** The Severity of Chronic Cough Diary (SCCD)- Development of a Novel Patient-Reported Outcomes Instrument

de la Orden Abad M, Haberland C, Filonenko A, **Karn H, Skalicky A, Vernon MK, Hareendran A**

## PUK: URINARY/KIDNEY DISORDERS

**PUK6:** Economic Modelling of Chronic Kidney Disease (CKD) Using Estimated Glomerular Filtration RATE (EGFR)- Slope: Effect on CKD Modelling of Acceptance of a New Surrogate Outcome

**Marczell K, Gal P, Benedict A,** Stavas JM, Coulston J, **Caro JJ**

# Upcoming Presentations

## ASH Annual Meeting

Dec. 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

## ACNP Virtual Meeting

Dec. 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

# Recent Presentations

## PROMIS International Conference

Oct. 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

Oct. 22-25, 2020 | VIRTUAL CONFERENCE

**ePOSTER**

Patient and Clinician Preferences for Hyperkalemia Treatment: A Qualitative Study

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

## ASN American Society of Nephrology Kidney Week

Oct. 22-25, 2020 | VIRTUAL CONFERENCE

**ePOSTER**

Patient Preferences Study for Treatments of Anemia in Chronic Kidney Disease (CKD) Patients Not on Dialysis (NDD)

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

## ISOQOL 2020 Virtual

Oct. 21-24, 2020 | VIRTUAL CONFERENCE

**ORAL PRESENTATION**

Engaging Patients and Caregivers in the Selection, Development, Implementation and Interpretation of Clinical Outcome Assessment (COA) Instruments: Co-Creation of Practical 'How To' Guidance

Delbecque L, Kruger P, **Duenas A**, Hamerlijnck D, Kaschinski D, Pakarinen C, Sargeant I, Hamoir AM

**SYMPOSIA**

Item Bank for your Buck: Successfully Harnessing the Power of Item Banks and Libraries to Assess Clinical Benefit from the Patient Perspective

Nelsen L, Cella D, **Gelhorn H**, Regnault A

The Application of Mixed Methods to Measure Health Outcomes in Clinical Trials, Clinical Practice, and Health Policy

**Dias-Barbosa C**, Ogunsanya M, Regnault A, **Martin M**, Barbic S

**POSTERS**

Symptom Experience and Content Validity of the Psoriasis Symptom Scale (PSS) in Patients with General Pustular Psoriasis (GPP) and Palmoplantar Pustulosis (PPP)

**Rentz A, Skalicky A**, Esser D, Gloede T, Thoma C

The Patient Experience with Symptoms of Hereditary Angioedema (HAE) Before, During, After and Between Attacks

**Jean-Baptiste M**, Supina D, Itzler R, Prusty S, **Martin M**

Where Do We Need Better Assessment to Evaluate Treatment for Hereditary Angioedema (HAE)?

**Jean-Baptiste M**, Supina D, Itzler R, Prusty S, **Martin M**

## Precision Medicine Leaders' Summit

Oct. 20-21, 2020 | VIRTUAL CONFERENCEE

**PODIUM**

Critical Success Factors for Addressing the Next Generation of Precision Medicine

**Faulkner E**

## ARM Cell & Gene Meeting on the Mesa

Oct. 12-16, 2020 | VIRTUAL CONFERENCE

**WORKSHOP**

Acceptance and Uptake of Cell and Gene Therapies: Lessons Learned and Future Focus

**Faulkner E**, Pitluck S, Salimullah T

## SMDM 2020 Annual Meeting

Oct. 6-27, 2020 | VIRTUAL MEETING

**SHORT COURSE**

Designing and Implementing DICE Simulations of Decision-Analytic Modeling

**Caro JJ, Moller J**

**POSTER**

Modeling Individual in-Hospital Trajectories with COVID-19 Using Discretely-Integrated Condition Event (DICE) Solution

**Caro JJ, Moller J**, Santhirapala V, Gill H, Johnston J, El-Boghdadly K, Santhirapala R, Kelly P, McGuire A

## 14th Vaccine Congress

Sept. 28-29, 2020 | VIRTUAL CONFERENCE

**POSTER**

Facilitating Site Selection for SARS-COV-2 Vaccine Trials Using WAVETM, a DICE Simulation

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

## ASGCT 2020 Summit

Sept. 23-25, 2020 | VIRTUAL CONFERENCE

**SESSION SPEAKER**

Evidence Generation Solutions to Support Regulatory and Payer Requirements

**Faulkner E**

## ISPOR 2020 Short Course Program

Sept. 23-Oct. 30, 2020 | VIRTUAL CONFERENCE

**SHORT COURSE**

Using Multi-Criteria Decision Analysis in Healthcare Decision Making: Approaches & Applications

**Marsh K**, Pagell N, Byun JH, Gangwon-Do

## ESMO 2020

Sept. 19-21, 2020 | VIRTUAL CONFERENCE

**POSTERS**

Real-World Evidence for Patients with Metastatic Castration-Resistant Prostate Cancer Treated with Cabazitaxel: Comparison with the Randomized Clinical Study CARD

de Wit R, Freedland S, Oudard S, **Marinov G, Capart P, Combest A,** Peterson R, Ozatilgan A, Morgans A

Real-World Treatment Patterns and Immunotherapy (IO) Sequencing Based on PD-L1 TPS in European Patients with Metastatic NSCLC

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

Real-World Treatment Patterns and Outcomes in Patients with Advanced, ALK+ Non-Small Cell Lung Cancer (NSCLC) in Europe

**Stoyanov N, Anderson D, Combest A, Nguyen B,** Ognar R, **Reitsma D, Capart P**

## ICPE 2020 All Access

Sept. 16-17, 2020 | VIRTUAL CONFERENCE

**POSTERS**

Analysing Patient Level Data from Norwegian Registries: Challenges and Considerations

**Graham S, Lambrelli D**, Schultze A, **Donaldson R**, Ghanima W, Carroll R, Ulvestad M

Factors Associated with Losses to Follow-up in Pregnancy Exposure Registries

**Covington D, Veley K, Buus R, Churchill P**

Heterogeneity of Patient Preferences for Benefits and Risks of Antiplatelet Therapies

Pinto CA, **Chua GN, Brookes E**, Hyacinthe J, **Tervonen T**

How Patient Preferences Can Inform Net Clinical Benefit: A Personalized, Patient-centered, Benefit Risk Assessment Using Real-world and Clinical Trial Data

**Tervonen T, Prawitz T, Chua GN**, Hyacinthe J, Pinto CA

Innovation and Pragmatism in Retrospective Chart Review Methodology for Post-Approval Drug Utilization Studies

**Saragoussi D, Rouleau A, Capart P, Deveras CC, Brett NR**, Ognar R, **Gazay H, Payne K**

Linaclotide Utilization and Potential for Off-Label Use or Misuse in Three European Countries

**Cid Ruzafa J,** Schultze A, **Duong M, Lu Y, Donaldson R,** Weissman D, Ukah A

Prevalence of Outcomes in Pregnancy Registries Versus General Population

**Veley K, Covington D, Chan RL, Churchill P**

Real-world Data Collection in Early Access Programs: An Additional Source Of Data To Inform Benefit-risk Assessment In The Pre-approval Phase

**Soni M, Saragoussi D, Stein D, Eckley D, Block J**

Sample Size Calculations for Pregnancy Registries: Improving Accuracy

**Veley K, Covington D, Buus R, Chan RL, Churchill P**

Trends in Post-Approval Pregnancy Safety Studies Required by the United States Food and Drug Administration, 2015-2019

**Simeone JC, Nordstrom BL**

## Global Genes Live! A RARE Patient Advocacy (un)Summit 2020

Sept. 15-25, 2020; VIRTUAL CONFERENCE

**PLENARY SESSION**

Be Heard: Patient Perspectives in Novel Therapeutics Value-Based Discussions

**Faulkner E**

## ISPOR 2020 Asia

Sept. 14-16, 2020 | VIRTUAL CONFERENCE

**ABSTRACT ONLY**

Real-World DATA Collection in China: Challenges and Recommendations to Ensure DATA Quality

**Soni M, Marshall L, Zaha R, Lee J, Huang Y**

## RAPS Convergence 2020

Sept. 13-16, 2020 | VIRTUAL CONFERENCE

**SESSION SPEAKER**

Regulatory-Grade Evidence: Is There Global Consensus on Existing Real-World Evidence (RWE) Frameworks?

Oztop I, **Faulkner E**, Kurz X, Shah D

## PAINWeek 2020

Sept. 11-13, 2020 | VIRTUAL CONFERENCE

**POSTER**

Creation and Validation of Algorithms to Identify Patients with Moderate-to-Severe Osteoarthritis of the Hip and/or Knee and Inadequate/Intolerable Response to Multiple Pain Medications

**Berger A**, Robinson RL, **Lu Y**, Zagar AJ, **Yue A**, Schepman P, **Bassel M**, Johnston B, **Slim M**, Thakkar, Hartrick C

## ACTRIMS-ECTRIMS Joint Meeting 2020

Sept. 9-12, 2020 | VIRTUAL MEETING

**POSTER**

Treatment Preferences of Patients with Relapsing Multiple Sclerosis: A Discrete Choice Experiment

Scherz T, Boyanova N, **Brooks A, Chua GN**, Beyer A, Levitan B, Hennessy B, **Tervonen T**

## ERS International Congress 2020

Sept. 7-9, 2020 | VIRTUAL CONFERENCE

**POSTER**

Frequency of Eosinophilic Granulomatosis with Polyangiitis in Europe by Meta-Analysis

Jakes RW, Kwon N, Goulding R, **Nordstrom B, Fahrbach K**, Van Dyke MK

## Patients as Partners US

Aug. 19-21, 2020 | VIRTUAL CONFERENCE

**ISSUE PANEL**

Creating and Executing an Outstanding and Inclusive Patient Experience from the CRO and Site Perspectives

Bechtel J, Andriote JM, Gray S, Prowisor E, **Henry R**

## HTAi 2020

July 28-30, 2020 | VIRTUAL CONFERENCE

**WORKSHOP**

Making HTA Easier: Discretely Integrated Condition Event (DICE) Simulation for Modeling

**Caro JJ, Moller J**

## Disease Prevention & Control Summit – America

July 28-29, 2020 | VIRTUAL CONFERENCE

**ROUNDTABLE**

The Clock is Ticking: Accelerating Vaccine Development During a Pandemic

**Kovac M, Schaumberg D, Rich T**

## ISPOR Virtual Journal Club

July 22, 2020 | VIRTUAL PRESENTATION

**ISSUE PANEL**

Being Precise About Precision Medicine: What Should Value Frameworks Incorporate to Address Precision Medicine? A Report of the ISPOR Personalized Precision Medicine Special Interest Group

**Faulkner E**, Holtorf AP

## ISTH 2020 Congress

July 12-14, 2020 | VIRTUAL CONFERENCE

**POSTER**

Oral Anticoagulation Therapy for Venous Thromboembolism in Norway: Time Trends and Treatment Patterns

Ghanima W, Schultze A, **Donaldson R**, Brodin E, Halvorsen S, **Graham S**, Carroll R, Ulvestad M, **Lambrelli D**

## DIA 2020

June 14-18, 2020 | VIRTUAL CONFERENCE

**WORKSHOPS**

Gaslighting at Work: How to Recognize and Respond to this Unique Form of Harassment

**Richards M**

Qualitative, Quantitative, and Mixed Method Approaches to Capture the Patient Experience

Dashiell-Aje E, Knoble N, Freeman E, **Gelhorn H**

**FORUM**

Quantitative Benefit-Risk Assessment: What Methods are Being Used? How Far Has Industry Come?

Smith M, **Marsh K**, Hauber B, DiSantostefano RL

## ADA 2020

June 12-16, 2020; VIRTUAL CONFERENCE

**ePOSTER**

Utilization of Glucose-Lowering Drugs in Patients with T2DM and Established CVD in US: A Descriptive Study Using MarketScan Claims

**Ganz ML**, Ustyugove AV, **Sawalhi-Leckenby N**, De Souza S, Zhang L, Gunnarsson E, Homsy D, Gao R, Desai NR

## EHA25 Virtual Congress

June 11-14, 2020 | VIRTUAL CONFERENCE

**ePOSTER**

Comparison of Safety Management Costs across Chimeric Antigen Receptor (CAR) T Cell Therapies in Relapsed or Refractory Large B-Cell Lymphoma

**Rivolo S, Xiao Y, Litkiewicz M**, Saint-Laurent Thibault C, Patel L, Zhang Y, **Dorman E**, Liu F, Kuruvilla J

**ABSTRACT ONLY**

DREAMM-1: Patient Perspectives from the First-In-Human Study of Single-Agent Belantamab Mafodotin for Relapsed and Refractory Multiple Myeloma (RRMM)

Eliason L, Opalinska J, **Martin ML, Correll J**, Gutierrez B, Popat R

## ERA-EDTA Congress

June 6-9, 2020 | VIRTUAL CONFERENCE

**POSTER**

A Qualitative Study of Patients' Preferences for the Treatment of Anaemia Associated with Chronic Kidney Disease

Alexandre AF, Morga A, **Marsh KM, Thomas C**

## American Academy of Developmental Medicine & Dentistry

June 4-6, 2020 | VIRTUAL CONFERENCE

**POSTER**

Impact of Possible TD on Caregivers: Results from a Prospective Real-World Screening Study (RE-KINECT)

Cutler AJ, Caroff SN, Tanner CM, Shalhoub H, **Lenderking WR, Wilcox T**, Franey E, Yonan C

## ASCO20 Virtual Scientific Program

May 29-31, 2020 | VIRTUAL CONFERENCE

**ABSTRACT ONLY**

Real-World Treatment Patterns and Clinical Outcomes of Advanced Melanoma Patients Following Disease Progression on Anti-PD-1-Based Therapy

Hernandez-Aya L, Burke M, **Collins J**, Earle D, Hamilton M, **Nordstrom B**, Zhang Y, Srivastava S

## ISCT 2020 Annual Meeting

May 28-29, 2020 | VIRTUAL CONFERENCE

**POSTER**

Clinical Trial and Value Demonstration Models for Cell and Gene Therapies: What Critical Success Factors are Relevant?

**Fontana T, Mayo T**, Ringo M, Koh M, Morgese P, Theocharous P, **Faulkner EC**

## EAN 2020

May 23-26, 2020 | VIRTUAL CONFERENCE

**ePOSTER**

Patient Attitudes and Valuation of Preventive Migraine Treatments: A Focus Group Study

**Thomas C**, Tockhorn-Heidenreich A, **Seo J**, **Smith C**, Ford JH, Stauffer VL, Nicholson RA, Duffy KH, **Tervonen T**

## DIA MASC 2020

May 6-7, 2020 | VIRTUAL CONFERENCE

**POSTER**

Readability Assessment of Clinical Trial Information on Pharmaceutical Product Websites Intended for Patients and Caregivers

**Watts R, MacIntyre B, Cash K**

**PODIUM**

Readability Assessment of Clinical Trial Information on Pharmaceutical Product Websites Intended for Patients and Caregivers

**Watts R**

# 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 Sep 11; S1743-6095(20)30840-7.

**Anatchkova M, Brooks A, Swett L** et al. Agitation in Patients with Dementia: A Systematic Review of Epidemiology and Association with Severity and Course. *Int Psychogeriatr.* 2019 Mar 11:1-14. doi: 10.1017/S1041610218001898. [Epub ahead of print]

Arlegui H, Nachbaur G, Praet N, Bégaud B, **Caro JJ**. Using Discretely Integrated Condition Event Simulation to Construct Quantitative Benefit-Risk Models: The Example of Rotavirus Vaccination in France. *Clin Ther.* 2020 Sep 25; S0149-2918(20)30419-7. doi: 10.1016/j.clinthera.2020.08.013. Online ahead of print.

Armstrong AW, Edson-Heredia E, Naegeli AN, Burge R, Poon JL, **Anatchkova M**, Sun L, Zhu B, Wyrwich KW. Development of the Psoriasis Symptoms Scale (PSS) in Patients with Moderate-to-Severe Psoriasis: Qualitative and Quantitative Analyses. *J Dermatolog Treat.* 2020 Aug;31(5):452-459. doi: 10.1080/09546634.2019.1623370.

Azzari C, Baldo V, Guiffrida S, **Gani R, O'Brien E**, Alimenti C, Daniels VJ, Wolfson LJ. The Cost-Effectiveness of Universal Varicella Vaccination in Italy: A Model-Based Assessment of Vaccination Strategies. *Clinicoecon Outcomes Res.* 2020 June 8;12: 273-283. doi: 10.2147/CEOR.S229685. eCollection 2020.

Besford M**, Graham S**, Sammon C, Mehmud F, Allan V, Alikhan R, Ramagopalan S. Factors Associated with Non-Prescription of Oral Anticoagulant Treatment in Non-Valvular Atrial Fibrillation Patients with Dementia: A CPRD-HES Study. *Age Ageing.* 2020 Jul 1;49(4):679-682. doi: 10.1093/ageing/afaa045.

**Betts MB**, Rane P, **Bergrath E, Chitnis M**, Bhutani MK, Gulea C, Qian Y, Villa G. Utility Value Estimates in Cardiovascular Disease and the Effect of Changing Elicitation Methods: A Systematic Literature Review. *Health Qual Life Outcomes.* 2020 Jul 27;18(1):251. doi: 10.1186/s12955-020-01407-y.

**Brooks AB**, Langer J, **Tervonen T**, Hemmingsen MP, Eguchi K, **Bacci ED**. Response to "Letter to the Editor Regarding: Patient Preferences for Glucagon-like Peptide-1 (GLP-1) Receptor Agonist Treatment of T2DM in Japan: A Discrete Choice Experiment." *Diabetes Ther.* 2020 Oct;11(10):2443-2446. doi: 10.1007/s13300-020-00900-3.

**Caro JJ**. Let's Make Sure We Are Doing Authorship Right. *Value Health.* 2020 Jul;23(7):889-890. doi: 10.1016/j.jval.2020.03.011.

**Caro JJ**, Maconachie R, Woods M, Naidoo B, McGuire A. Leveraging DICE (Discretely-Integrated Condition Event) Simulation to Simplify the Design and Implementation of Hybrid Models. *Value Health.* 2020 Aug;23(8):1049-1055. doi: 10.1016/j.jval.2020.03.009.

**Caro JJ, Moller J**. DICE Simulation: A Unifying Modeling Approach for Pharmacoeconomics. In: Arnold RJG, ed. *Pharmacoeconomics From Theory to Practice*. Boca Raton, FL: *CRC Press*, 2020:171-188.

**Caro JJ, Moller J**. Speculations on the Future Challenges and Value of Pharmacoeconomics. In: Arnold RJG, ed. *Pharmacoeconomics From Theory to Practice*. Boca Raton, FL: CRC Press, 2020:295-304.

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**Chapman R, Sutton K, Dillon-Murphy D**, Patel S, Hilton B, Farkouh R, Wasserman M. Ten Year Public Health Impact of 13-Valent Pneumococcal Conjugate Vaccination in Infants: A Modelling Analysis. *Vaccine.* 2020 Oct 21;38(45):7138-7145. doi: 10.1016/j.vaccine.2020.08.068.

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Cohen AT, Hill NR, Luo X, Masseria C, Abariga SA, Ashaye AO. Response to "LTTE concerning: 'A Systematic Review of NMAs among Patients with Nonvalvular Atrial Fibrillation: A Comparison of Efficacy and Safety Following Treatment with DOACs'". *Int J Cardiol.* 2020 May 1; 306:101. doi: 10.1016/j.ijcard.2019.11.141.

Cohen JL, Sadick NS, Kirby MT, McLane MP, **Lenderking W**, Bender RH, **Chen J** et al. Development and Validation Clinician and Patient Reported Photonumeric Scales to Assess Buttocks Cellulite Severity. *Dermatol Surg.* 2020 Sep 29. doi: 10.1097/DSS.0000000000002756. Online ahead of print.

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Cotarla I, Boron ML, Cullen SL, Spinner DS, **Faulkner EC**, Carroll MC, **Shah S**, Yagui-Beltran A. Treatment Decision Drivers in Stage III Non-Small-Cell Lung Cancer: Outcomes of a Web-Based Survey of Oncologists in the United States. *JCO Oncol Pract.* 2020 Oct;16(10): e1232-e1242. doi: 10.1200/JOP.19.00781.

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**Fahrbach K, Tarpey J, Bergrath Washington E, Hughes R**, Thom H, Neary MP, Cha A, Gerber R, Cappelleri JC. Correction to: Crisaborole Ointment, 2%, for Treatment of Patients with Mild-to-Moderate Atopic Dermatitis: Systematic Literature Review and Network Meta-Analysis. *Dermatol Ther (Heidelb).* 2020 Oct 6. doi: 10.1007/s13555-020-00452-1. Online ahead of print

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