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THE EVIDENCE FORUM

FALL 2018

SPECIAL FEATURE

Interview with Head of NICE Scientific Advice

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Interview with **Dr. Leeza Osipenko**, Head of NICE Scientific Advice

HTA Scientific Advice – Is it Becoming More Important?

Dr. Susanne Michel, Vice President and Practice Lead, Market Access Consulting, of Evidera recently spoke with Dr. Leeza Osipenko, Head of NICE Scientific Advice, about the evolution and importance of HTA Scientific Advice.

How has the process of working with manufactures to provide scientific advice evolved over the past five years?

There is now a greater acceptance of a dialogue between manufacturers and Health Technology Assessment (HTA) bodies. This is a very welcome development, however, there is still a lot of room to grow and to make sure that sponsors see the value in generating evidence relevant to patients and clinical practice and are not simply trying to fulfil minimal requirements set by the Food and Drug Administration (FDA). At NICE, we have significantly expanded our services and in addition to providing advice in parallel with the European Medicines Agency (EMA) and European HTA agencies, we offer an express service for the national advice, an abridged service for Small and Medium Enterprises (SMEs), advice for developers of devices and diagnostics, and quality assurance and sense checking of economic models. We are currently developing links with our North American colleagues and starting a project with the Canadian Agency for Drugs and Technologies in Health (CADTH) as well as running pilots with organisations in the U.S. Our team continues to deliver educational seminars and conduct site visits to companies. Such a diversity of activities has increased the awareness and uptake of scientific advice. Overall, as we hear from the NICE committees, the quality of sponsors' submissions is becoming better. There is still a lot of variation but more companies now make attempts to collect quality of life and longer-term outcomes data.

From our experience manufacturers most often seek scientific advice due to specific data or trial design uncertainties, do you agree? What are the other motivations for seeking NICE scientific advice? Have these motivations shifted or changed over the last years?

This is a question for manufacturers not for NICE. I suppose motivations range widely and in big companies they can often be political rather than methodological. Sometimes we receive genuinely interesting methodological questions and sometimes companies come for a check-box exercise. The latter is something NICE does not provide as we always

Susanne Michel

This interview was conducted in conjunction with ongoing efforts by Evidera's Market Access Center of Excellence, currently led by Katie Gardner, Senior Director, Market Access Communications, to provide relevant and up-to-date information to help support our clients' needs for product access.

take a critical view of the proposed plans and scrutinise them to ensure methodological rigour. We never endorse a company's plans but focus on explaining outcomes of different options and approaches.

What specific data and trial design uncertainties do you see being brought forward repeatedly in scientific advice sessions? Is that in specific indications?

Whilst there are some examples of innovative trial designs that are of interest, overall our experience is that the quality of clinical trials is going down, and this is very worrying. The regulatory bar for approval is falling lower and we see more and more single arm trials, surrogate endpoints, trials stopped for efficacy reasons, etc. This is in addition to the just generally poor scientific rigour of many clinical trials. There are clear situations where randomised trials are not possible and where powering on overall survival is not feasible, but unfortunately there is a strong push for suboptimal trial designs and trial durations. This is a potentially dangerous practice which can put patients at risk of being exposed to products licensed on a very weak evidence base. For the manufacturers, it is a disadvantage as well, because once they bring their products to NICE with weak clinical evidence, they are forced to make much greater discounts to mitigate uncertainty. The latter is a massive problem in oncology but for other indications we see many instances of inadequate quality of life data collection, and inability to define treatment stopping rules and to appropriately select clinically relevant endpoints. There is currently a lot of effort going into the design of new patient-reported outcomes (PRO) instruments but validation of these is a problem. We also receive many questions about real-world evidence (RWE) and unfortunately there is a strong move to start using RWE in place of, rather than in addition to, properly collected and analysed data which are needed to establish relative clinical effectiveness of the intervention. RWE often produces more noise than clinically relevant information.

We are aware of the new EMA/EUnetHTA advice scheme called Post-Licensing Efficacy Generation (PLEG), focusing specifically on post-launch data generation. How much is the post-launch development of data an issue for the scientific advice delivered by NICE?

Sometimes we receive questions on post-authorisation data collection and I wish these questions accompanied every project. With an increase in CMA (conditional marketing authorisation), PLEG becomes more and more favoured. Unfortunately, PLEG is poorly enforced by the regulators and many companies either do not produce these data or present them with significant delays. These data are crucial, but often, even when available, they rarely prompt the initial decision review or translate to changes in clinical practice. It is also important to remember that the quality of the PLEG data is paramount but rarely do we see PLEG data being generated up to required scientific standards. Reforms are needed at the regulatory level and in the HTA field to enforce PLEG, ensure its quality, and then to act on its results.

What is the role of Advanced Therapy Medicines Products (ATMPs) in scientific advice? Do you see these technologies being increasingly the subject of scientific advice submissions? Are the questions in scientific/ rationale for seeking scientific advice somewhat different? If so how? Can you explain?

We've had a significant increase in requests for scientific advice on ATMPs. To date we have given advice on 19 products. Usually such projects are very interesting and they bring along many methodological questions and issues that neither regulators or HTA agencies have seen before. At NICE, we commend companies coming to us to discuss their plans and enhance learning of the changing drug development landscape for all stakeholders. However, frequently companies think that because they are developing ATMPs this gives them an option of disregarding methodology of clinical trial conduct and proper evidence generation. While for many indications, where ATMPs are currently being developed, the populations are small and trials are challenging, scientific rigour is of utmost importance. These products are likely to carry a hefty price tag and risky side effects. The developers of these products must produce clinical evidence according to the highest standards of clinical research. ■

Advice requests on ATMPs pose questions on managed access agreements. This is a welcome discussion which we encourage companies to have before appraisal through NICE's Office for Market Access.

Dr. Osipenko joined the National Institute for Health and Care Excellence (NICE) in 2012 and has been leading the Scientific Advice (SA) service since 2014. She works closely with EMA, MHRA, and European HTA agencies. She chairs most of the national, international, and parallel scientific advice meetings for medical device and pharmaceutical product developers. She also signs off key deliverables produced by NICE SA and is responsible for the team's operations and performance. Dr. Osipenko's research interests focus on methodologies of trial design, evidence generation for economic modelling, and policy implications of HTA.

She holds an Honorary Fellow post at the University of Warwick Medical School, Senior Visiting Fellow post at London School of Economics, and represents NICE as a Chief Analyst at the Department of Health Appraisal Alignment Working Group. She is also a reviewer of a number of academic journals.

After completing a PhD in Systems Engineering, Dr. Osipenko was Senior Research Fellow at the University of Warwick and between 2010 and 2012, she worked as Principal Economist at a public sector consultancy, Optimity Matrix.

The EU HTA Harmonization Initiative
What is the Significance to Manufacturers of the New Directive?

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Introduction

Comparative clinical benefit assessments are at the core of health technology assessments (HTAs) in Europe. HTAs are a multi-disciplinary process considering input and evidence from different areas, such as medical, social, and economic sources. These assessments are then used to inform the design of health policies that allow the safe and effective use of new technologies within individual health systems and their specific conditions.

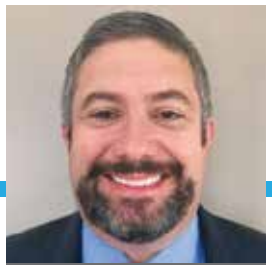
Currently, HTAs are conducted separately by individual European countries using their own assessment criteria. This multiplicity of HTA methodologies can create considerable work for manufacturers, which currently need to submit HTAs to multiple European Union (EU) member states.

The idea of a pan-EU HTA has long been discussed, but has taken considerable time and effort to come to fruition.[1] On 31 January 2018, the European Commission (EC) requested EU Member States to adopt a new proposed Directive (2018/0018) which outlined several activities required for a European Health Technology Assessment (EU HTA). Despite being vetoed by Germany, France, the Czech Republic, and Poland, **the Directive was adopted on 3 April 2018 and is expected to be implemented on 30 March 2019.**

This white paper aims to outline the new Directive, highlighting the changes from existing HTAs, and to provide commentary on the potential impact of this legislation to key stakeholders, manufacturers in particular.


Susanne Michel


Elsa Navarro


Mike Epstein

Summary of the New Directive

- A major component is a **consistent, comparative, clinical efficacy assessment**, facilitated centrally for all EU member states and used for all European Medicines Agency (EMA) assessed pharmaceuticals, medical devices (within defined criteria), and diagnostics.
- This Directive specifies that **no separate comparative clinical assessment** may be carried out at individual member state levels.
- In contrast to the clinical assessment, the value assessment of **all non-clinical domains** (including social, economic, or organizational) and the determination of price will **remain with individual member states**.
- The EC outlines expectations of the new integrated approach, including increased transparency and potentially faster patient access to new technologies across the EU.
- It also sees benefits to the pharmaceutical and medical device industry, such as improved business predictability, enhanced competitiveness, and stimulating innovation.

As the implementation and methods associated with the Directive evolve over the short- and medium-term, it is vital for stakeholders, in both the public and private sectors, to understand the Directive's background and the proposed framework to prepare for the changes and leverage the opportunities this Directive presents.

Background

Recognizing that there are differences in the conduct of HTAs within the EU, a pan-European HTA has long been discussed as a fundamental method of harmonizing drug assessments within the member states. In 2004, the High-Level Group on Health Services and Medical Care, within the EC's Health and Consumer Protection Directorate, called for the development of an EU-level HTA network:

> *"[T]he usefulness of establishing a sustainable European health technology assessment network has been recognized. Such a network should address methods for developing common core information packages, methods to support transferability of assessments, methods for helping Member States to identify and prioritize topics and commissioning reports, tailoring common core information to national health policy processes and sharing methodologies, expertise and practice issues."*[1]

In response to the EC's call for action, the Danish Centre for HTA led a coalition of 35 organizations to develop the European Network for Health Technology Assessment (EUnetHTA) Project in 2005.[2] Since then, EUnetHTA has grown into a consortium of over 81 governmental and non-profit organizations from 29 countries (i.e., EU member states, EU-accession countries, European Economic Area countries, and European Free Trade Association countries) that collaborate on HTA – on a ***voluntary*** basis.[2] The movement for EU-wide HTA picked up steam in 2011, with Directive 2011/24/EU on patients' "cross-border rights." The push culminated in this year's developments, which shift participation from voluntary to ***mandatory.***

There has long been rumor of such a supra-nationalization, so readers may be skeptical that the regulation will be put into effect. A healthy skepticism is natural, but we advise against it in this case. Two-thirds of the 28 EU Member States' legislatures would have to lodge objections with the EC for the new initiative to fail. This means that 19 Member States would have to vote to oppose the Directive for it to fail. Only 4 Member states, Germany, France, the Czech Republic, and Poland vetoed the Directive. An additional 15 member states would therefore have to change their position, which is unlikely since many Member States, particularly those smaller ones with fewer resources to conduct clinical HTA themselves, stand to benefit from the regulation.

Manufacturers developing health technologies due to launch between 2019 and 2021 (i.e., the transitional period during which Member States participation remains voluntary), and especially those launching from 2022 onwards (i.e., at which point all Member States will be bound by the EU-level clinical HTA) should closely track developments and prepare accordingly.

Structure of EU Clinical HTA Decision-Making

Article 3 of the regulation provides details on what it calls, "The Member State Coordination Group on Health Technology Assessment," or the "Coordination Group" for short.[3]

Structure and decision-making rules are as follows *(additional details can be found in Article 6).*[3]

- **Who?** The Coordination Group will be comprised of national HTA organizations designated by Member States.
- **How?** The Coordination Group will make decisions by consensus or, failing consensus, majority rule. There will be no representation based on relative Member State population; rather, each Member State will have one vote. The Group may create committees/subgroups for each type of health technology: drugs, devices, and "other health technologies." Each committee/

Figure 1. New Structure Designed to Facilitate EU HTA Harmonization Initiative

subgroup will appoint an assessor and co-assessor who will prepare the assessment report. In case the assessor requires additional evidence, he/she may suspend the assessment and request that the manufacturer submit those data. The manufacturer will have an opportunity to comment on the draft assessment report, as will patients and clinical experts, prior to finalization and publication.

- **Points to note**
  - "The Coordination Group shall …
    - ensure cooperation with relevant Union-level bodies to facilitate additional evidence generation necessary for its work;
    - ensure appropriate involvement of stakeholders in its work …"[3]
  - "The members of the designated sub-group shall provide their comments during the preparation of the draft joint clinical assessment report and the summary report. The Commission may also provide comments."[3]

This description raises more questions.

- **Cooperation with Union-level bodies.** It is unclear what this means. The EC may envision closer cooperation between the EMA and the Coordination Group. Does it envision joint regulatory and clinical HTA? Harmonization of additional evidence collection for regulatory and clinical HTA purposes?
- **Appropriate involvement of stakeholders.** Which stakeholders? What level of involvement is "appropriate"? What role will key opinion leaders (KOLs) play? Patient advocacy organizations? How will national-level organizations be handled versus EU-level organizations? Will the latter be privileged?
- **The Commission will comment?** It is not clear why the Commission should wish to reserve the right to comment on clinical HTA assessments, which are meant to be objective, technical, science-based reviews of evidence. In Article 25, the regulation also notes that the EC will co-chair Coordination Group meetings. It is unclear what role the EC envisions for itself in this process, though there are mentions in the regulation of a supervisory role for the EC to ensure the regulation is being executed appropriately.

Regulation's Scope

The scope of the Joint Comparative Clinical Assessments (JCA) includes:

Pharmaceuticals

- Medicinal products with central marketing authorization
- New active substances
- New therapeutic indications for existing substances

Medical devices - Class IIb and III

- For which the relevant expert panels have provided a scientific opinion in the framework of the clinical evaluation consultation procedure

In vitro diagnostic medical devices - Class D

- For which the relevant expert panels have provided their views in the framework of the clinical evaluation consultation procedure

While *all drugs* with EMA approval are in scope, only those **devices and diagnostics** entering areas with the **following criteria** are in scope.

- Unmet medical needs
- Potential impact on patients, public health, or health care systems
- Significant cross-border dimension
- Major Union-wide added value
- Available resources

During the 3-year transition period (i.e., 2019-2021), 65 assessments are expected annually.[4]

Elements of the Joint Clinical Assessment

The Joint Clinical Assessment (the assessment hereafter) will cover four domains:[3]

- Description of the health problem and how it's treated today
- Description and technical specifications of the new health technology
- Comparative efficacy
- Comparative safety

Evidence quality, described by the regulation in Article 6, Section 5 as, "degree of certainty on the relative effects based on the available evidence," will factor into the assessment.[3] Manufacturers face many uncertainties based on this description.

- **Whose standard of care? Whose health care delivery system?** It is not clear how the assessment will handle variation in standard of care and health care delivery across Member States. Will the assessment consider all Member States' standards of care? All manners of delivering that care? If so, won't the assessment become unwieldy? If not, won't some Member States' status quo be ignored? Over time, the vision is presumably to homogenize standards of care across the Union, but what will constitute the baseline?
- **Role of real-world evidence (RWE).** It is not clear how RWE will factor into the assessment. What sorts of RWE will be acceptable to establish burden of illness? Treatment patterns? From which country or countries? How many countries are "enough" to represent the EU as a whole? Must some "key" countries be included? What study designs are required? How, if at all, do requirements in orphan disease differ from non-orphan?
- **Acceptability of indirect treatment comparison.** The Member States currently differ on acceptability and, thus, the use of indirect treatment comparison (ITC). Will the assessment's approach be stricter, like that of the Institute for Quality and Efficiency in Health Care (IQWiG) in Germany, or more accepting, like that of the National Institute for Health and Care Excellence (NICE) in the UK?
- **Endpoints and outcomes.** The Member States also differ significantly on the use of certain categories of endpoints, such as so-called "surrogate" endpoints. How will the assessment manage surrogates? The regulation does mention, "patient-relevant health outcomes chosen for the assessment," but does not specify how these outcomes will be selected.[3]

No National Clinical HTA as of 2022

Article 8 of the regulation specifically forbids Member States from conducting clinical HTA on technologies assessed by the Coordination Group, and requires that Member States "apply" the reports in their national HTA.[3] Member States must notify the EC of any national HTA on technologies assessed by the Coordination Group, and must tell the EC how the joint assessment report was used in their national HTA.

What is uncertain is the recourse Member States will have if the assessment fails to provide the evidence they need to carry out the other elements of their national pricing, reimbursement, and market access (PRMA) process? For instance, what if the standard of care selected for the comparative efficacy and safety analysis is not used in their country? The regulation currently offers no guidance on this point.

Restrictions during Transitional Period (2019-2021)

Coordination Group members from any Member State who opt out during the transitional period will not be permitted to act as assessors or co-assessors during that period, or to comment on or participate in approval voting on joint clinical assessments during that period (per Article 10 of the regulation).[3]

Early Scientific Advice (ESA)

ESA will be available from the Coordination Group, including parallel advice with the EMA (per Article 12).[3] The Coordination Group will prioritize for ESA health technologies that are likely to undergo joint clinical assessment.

Conclusion

The Directive is driving European HTA towards significant change and yet, as currently written, significant uncertainty remains around its implementation and potential impact.

Major unanswered questions include:

- How will the comparator be chosen?
- How will the assessors be determined?
- What will be the assessment methods?
- What are the expected timelines for the assessments?
- How will Member States apply assessment findings?
- What will Member States do if/when assessment findings don't apply to their specific circumstances?
- How will Member States incorporate assessments into those parts of the PRMA process for which they retain authority, including health economic assessment, access, pricing, and reimbursement?
- What is the role and importance of patient-reported outcomes?
- What is the role and importance of RWE?

As the industry watches for further developments, it is suggested that manufacturers take some immediate steps.

- **Pipeline and portfolio management.** Not only pipeline products, but also inline products gaining new indications from 2019, will be affected. Once these uncertainties are resolved, HTA-geared trial evidence and RWE plans may need to be revamped.
- **ESA strategy.** All ESA will be facilitated at the EU level. Market-focused efforts need to be retooled.
- **Price negotiation dynamics.** Well-understood price negotiation dynamics (e.g., in France, negotiating with the Economic Committee for Health Products [CEPS] based on the improvement of medical benefit assessment [ASMR]) will be upended. Preparations must be made to negotiate based on the assessment report.
- **Expertise evolution.** There will be a shift in required expertise from knowledge of decision-making by bodies like IQWiG, to experience and expertise in pricing, contracting, and tendering.
- **Dual assessments during the transitional period.** During the transitional period, manufacturers of in-scope technologies should prepare for dual clinical assessments – particularly for countries likely to opt out of the assessment process during this time (i.e., Germany, France, Poland, Czech Republic). ■

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Bucher Versus Bayesian NMA Approaches for Indirect Treatment Comparisons

What Do HTA Agencies Want?

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When considering potential reimbursement of a new treatment, health technology assessment (HTA) bodies worldwide need to evaluate how the product's clinical effects compare with already available treatment options for the indication in question. One obvious source of such evidence is the randomized controlled trials (RCTs) conducted to obtain regulatory approval since these will have explored whether the new product offers superiority, equivalence, or non-inferiority compared to a standard of care or placebo. However, these studies alone are unlikely to provide enough information, given that it is usually impractical to compare the new treatment with all the available active comparators in RCTs, particularly where there is a rapidly changing treatment landscape populated by multiple competitor interventions. Consequently, it is common for there to be an absence of any direct comparisons between a new treatment and one or more relevant comparators. For this reason, indirect treatment comparison (ITC) is a standard approach manufacturers rely on for their HTA reimbursement submissions. Of various approaches for comparing treatments indirectly, two are most commonly used in the HTA setting: an adjusted indirect treatment comparison method first proposed by Bucher et al.[1] and the mixed treatment comparison (MTC) of interventions combining direct and indirect evidence within a Bayesian framework proposed by Lu and Ades.[2] There have been several extensions to the Bayesian NMA (network meta-analysis) methods proposed by Lu and others, especially around evaluating consistency between the direct and indirect evidence.[3-4] Here we consider the Bucher ITC and Bayesian NMA techniques, some common misconceptions surrounding their use, and how they are regarded by various HTA bodies worldwide.

About Bucher ITC

Bucher and colleagues developed a method to compare treatments indirectly by preserving the randomization of the originally assigned patient groups. This approach contrasts with the unadjusted indirect comparisons or


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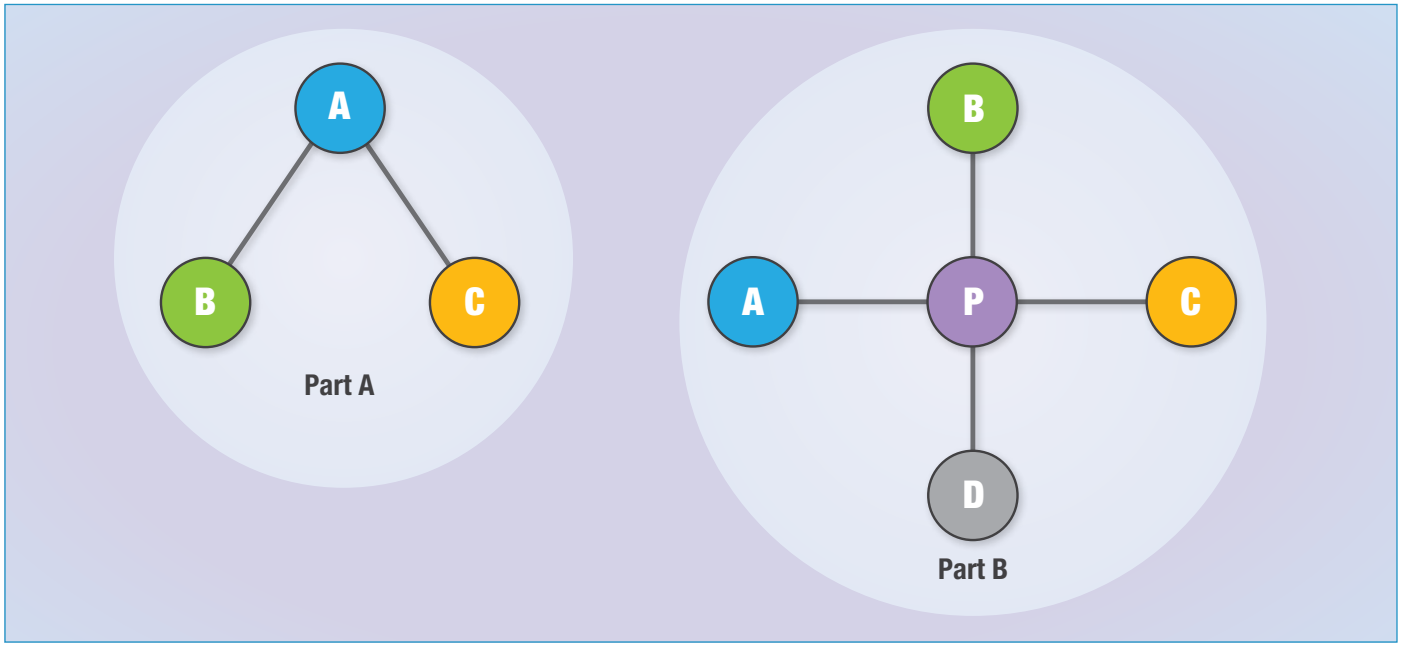
Figure 1.

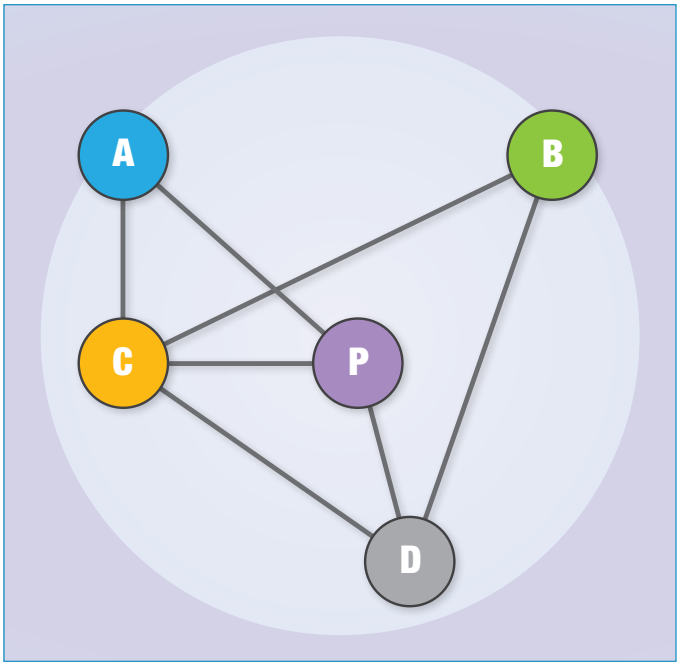


naïve comparisons of treatments, in which randomization between the treatment groups cannot be preserved.[1] Bucher analysis can be used in a simple indirect comparison to compare outcomes (either binary or continuous) between treatment B and treatment C (as in Part A of Figure 1) or across a star-shaped network of treatments, where several different interventions are compared to common comparator P (as in Part B of Figure 1). It assumes that the trials included in the ITC are similar with regards to the study population, study design, outcome measurements, and the distribution of treatment effect-modifiers (i.e., study and patient characteristics that have an independent influence on treatment outcome). However, this approach is unsuitable for performing indirect treatment comparisons within more complex networks of treatments with multi-arm trials, for which the Bayesian NMA methods are widely used instead.

About Bayesian NMA

The NMA method proposed by Lu and Ades, also commonly known as Bayesian NMA, differs from a standard meta-analysis. Specifically, it extends the concept of standard pairwise meta-analysis to conducting multiple pairwise comparisons across the interventions studied to yield the relative treatment effects. This approach combines both the direct and the indirect evidence for the interventions being compared.[2] It can be applied to networks with multi-arm trials and complex networks with closed loops, such as that shown in Figure 2. In addition to the continuous and binary outcomes, this approach can also be used to analyze counts and survival outcomes in trials. Similar to the Bucher ITC approach, the Bayesian NMA approach also has assumptions such as homogeneity, transitivity (similarity), and additionally, consistency, another key assumption of any NMA. Homogeneity occurs when the relative treatment effects of two interventions compared directly are similar across the trials including such a comparison in a network, and this can be tested using a statistic such as I^2. Similarity or transitivity looks at all the comparisons involved in the network to see if the trials included in the network are similar enough to be combined into a network. Similarity assumption requires that the distribution of the treatment effect-modifiers be similar across the studies included in the NMA, and this assumption can only be evaluated qualitatively not quantitatively. Consistency assumption of an NMA requires that when direct and indirect evidence are available for a pairwise comparison, the direct and indirect estimates should be similar statistically, and this assumption can be evaluated quantitatively using various methods.

Figure 2.



Common Misconceptions about the Methods

Although both Bucher ITC and Bayesian NMA are widely used, the following misconceptions are often expressed about both how they can and cannot be applied and the information they yield.

Bucher analyses can be used only when there is a single study per treatment comparison. The Bucher method is suitable, or even ideal, in such situations. However, it can also be used when multiple studies are available for one or more comparisons. If so, estimates from multiple studies for a treatment contrast are pooled into one estimate using classical (pairwise) meta-analysis approach before computing Bucher indirect estimate for a different treatment contrast.

Bucher ITC and Bayesian NMA are different statistical approaches, and so the results they provide will inevitably be different. In reality, where the treatment comparisons involve simple networks with two pairwise comparisons or a star-shaped network with a single common comparator, Bucher ITC and Bayesian NMA are likely to provide similar, if not identical, results. However, with more complex networks involving closed loops and multi-arm RCTs, the Bucher methodology cannot be applied, as it assumes independence between pairwise comparisons – something not found in multi-arm studies. The Bucher method has been formally compared to other ITC methods to evaluate whether both approaches produce mutually consistent results when used to conduct a given treatment comparison. For example, O'Regan and colleagues have compared Bayesian NMA and Bucher's method across a range of network types and concluded that in most cases, the two methods produced similar results, especially where all studies share a same comparator.[5] Also, Glenny et al. have compared Bucher's method with meta-regression, logistic regression, and mixed models from sample data of 15 trials, and concluded that, except for mixed models, other models provided comparable effect estimates and confidence intervals.[6]

What Do HTA Bodies Think?

The Bayesian NMA method can handle more complex networks with more than two treatment arms per trial, and can also incorporate meta-regression with study level covariates, analysis that is not possible with Bucher's method. Although Bayesian NMA offers these distinct advantages in the context of HTA submissions, both Bucher's and Bayesian methods are widely recognized as having a place by HTA bodies. However, there is some geographical variation across these organizations in how the two techniques are regarded.

IQWiG

Germany's Institute for Quality and Efficiency in Health Care (IQWiG) has made recommendations regarding the acceptability and use of indirect treatment comparisons. Specifically, it advises that ITC should only be considered when the analysis is targeted towards the overall research question rather than individual outcomes. Under these circumstances, IQWiG considers Bucher's adjusted ITC and Bayesian NMA methods to be appropriate for indirect comparisons in health economic evaluations.[7]

EUnetHTA

The European Network for Health Technology Assessment (EUnetHTA) also recognizes the use of both Bucher's method and Bayesian NMA for submissions. However, it notes that when the evidence supports the use of either method, Bucher's method offers the most in terms of transparency and ease of application. By contrast, EUnetHTA considers that the complexity of the Bayesian NMA models renders them less advantageous than Bucher's ITC.[8]

CADTH

The Canadian Agency for Drugs and Technologies in Health (CADTH) has reviewed the ITC methods in detail and recognizes the use of both Bucher's method and the Bayesian NMA. In doing so, it argues that the Bucher is appealing because it is designed to be applied with minimal information to the common ITC involving a simple star design. CADTH also considers the complexity of Bayesian NMA as a limitation to its use in comparing treatments indirectly.[9]

PBAC

Australia's Pharmaceutical Benefits Advisory Committee (PBAC) also acknowledges that Bucher's method is a widely accepted approach to ITC and suggests that more complex methods such as NMA may be presented as an appendix in the submissions.[10]

HAS

France's Haute Autorité de Santé (HAS) states that in the absence of any known differences between adjusted ITC methods and Bayesian NMA, it is difficult to recommend any approach. Therefore, HAS accepts the use of both Bucher's and Bayesian NMA, although it observes that the Bayesian NMA is the most useful method as it is flexible.[11]

Although HTA agencies differ subtly in their recommendations about using Bucher methods or Bayesian NMA, they all well understand from their wide experience that it is generally unwise to find statistically significant differences between active treatments in such analyses. Unlike the direct comparisons in clinical trials, an indirect comparison does not have to show statistical significance to be relevant or useful. Indirect comparisons (whether Bucher or Bayesian) inevitably have wider (95%) confidence/credible intervals than any given direct comparison included, and relative effects in comparisons between active treatments are generally expected to be smaller than those in comparisons between an active treatment and either no treatment or placebo.

Conclusion

Indirect treatment comparisons using Bucher's method or Bayesian NMA are generally accepted by HTA bodies for submissions to assess new technologies for potential reimbursement. Both approaches have key strengths and limitations, and these may determine whether one or the other is more appropriate to use in a given situation. However, in situations where both approaches can be applied, they can be used interchangeably, with the reasonable expectation of generating similar results. ■

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How Similar is "Similar"?
A Deeper Dive into Bucher Versus Bayesian Network Meta-Analysis

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Introduction

The companion article, *Bucher Versus Bayesian NMA Approaches for Indirect Treatment Comparisons: What Do HTA Agencies Want?*, in this issue of *The Evidence Forum* describes Bucher and Bayesian network meta-analysis (NMA) methods and how they are viewed by payers and health technology assessment (HTA) bodies. Here we elaborate on one of its key conclusions – that the two approaches usually yield similar, but not necessarily identical, findings. This potential for observed differences – even slight ones – can cause confusion and pose challenges around interpretation and use of the results. With this in mind, we examine what sort of numeric differences might be expected between the two methods and the possible causes.

As summarized in Table 1, there are three primary reasons why Bucher and Bayesian results might differ. Each reason is independent of the other two, and discrepancies between analyses can come from more than one source.

This potential for discrepancies between analyses is concerning on its own for a pharmaceutical company, however, it may be compounded by another challenge – that is, differences between the results in the company's (single) key trial and the results from a Bayesian NMA that includes that trial. This complication raises two additional points for consideration:

1. Why do Bayesian NMAs sometimes give results for a treatment comparison that differ from those reported in a single trial involving that comparison?
2. Why would a Bayesian NMA **give results that do not show statistical significance, unlike those from the head-to-head, single-trial comparison?**

We discuss all these issues in more detail below, using an invented treatment network for illustration.

Table 1.

Reason for Discrepancy (Bucher vs. Bayesian)	**Potential Discrepancy** (Central Point Estimate)	**Potential Discrepancy** (95% Interval)	**Scenario**
Bayesian "noise"	Extremely Small	Extremely Small	Any
(Slight) differences in statistical modeling	Extremely Small to Small	Extremely Small to Small	Any
Difference in the estimates of heterogeneity between the analyses	Extremely Small to **Moderate**	Small to **Large**	Random-effects analysis only


Kyle Fahrbach

The Treatment Network

Figure 1 shows our invented network – one in which most studies have involved a common comparator (in this case, placebo), with one or two studies in the periphery. In this network, there is only *one study* per individual treatment comparison. For purposes of instruction, the network has no "closed loops", i.e., no instances where for any given comparison there is both direct and indirect evidence, or multiple paths of indirect evidence. (As noted in the companion article, networks with many "closed loops" are generally best analyzed with full network approaches rather than multiple, parallel Bucher analyses, although the latter remains an option.)

We use this network to provide examples of analyses using the Bucher and Bayesian approaches and to describe how discrepancies might arise when the techniques are applied side-by-side. As might be expected, the size of the potential discrepancies in estimates between the two methods is proportional to the complexity underlying that discrepancy. We begin, then, with the issue of "Bayesian noise."[a]

Table 2a. Estimates of Sucrosa vs. Pacifex
(Mean Differences with 95% Confidence/Credible Intervals)

Analysis Technique	Network 1A
Bucher	8.50 [4.63, **12.37**]
Bayesian (fixed-effects [FE] model)	8.50 [4.63, **12.36**]
Bayesian (FE, increased # of simulations)	8.50 [4.63, **12.37**]

Example 1. Discrepancies from "Bayesian Noise" for Mean Differences

In the simplest case – a two-study network (Network 1A) with an outcome such as a hazard ratio (HR) or mean difference – the similarity between results from a Bucher and a Bayesian (fixed-effects model) approach is obvious, but with a small catch. (Table 2a)

Specifically, both approaches give substantively identical point estimates and 95% intervals (as seen in the first two rows of Table 2a) – but they are not **completely** identical, as there is a 0.01 difference in the upper end of the 95% intervals. Similar discrepancies, on the order of a rounding error, often occur when conducting Bayesian NMAs. This is due to the analytical approach used in Bayesian estimation – the Markov chain Monte Carlo (MCMC) method – in which statistical models are used to simulate, and thereby predict outcomes of, treatment comparisons. This use of simulations means the Bayesian approach does not calculate estimates exactly, and changes to the key model inputs and/or the number of simulations can result in minor variations in the results.

The solution to this problem (if, indeed, one is deemed necessary) is usually simple: increase the number of simulations per chain (i.e., run 100,000 simulations instead of 50,000) and/or increase the number of MCMC chains (as each chain has its own unique set of simulations); as the total number of simulations increases, random noise will decrease.

[a] This section is dedicated to every pharmaceutical company who has asked why a result changed by 0.01 after an update.

Figure 1. Single-Study-Per-Comparison Network (Mean Difference Example)

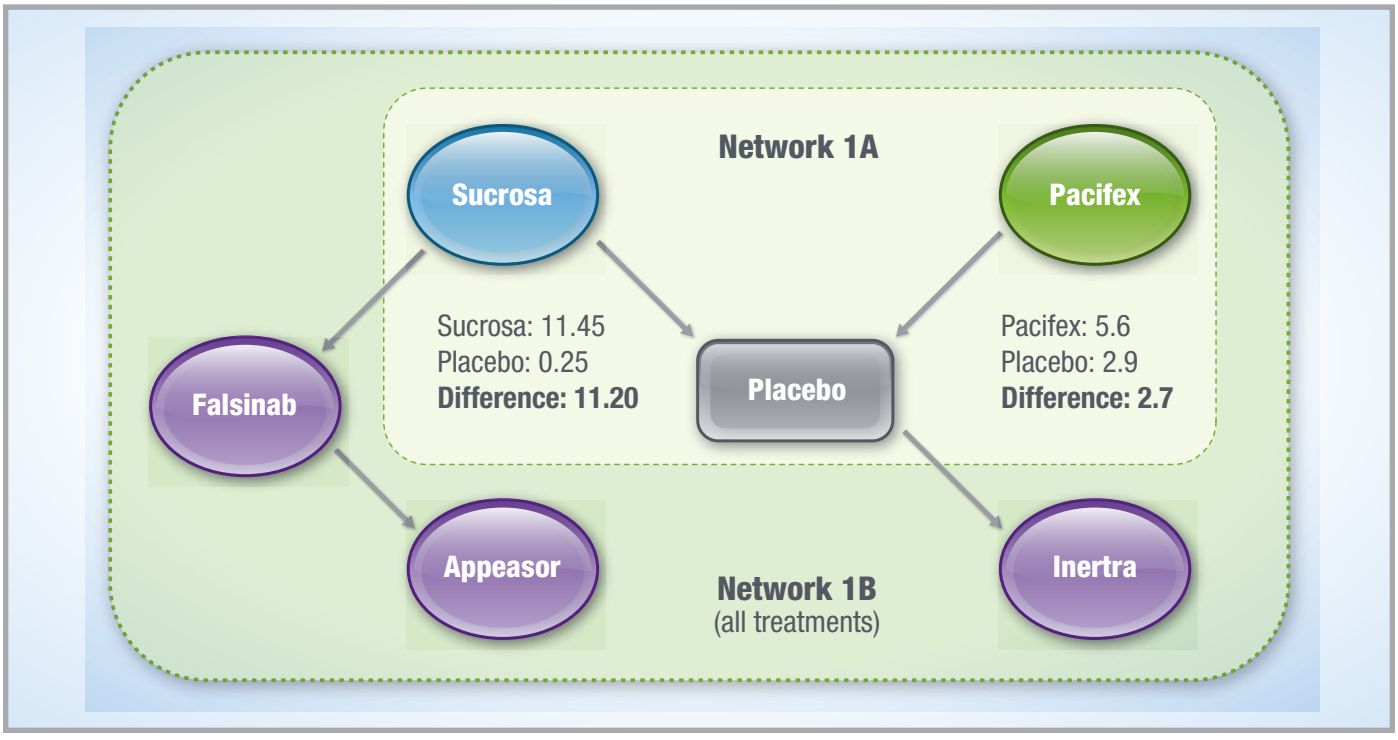


Table 2b. Estimates of Sucrosa vs. Pacifex
(with 95% Confidence/Credible Intervals)

Analysis Technique	Network 1A	Network 1B (Full Network)
Bucher (extra decimal place in reporting)	8.500 [4.632, 12.368]	8.500 [4.632, 12.368]
Bayesian (FE) (extra decimal)	**8.502** [4.632, 12.373]	**8.499** [4.629, 12.370]

That said, increasing the number of simulations does not make Bucher and Bayesian estimates equivalent – it simply reduces the discrepancy from trivial to even more trivial. In this context, it is worth considering what the estimates look like after we expand the treatment network to include peripheral studies (i.e., those that did not include placebo as a comparator). As shown in Table 1b, the Bucher comparison for Network 1B gives the exact same estimate as found for Network 1A, and as before, essentially the same estimate as in the Bayesian analysis.

In Table 2b, we also add an extra decimal place to the reporting; not because these numbers are meaningful (imagine, for instance, meta-analyzing blood pressure change and thinking about the third decimal place) but to re-emphasize the point that Bayesian estimates change slightly from analysis to analysis. The difference between the Bayesian results for Network 1A versus Network 1B has nothing to do with the content of the extra studies - it is simply different "Bayesian noise" at work.

The important takeaway of the Network1B results is that adding studies to the periphery does not *meaningfully* change NMA estimates. In this example, while the Falsinab vs. Sucrosa study may have information on the efficacy of Sucrosa, the study does not provide information about the *relative effect* of Sucrosa vs. Placebo, and so its addition does not change the Sucrosa vs. Pacifex estimate.

Example 1 Takeaways

For mean differences and hazard ratios (HRs) in simple one-study-per-comparison networks:

- Bucher and Bayesian analyses give essentially identical results
- Bayesian results can be very slightly different depending on the number of simulations run (Bayesian results are not "exact" as they incorporate some random noise)
- Peripheral studies do not meaningfully change estimates for the treatment comparisons of primary interest

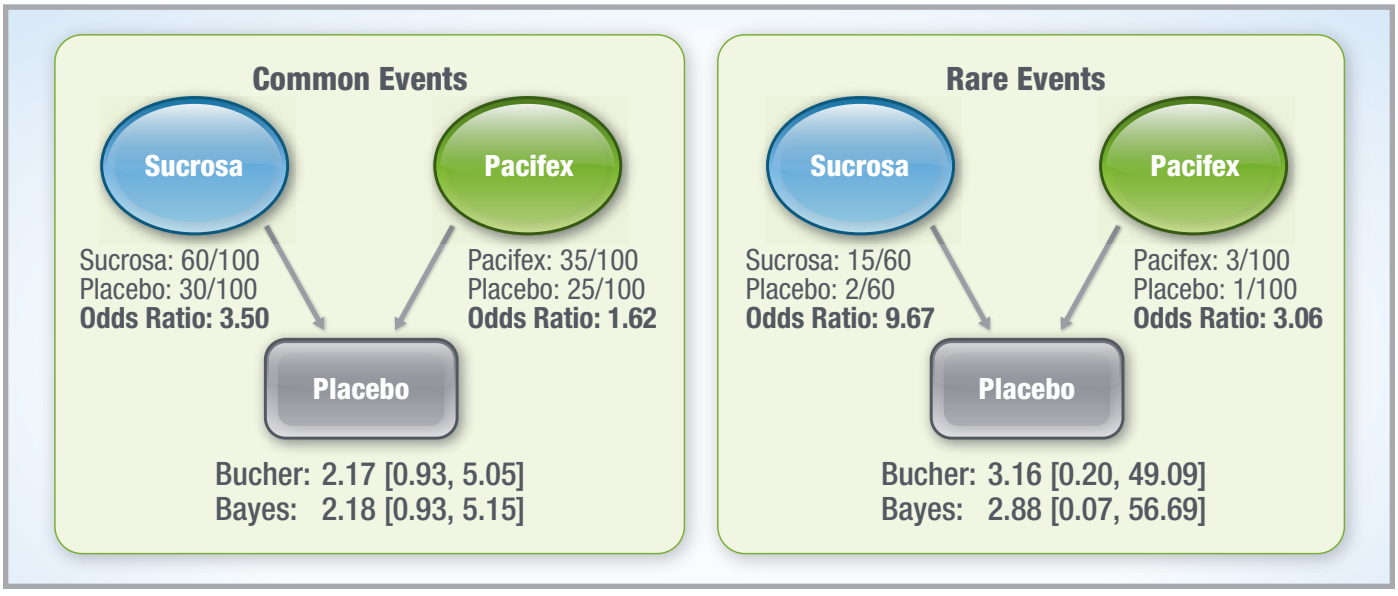
Example 2. Discrepancies from (Slight) Modeling Differences (Odds-Ratios)

The standard Bucher and Bayesian approaches use different statistical techniques; this accounts for why they often produce similar, but not identical, results. Specifically, the Bucher method is based on a classical odds-ratio calculation, while the Bayesian approach (usually) uses arm-level data and assumes a binomial distribution to model the event rate in each arm (Figure 2 and Table 3).

Table 3. Estimates of Sucrosa vs. Pacifex
(Odds-Ratios with 95% Confidence/Credible Intervals)

Analysis Technique	Common Events	Rare Events
Bucher	**2.17** [0.93, **5.05**]	**3.16 [0.20, 49.09]**
Bayesian (FE)	**2.18** [0.93, **5.15**]	**2.88 [0.07, 56.69]**

Figure 2: Single-Study Network: Odds Ratios Examples



For common events, (i.e., where all arms have at least four events), results are only trivially different. However, in this case, the discrepancy is not primarily due to random noise and , therefore, cannot be addressed by increasing the number of simulations in the Bayesian MCMC estimation. By contrast, for rare events (roughly defined as <4 events in at least one arm), the discrepancy is often greater. This difference, however, is arguably not substantive. While a difference in odds between 3.16 and 2.88 may seem important, consider the two 95% intervals, which imply that Sucrosa may have 30 to 50 times the odds of an event compared to Falsinab, or, alternatively, perhaps only have 1/5th to 1/10th the odds. This high level of uncertainty (which would increase the more disconnected the network)[b] illustrates how indirect comparisons for rare events are *extremely* susceptible to slight differences in study methodology, event definitions, and treatment effect-modifiers (i.e., patient or study characteristics that influence treatment outcomes). The primary concern, therefore, should not be whether the Bucher or Bayesian estimates represent the "better" option but the interpretability and usefulness of the result given the wide 95% intervals.

Example 2 Takeaways

- For some outcomes, such as odds-ratios, Bayesian and Bucher results are very similar, but not identical, due to a slight modeling difference between the two approaches.
- The differences are biggest when there are data with rare events; however, these differences pale in comparison to other issues that arise with indirect comparisons at that point.

Note that we do not need to see what would happen if we expanded the network as we did in the first example. The only change would be a miniscule difference in Bayesian results due to Bayesian noise. The peripheral studies would not affect anything else in the Sucrosa vs. Pacifex comparison.

Example 3. Discrepancies Caused by Differences in Random-Effects Estimation

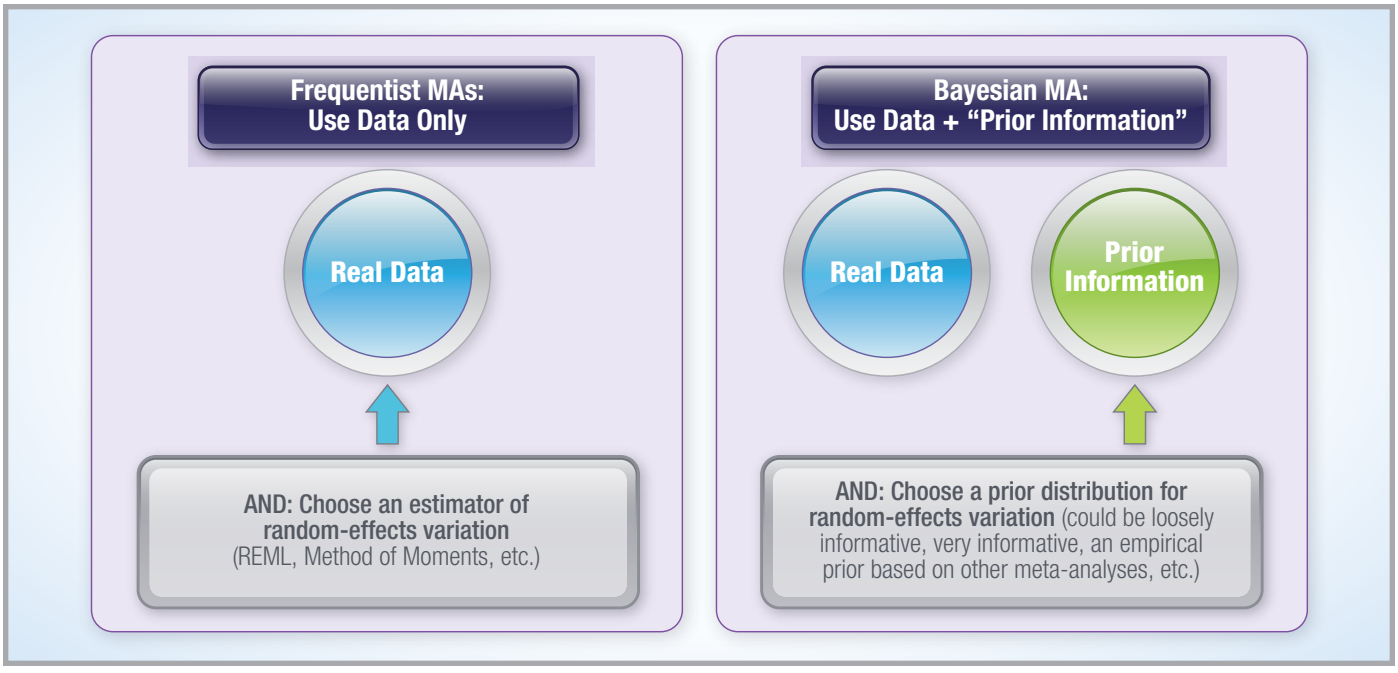
When more than one study exists for any given comparison, random-effects analyses are possible (i.e., analyses that measure and account for statistical heterogeneity – that is, variation in study effects greater than that expected from sampling error alone).

As summarized in Figure 3, Bucher random-effects analyses use classical (frequentist) random-effects meta-analyses to aggregate data for each pair-wise comparison of two or more studies, and then apply the usual Bucher calculations. If there is only one trial for a given link between treatments in the network, then the data from that study is used. Bayesian random-effects analyses start with a prior distribution for the random-effects variance and incorporate it into all estimates (Figure 4).[c]

[b] Indirect comparisons on outcomes with rare events sometimes lead to outrageously wide 95% intervals when two treatments of interest can only be compared though a long chain of studies in the evidence network. For instance, in Network 1B, an Appeasor vs. Pacifex comparison on rare events could have an upper 95% interval in the thousands.

[c] While it is not commonly done, it is possible to conduct a random-effects analysis on data from networks in which there is only a single study per comparison. In this situation, because there are no data available to help estimate a variance, the Bayesian estimate of the RE variance will be 100% dependent on whatever "prior" chosen. This might be done in situations where it is known that treatment effects tend to vary in efficacy but the dataset at hand has only one study per comparison. The only effect would be an inflation in the 95% credible intervals.

Figure 3. Random-Effects Bucher (Frequentist) vs. Bayesian



Before we visit our examples, however, it is important to note the difference in the "fixed vs. random-effects" choice being made for Bucher, compared to that for Bayesian.

Bucher
Fixed- vs. Random-Effects Analysis
(as traditionally conducted)

- Each individual meta-analysis gives its own estimate of random-effects variance, which might be zero. When it *is* zero, random-effects results are **equivalent** to fixed-effects results.
- There is no one "true" estimate of random-effects variation; different frequentist methods can give different estimates, and the "better" approach is a matter of judgment (e.g., see Veroniki 2015[1]).

Bayesian
Fixed- vs. Random-Effects Analysis
(as traditionally conducted)

- Random-effects results generally have (at least slightly) **wider 95% credible intervals** compared to fixed-effects results even when there is no apparent statistical heterogeneity (because we start with a prior distribution that, on average, assumes some heterogeneity).
- One global estimate of random-effects variation is used and applied to all treatment comparisons **(even single-study treatment comparisons)**
- There is no one "true" estimate of random-effects variation; different Bayesian prior distributions methods can give different estimates, and which method represents the "better" approach is a matter of judgment (see Lambert 2005,[2] Turner 2014[3])

There are three main drivers in differences between Bucher and Bayesian results.

1. The amount of heterogeneity seen in the data (e.g., none, low, moderate, high)
2. The number of studies available for each comparison (e.g., two studies available for one comparison vs. many studies available for multiple comparisons)
3. The level of variability used in the Bayesian "prior" (e.g., "zero to moderate heterogeneity" vs. "zero to high heterogeneity" vs. "zero to very high heterogeneity"). Note the last seems "safest" in that it seems to allow for the greatest range of values; however, as extremely well described by Lambert et al.,[2] such a prior also can have the effect of inflating the estimate of the random-effects (RE) variance.)

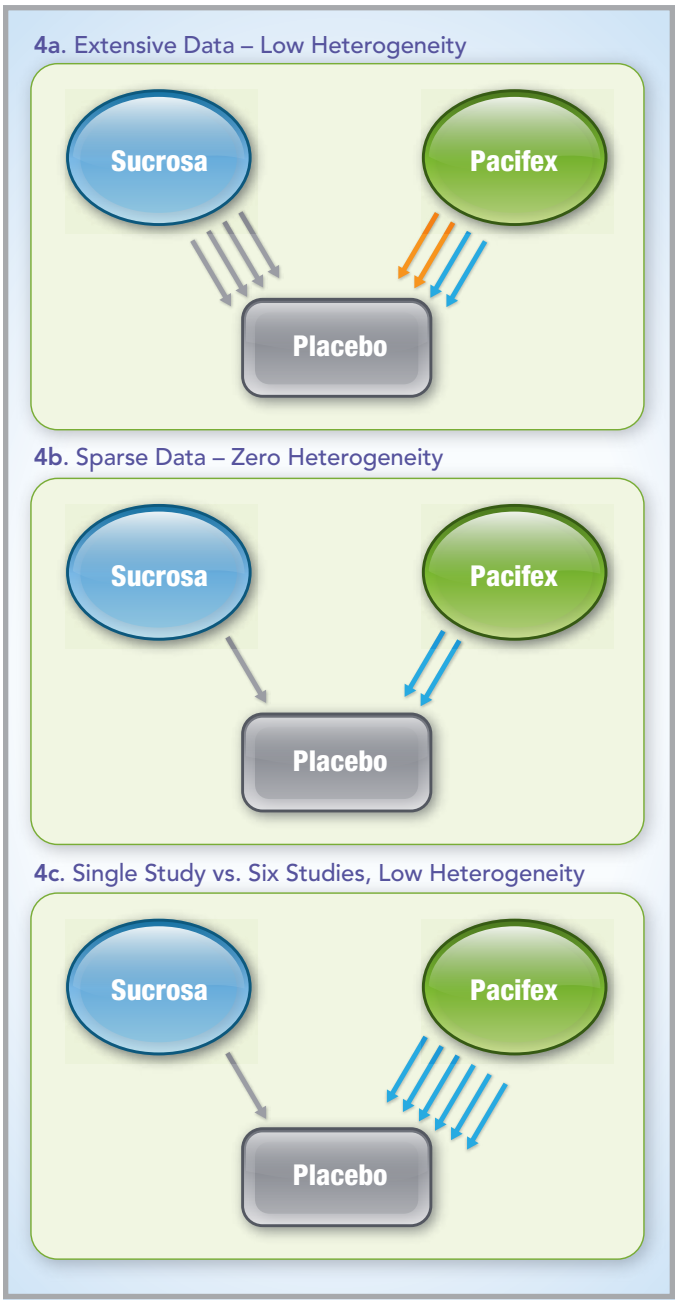
Summary

Drivers of potential discrepancies between Bucher and Bayesian for random-effects include:

- Amount of heterogeneity
- Number of studies
- Bayesian prior used

As is obvious, adding in estimates of random-effects variation to the equation leads to a great deal of complexity in explaining potential differences between Bucher vs. Bayesian results. While we cannot cover all combinations of factors here, three exemplars will help demonstrate what sorts of differences might be expected.

Figure 4.



Example 3a. Many Studies Per Comparison, Low Statistical Heterogeneity

Where there are many studies per comparison and low statistical heterogeneity (see Figure 4a), Bucher and Bayesian analyses result in similar estimates (see Table 3a). This is because they have similar estimates of random-effects variation. However, the 95% intervals generated by the Bayesian approach are slightly wider than those under the Bucher approach – a function of the prior used.

It is worth recalling that Bayesian results are driven by a combination of the data and the selected prior (Figure 3), so unless there is an overwhelming amount of data, the choice of prior will have some noticeable impact on the results. In this example, while our data suggest there is little heterogeneity, the Bayesian prior used here assumes (as a start) that heterogeneity is, on average, moderate or high. This prior pulls up the final estimate of random-effects variance a small amount.

*While rare, the opposite situation can also occur. If a very informative (i.e. narrow) prior distribution is used, and the variability in the observed data is *higher* than the average guess at heterogeneity represented in the prior, then the 95% interval obtained through the Bucher approach can be wider than that from a Bayesian analysis.*

Example 3b. Two Studies for One Comparison, Zero Statistical Heterogeneity

Figure 4b presents the "worst case scenario" for discrepancies between Bucher and Bayesian results, which occurs when:

1. There is minimal information with which to estimate a random-effects (RE) variance,
2. What little information there is, suggests that there is zero RE variance, and
3. The Bayesian prior suggests that there could be a lot of RE variance.

In such a case, the Bucher approach will estimate (based on the observed data) zero RE variation, while the Bayesian approach will estimate a large amount of RE variation. This leads to much wider intervals for the Bayesian approach (see Table 3b). The Bayesian results here rely heavily on the choice of prior, since there is little observed data from which to estimate RE variation; thus, not fully trusting the observed data, the conclusion is that there most likely is a lot of RE variation.

When observing the results on the logscale, the width of the Bayesian 95% interval based on a less informative prior is almost three times the width of the Bucher interval. By comparison, when the analysis is based on a more informed prior, the interval is about one and a half times the width. The main cause of this discrepancy is as stated previously – the Bucher result is basically the fixed-effects result, while the Bayesian approach estimates substantive random-effects variance, and the width of the 95% intervals are very sensitive to the choice of prior. (The point estimates, ranging from 1.30 to 1.36, are not nearly as sensitive. The methods have different estimates of random-effects variation, and so weight the studies slightly differently, which leads to small differences in point estimates between the two analytical approaches.)

The last two examples suggest that when there are robust data and zero-to-low heterogeneity, Bayesian results tend to have *slightly* wider 95% intervals than Bucher results, and when there is sparse data, Bayesian results tend to have *much* wider 95% intervals. In cases where there is robust data and more heterogeneity, Bayesian and Bucher results are more closely aligned, as the Bayesian priors match more closely with what is seen in the data.

Example 3c. Six Studies for One Comparison, Low Statistical Heterogeneity

Figure 4c illustrates a commonly observed network, wherein there is a well-studied (but ineffective) standard-of-care treatment (in this case, Pacifex), and a new (and believed to be more effective) treatment (Sucrosa) for which there is a single study presenting statistically significant results.

Table 3c presents the study-level data and results of an analysis that, if viewed from a manufacturer's perspective, may well prompt the following questions.

1. ***"Why isn't Sucrosa statistically significantly better than Pacifex?"*** (i.e., the HR estimated for Sucrosa vs. placebo is statistically significant, with an upper 95% confidence interval of 0.90, while the average HR for Pacifex vs. placebo is 0.93).

Table 3a. Estimates of Sucrosa vs. Pacifex
(Hazard Ratios; Four Studies per Link, Low Heterogeneity)

Analysis Technique	Common Events
Bucher	1.36 **[0.96, 1.93]**
Bayesian (wider, i.e., less informative, prior)	1.36 **[0.86, 2.16]**
Bayesian (narrower, i.e., more informative, prior)	1.36 **[0.91, 2.04]**

Table 3b. Estimates of Sucrosa vs. Pacifex
(Hazard Ratios; Two Studies for One Link, Zero Heterogeneity)

Analysis Technique	Common Events
Bucher	**1.30 [0.87, 1.96]**
Bayesian (wider, i.e., less informative, prior)	**1.36 [0.38, 5.15]**
Bayesian (narrower, i.e., more informative prior)	**1.34 [0.69, 2.73]**

2. *"Why does the Bayesian estimate for our drug vs. placebo no longer look statistically significant?"* (i.e., the Bayesian 95% interval estimated for Sucrosa vs. placebo is not the same as the 95% interval reported for our trial)

The answer to the first question was touched upon previously. The results of both Bayesian and Bucher NMAs are always less precise than any individual-study result or any single meta-analysis, i.e., the 95% intervals for indirect comparisons are always wider than those for any individual direct comparison. In fact, it would not be difficult to construct a scenario in which there is a significant result vs. placebo and a non-significant result vs. Pacifex even though Pacifex performed "worse," on average, than the placebo. With indirect comparisons, it is best to focus on the size of the point estimates and the width of the 95% intervals and not on whether the intervals overlap 1.0 (or 0.0 for mean differences).

The answer to the second question has to do with the nature of Bayesian analysis. Conventionally, in this approach, one global estimate of random-effects variation is used, and applied to all comparisons in the network. In this example, the study result for Sucrosa vs. placebo gives a 95% confidence interval of the treatment effect in a specific study population, while the Bayesian analysis gives a 95% credible interval for the effect across *all* similar study populations. So, while there is no between-study heterogeneity observed for the comparison of Sucrosa vs. placebo (because there is only a single study), the (non-zero) estimate of heterogeneity for Pacifex vs. placebo is applied to the Sucrosa vs. placebo result. This leads to a wider 95% interval.

If the populations in the Sucrosa and Pacifex studies are considered clinically similar, it is realistic to believe that Pacifex vs. placebo estimate of random-effects variance is generalizable to the Sucrosa vs. placebo results. Simply put, if there is heterogeneity for the comparison of Pacifex vs. placebo, we can expect that upon further investigation of Sucrosa vs. placebo that there would be heterogeneity there as well – we just can't see it yet, as there is only the one study. This means that while the single-study result for Sucrosa vs. placebo may not overlap 1.0, the Bayesian estimate of that effect across all studies may indeed do so.

Table 3c. Estimates
(Hazard-Ratios; Six Studies for One Link, Low Heterogeneity)

Comparison	Source/Analysis Type	Result
Sucrosa vs. Placebo (1 study)	Study Result	0.60 [0.40 – 0.90]
	Bayesian Estimate	0.60 [0.34 – 1.07]
Pacifex vs. Placebo (6 studies)	Frequentist Meta-Analysis	0.93 [0.76 – 1.13]
	Bayesian Estimate	0.93 [0.73 – 1.17]
Sucrosa vs. Pacifex	**Bucher Estimate**	0.65 [0.41 – 1.01]
	Bayesian Estimate	0.65 [0.34 – 1.20]

Example 3 Takeaways

- Bayesian and Bucher random-effects point estimates are usually very similar
- Bayesian 95% intervals are usually wider than Bucher 95% intervals
- Bayesian priors can be wide or narrow
- When these priors are averaged with the data, substantive random-effects variation may be estimated even if it is not seen (yet) in the data

In Defense of Wider (Bayesian) Intervals

Our exploration of the source of discrepancies between the results of Bucher vs. Bayesian analyses started simply enough, with the finding that the two sets of results ranged from being "identical-within-rounding-error" to "extremely similar" to "still, pretty similar." However, once random-effects variation had to be considered, the low level of

Bayesian Priors for Random-Effects Variation

Bayesian Estimates = Prior information + Data

- All Bayesian models start with a "first guess" for each statistical parameter. Each guess has the form of a probability distribution – the so-called *prior distribution*.
- For many parameters, data drives all estimates, and priors are truly "non-informative."
- For random-effects variation, however, the prior information chosen can have a noticeable effect. There is no such thing as a truly "non-informative" prior.
- Conventional priors for random-effects variation have a wide range (e.g., the guess is that variation is zero to "very high"), though it is increasingly common to use less vague, more informative priors (e.g., zero to "moderate").
- If the average guess at variation in Prior Information is different than what is in the Data (either higher or lower), the Bayesian Estimates will get pulled in that direction. The amount of the pull depends on how much data is available.

discrepancy between the analytical approaches held for point estimates, but not for the width of the 95% intervals. While the size of the discrepancies was heavily dependent on the number of studies available and the amount of heterogeneity in the data, another key driver for the difference was the "prior information" used in the Bayesian analyses for random-effects variance.

The argument about which of the two approaches is better varies and in some cases, is quite philosophical with regards to the applicability of estimates of variation from prior meta-analyses; the difference in interpretation of results for frequentists vs. Bayesians; the meaning of "prior knowledge"; and so on. However, from a practical standpoint, most HTA bodies see little harm in being conservative by risking an overestimation of the width of 95% intervals as opposed to risking underestimation, and they understand how poor the estimate of random-effects variation is when, for example, only two or three studies are available for a particular treatment comparison. Simply because a small number of available studies show no heterogeneity does not mean there is none, yet that simplistic implication is inherent in a Bucher ITC (indirect treatment comparison). Furthermore, it is rare for indirect comparisons to show "significant" differences (i.e., 95% intervals that do not overlap 1.0 for ratios, or 0.0 for mean differences). So generally, little is lost in basing conclusions about the treatment comparisons on the potentially more conservative 95% intervals generated by the Bayesian approach. Finally, the growing popularity of empirical prior distributions (which tend to be less conservative/more informative than the common default priors, e.g., Pullenayegum 2011,[4] Turner 2014,[3] Rhodes 2015[5]) will lead to even less of a discrepancy between Bucher and Bayesian results.

Final Takeaways

- For single-study-per-link networks, Bucher vs. Bayesian results are near-identical
- For multiple-study-per-link networks, Bayesian results are likely more conservative (but arguably more realistic)
- There may not be much risk in 95% intervals being conservative
- Bayesian models as the base-case will offer more flexibility in general

Given that the Bayesian approach copes better with "closed-loop" evidence networks and also allows the use of meta-regression and other model additions, it is not surprising that it is the approach preferred by NICE and many other HTA bodies. But as indicated above, Bucher analyses certainly still have a place. ■

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Meaningful Treatment Benefit from the Patient's Perspective

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Have you been told by the U.S. Food and Drug Administration (FDA) to include the patient's perspective about treatment benefit in your drug development program? The feedback could be a question such as *"what magnitude of change does the patient consider to be a meaningful treatment benefit?"* or a statement such as *"patient input on what amount of change they consider meaningful is recommended."* With the 21st Century Cures Act, there is an increased focus on the patient's perspective and now, more than ever, regulators are seeking feedback from patients throughout the drug development process.

There are a few critical issues to be addressed during the drug development process. First, the concepts being evaluated from the patient's perspective should be meaningful and relevant to the patients. While this seems like an intuitive and unnecessary statement, evidence demonstrating the relevance of an outcome to the patient is critical.[1] The evidence can be obtained from qualitative patient interviews or focus group discussions. After confirming that the concept/outcome is relevant and meaningful to the patient, patients should be consulted about the benefit of their treatment. This can occur pre-study as a hypothetical exercise or can occur during exit interviews during the clinical trial program. Finally, patients can work closely with their clinicians to monitor their treatment to fit their individualized treatment goals (this is beyond the scope of this article). This article will focus on the qualitative research that can be conducted to evaluate a meaningful treatment benefit both before and during clinical trial implementation.

Pre-trial interviews are one approach to gain patient insight as to meaningful treatment benefit. There are multiple goals that should be kept in mind when pre-trial interviews are designed, the first of which is to identify the concept(s) of interest. In other words, determine the primary symptom(s) or impact(s) that are drivers for that patient population of interest (for example, a key concept in many disease areas is pain). A second goal of pre-trial interviews is to assess the current severity/intensity/frequency of the experienced concept(s). A third goal may be to explore meaningful outcomes related to the concept(s) of interest that patients would like to see improved, e.g., a meaningful outcome related to the experience of pain may be to sleep better or to return to work. The final goal is to ascertain the amount of change on the assessment that is measuring the

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concept that would need to be experienced for the patient to perceive having experienced a meaningful treatment benefit.

In conjunction with each of these four goals, some example questions that can be tailored, and incorporated into pre-trial interview guides, are shown below in Table 1.

There are multiple challenges of pre-trial interviews to keep in mind. For one, there is no existing guidance within industry on how best to conduct pre-trial interviews. Secondly, conceptually, the idea of meaningful treatment benefit can be very difficult for patients to grasp. Add in the fact that the conversation about the expected/anticipated/desired benefit is hypothetical, and it is easy to see how experienced methodologists are needed for the design and execution of the interview guides. Another challenge is the COA itself, typically a patient-reported outcome (PRO). Some COAs, like the numeric rating scale (NRS) for pain, are a single item, a single concept, and are easily scored from 0-10. Meanwhile, others are multi-item, multi-scale instruments, sometimes with complex scoring algorithms. Discussing score changes on multi-item, multi-scale instruments with patients requires the input of skilled methodologists with creative approaches for establishing patient understanding and engagement.

Once meaningful concepts have been identified and a meaningful outcome included in the trial program (e.g., PROs), another opportunity to receive feedback directly from the patient (including assessment of meaningful treatment benefit) is during the clinical trial itself. These interviews are often referred to as "exit interviews" but do not necessarily need to be conducted at the end of the trial period. The study's primary efficacy endpoint time may be a better fit to receive patient insight.

There is no formal regulatory guidance on how best to conduct exit interviews in terms of the proportion of trial subjects to be interviewed, timing of the interview, handling of qualitative data analyses against the quantitative data, etc. Often, the Sponsor's impetus for exit interviews is in reaction to regulatory feedback but often the Sponsor does not receive direct reaction about the study design. This is likely a reflection of the increased focus on the patient's perspective during drug development. Guidance for best practices should be developed. In terms of an adequate sample size, there is evidence that the FDA has received exit interview data from as few as three interviews, which was related to Amgen's Aimovig™ (erenumab).[2]

Patients from all treatment arms should be included in the exit interviews; both treatment and placebo. Of course, the randomization assignment will be masked during data collection and the sample size should be large enough to accommodate a representative reflection of randomization arms. Even patients who withdraw early from the trial may hold deep insight as to why the treatment did not provide a treatment benefit. If the patient withdraws early it could be because of perceived lack of efficacy, adverse events, or simply personal barriers in the trial (e.g., travel, time at the clinic site, etc.).

One could argue that the exit interview feedback about meaningful treatment benefit is more insightful than pre-trial, abstract interviews as these patients can be directly interviewed about their study experience. Patients from both active and placebo arms can provide valuable feedback about their experience. Interviews can be targeted to include the patient's experience with their condition before the study, their expectations for the study, the changes they experienced during the study, how those changes impacted their daily life, and about potential

Table 1. Example Pre-Trial Interview Questions

Goal	Example Questions
Identify Concept(s)	• What symptoms do you experience as a result of your *condition*? • Do some symptoms from your *condition* bother you more than others?
Assess Current Intensity/Severity/ Frequency Level	• How often do you experience *symptom*? • How severe is the *symptom*? • This questionnaire is about your current experience of *symptom*. How did you rate your *symptom*?
Explore Meaningful Outcome(s)	• How does *symptom* impact your daily life/activities? • Tell me how your life would be different if you didn't experience *symptom*? • Assuming there is no complete cure for *condition/symptom*, what improvements to your *condition/symptom* would make you say that a treatment is effective?
Ascertain Meaningful Change on Clinical Outcome Assessment (COA)	• If you received a treatment for *condition/symptom(s)*, what is the smallest level of change on this scale that you would have to experience to know the treatment is working? • If you received a treatment for *condition/symptom(s)*, what level of change on this scale would be meaningful to you? • If you received a treatment for *condition/symptom(s)*, what amount of change in *relevant anchor* would be meaningful to you?

Table 2. Example Exit Interview Questions

Goal	Example Questions
Pre-Trial Experience with Condition	• What were your *symptom(s)* from *condition* before the start of the study? • Before the start of the study, how did your *symptom(s)* impact your daily life/activities?
Expectations of Treatment	• What were your expectations in terms of a change in your *condition/symptom(s)/impact(s)* through participation in this study?
Experiences During the Trial	• Tell me about how your *symptom(s)/impact(s)* changed from the beginning to the end of this study.
Impact the Changes had on Daily Life/ Activities	• How did the changes in *symptom(s)* affect what you were able to do in your daily life?
Were the Changes (Symptoms/Impacts) a Benefit that was Meaningful?	• Did the changes that you noticed in *symptom(s)/impact(s)* matter to you? • Did your *symptom(s)/impact(s)* improve enough that you would continue this treatment?
Other Questions Unique to the Intervention	• Would you change the device in any way to make it easier to use?

treatment benefits. The rich detail patients provide about their experiences helps enrich the comprehension about the patient's understanding of treatment efficacy. Finally, patients can also be asked about the intervention itself or other unique aspects specific to the intervention. Table 2 displays some example questions for these exit interviews.

One recent example of a mixed methods exit survey and interview study involving 242 quantitative exit surveys and 80 qualitative telephone interviews is arguably a gold standard for this type of exit study.[3,4] The survey asked trial participants to assess specific experiences using the following responses:

- Overall, I did not benefit
- Overall, it was beneficial but was not meaningful to me
- Overall it was beneficial and was meaningful to me

Statistically significant group differences between treatment and placebo groups were demonstrated in terms of proportion of patients reporting meaningful benefits. Further, the research was able to illustrate the patient-centered findings using the richness of the qualitative data – the verbatim patient quotes.

Together, the pre-trial interviews and trial exit studies can help inform drug development programs of the patient's perspective about meaningful treatment benefit. There are a number of methodological considerations for both approaches. For example, how easy or difficult the conceptual exercise of a pre-trial interview about meaningful benefit can be to the target population. Are the patients being realistic with their expectations? Strategic considerations for exit interviews should also be considered, such as the sample size, the operational aspects of planning such interviews (e.g., stand-alone protocol or included in the trial protocol; clinic site contracting; ethics approvals with the trial applications or stand-alone applications, etc.), handling of suspected adverse events, and timing of exit interviews. Without question, patients are at the center of any drug development program. Obtaining patient feedback about meaningful treatment benefits is an integral component of a patient-centric approach to drug development. ■

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Machine Learning
Biopharma Applications and Overview of Key Steps for Successful Implementation

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Introduction

Machine Learning (ML) is the science of programming computers to perform tasks based on rules learned from data instead of rules explicitly described by humans. Although statistical methods in health care for tasks such as stroke risk prediction[1] have been in use for a long time, three trends enabled the widespread adoption of ML applications in the past decade: increase in computing resources and cloud services that allow generation and storage of massive quantities of data; availability and digitization of diverse data sources (e.g., genomics databases, electronic health records, patient registries, large commercial databases, social media, and data collected through wearable technologies), and improvements in ML algorithms such as random forests, support vector machines, and deep learning, which can reveal complex relationships in data that simpler algorithms might miss.

Despite the advances in the adoption of ML methods in the pharmaceutical industry, there is room for increased application, especially in late stage development. According to a 2017 survey of 3,073 companies globally from 14 business sectors, only about 16% of health care firms adopted at least one artificial intelligence (AI) technology at scale or in a core part of their business, putting the health care sector behind high-tech and telecommunications (31%), finance (28%), and transportation (21%).[2] One reason behind the comparatively slow pace of adoption is a lack of clarity on the impact of AI methods on workflows in the pharmaceutical industry.[3]

In this article we review ML applications in the pharmaceutical industry that increase efficiency and allow more convincing value demonstration, broadly following a product's lifecycle from drug discovery to drug repositioning. Going from big data to improved efficiency in business and clinical benefits, however, requires at least a


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broad understanding of the steps a project team needs to take to implement a successful data analysis project. In the second section, we describe these steps.

Applications of ML in the Pharmaceutical Industry

Drug Discovery

One of the most promising application areas for ML methods is new drug development, which is estimated to cost $2.6 billion on average.[4] Although computational methods have been employed for drug discovery for decades[5,6] (see Hiller, et al. for a 1972 study that applied artificial neural network in drug design), ML methods combined with large data sources enable access to deeper insights faster compared to traditional methods that mostly rely on numerous costly biochemical experiments.[7] For example, deep learning, an ML method based on discovering hidden layers of variables that connect the input data to outcomes, is used to predict drug-target interactions (DTIs)[8]; generate novel molecules predicted to be active against a given biological molecule[9]; predict cell-penetrating peptides for antisense delivery[10]; and, to model quantitative structure – activity and structure – property relationship (QSAR/QSPR) of small molecules to predict blood-brain barrier[11] permeability (see Ying Y, et al.[12] and Lo, et al. [5] for other ML applications on drug discovery).

Clinical Trial Site and Patient Selection

A study that analyzed data from 151 global clinical trials conducted by 12 companies at 15,965 sites found that 52% of clinical trials exceeded their planned enrollment timelines, with 48% taking significantly longer to complete enrollment.[13] Delays were more pronounced in clinical trials of the disease of the central nervous system, with an average planned timeline of 11 months vs. average actual timeline of 12.7 months. Companies also reported that on average 11% of sites in clinical trials failed to enroll any patients at all. ML algorithms can leverage historical data on site performance to maximize the probability that selected sites can deliver patients quickly, minimize drop-out rates, and adhere to the clinical protocol. ML models can be built using historical data on past performance, focusing on clinical trials, infrastructure, and time to first patient enrollment, which are predictive of future performance according to studies conducted by the industry.[14,15] Text mining of social media with natural language processing and predictive analytics applied to electronic health records are already being used by the industry to identify potential patients who might not have been formally diagnosed and who might be ideal candidates for recruitment into clinical trials for rare diseases.[16]

Wearables in Observational Studies and Clinical Trials

Increased miniaturization and longer battery life of electronics enabled the manufacturing of wearable devices that make collection of continuous and accurate medical data more practical than ever.[17] Wearable technologies include smartwatches, wristbands, hearing aids, electronic/optical tattoos, head-mounted displays, subcutaneous sensors, electronic footwear, and electronic textiles. ML methods are routinely employed to convert raw data collected from these technologies in observational studies and clinical trials to meaningful clinical end points. For example, Willetts et al. collected accelerometer data from 132 participants whose physical activities were labeled using video cameras to train ML models that can predict physical activity and sleep patterns.[18] The authors then used their results to label physical activity data collected from more than 96,000 UK Biobank participants. These algorithms can also be potentially used to classify patient data from clinical trials. A review of medical literature put the number of clinical trials that collected data from wearable devices as of late 2015 at 299.[19] An important disease area where biosensors can collect data that were previously unavailable to researchers is neurodegenerative diseases such as Alzheimer's disease. Biosensors worn by the patient and placed in the patient's home as part of a clinical trial can provide quantitative and continuous information on a subject's cognitive status and ability to perform daily tasks.[20]

> ML and natural language processing methods are commonly used to identify patient experiences related to treatments in the real world.

Pharmacovigilance

ML and natural language processing methods are commonly used to identify patient experiences related to treatments in the real world. Social media in general and patient forums in particular offer a rich source of information about adverse events and other problems associated with treatments. The U.S. Food and Drug Administration (FDA) encourages "external stakeholders to explore the use of social media tools such as medical community blogs, crowdsourcing, and social media pages" to identify patient perspectives regarding disease symptoms.[21] Social media content can be used to complement literature review findings, supplement focus groups, gather expert opinions, and elicit patient interviews. The FDA is also exploring the value of social media to inform occurrence of adverse events.[22] Extracting useful signals from large volumes of text data in social media is an active area of research. Recent examples include a study by Gupta and colleagues who used recurrent neural networks for semi-supervised learning of models to extract adverse event mentions from social media posts.[23]

Precision Medicine

Precision medicine is a prevention and treatment approach that considers a patient's genes, environment, and lifestyle.[24] According to a survey of 100 pharmaceutical

industry leaders, precision medicine has the potential to help accurately identify new drug targets; provide clarity regarding target patient profiles, thus, enabling more targeted clinical trials with smaller patient numbers and faster market access; reduce research and development (R&D) cycle length; and, more convincingly demonstrate benefits.[25]

Delivery of the premise of precision medicine depends on the ability to harmonize diverse data sources such as genomics, clinical trials, electronic health records, clinician notes, and wearables, and to develop predictive models to optimize treatment strategies. Recent studies on precision medicine emphasize methods to harmonize these different data sources. Rajkomar and colleagues[26] used deep learning methods to develop predictive models of mortality based on electronic health records and free text records from two hospitals; these models predicted the risk of inpatient mortality, unplanned readmission within 30 days, long lengths of stay, and discharge diagnosis. Recently Pai and Bader[27] reviewed ML algorithms that leverage patient similarity scores based on genomics data and electronic health records to identify subgroups of type 2 diabetes patients, predict tumour subtype in ependymoma, and predict treatment response.

Adherence Prediction

Non-adherence to medication is a major cause of revenue loss for the pharmaceutical industry and imposes a very high cost to public health care systems. A report on economic costs of medication non-adherence estimated the industry's annual revenue loss from non-adherence at $188 billion (or 37% of the $508 billion potential total revenue) in the U.S. alone and $564 billion globally.[28] The report further estimated that even a 10% increase in medication adherence across disease areas would increase the total annual revenue of the industry by $41 billion in the U.S. A systematic literature review in 2017 estimated that disease-specific, per patient, per year cost of non-adherence to medication ranges between $949 and $44,190 (in USD 2015).[29]

Predicting risk of non-adherence allows more targeted interventions to decrease non-adherence rates. Unsupervised ML methods can be used to identify non-adherent patient segments that display different characteristics and reasons for non-adherence to allow tailoring interventions to different patient groups. A recent example of non-adherence risk estimation includes a study by Krumme and colleagues[30] who used pharmacy and demographic predictors, pre-index adherence levels, and medical claims data to predict one-year adherence to statin treatments.

Drug Repositioning

Faced with growing R&D costs and low approval rates for new compounds, repositioning of existing drugs is a potential way to cut costs and expand to new indications. Drug repositioning has the benefit of reducing drug development time, since toxicity and safety profiles of drug candidates for repositioning have already been studied.[31] Before widespread use of systematic approaches and computational methods, such as similarity searching, text mining, and network analysis, drug repositioning was largely based on unexpected associations observed in clinical trials or in medical practice.[32] ML methods promise to accelerate this process. Examples include neural networks for prediction of sensitivity of cancer cells to drugs; support vector machines for prediction of drug therapeutic class; collaborative filtering and network analysis to predict drug-disease associations; and, text mining to leverage medical literature to highlight potential new indications for existing drugs.[33]

Implementing a Successful ML Project

Machine learning and artificial intelligence are written about and discussed extensively, in print and on websites, by a multitude of authors, including both companies and organizations involved in ML. The impression is often given that ML can be performed automatically in a "point and click" manner without particular specialist knowledge from analysts. Companies advertise services and packages that are able to apply ML and AI to problems in an automated manner. Whilst this may be true for certain specific applications like image classification, language translation, and other applications where no unmeasured variables are present and large volumes of data are available for pre-trained models, this is not the case for applications in the pharmaceutical and medical industries. Like other analytical approaches, such as that of traditional statistics, a detailed review and understanding of the problem and the data, as well as rigorous attention to methodological considerations is absolutely crucial. Inappropriate application of ML methods can lead to erroneous conclusions and inaccurate performance assessment. At worst, this can lead to mistakes in health care decisions which might be based on evidence derived from ML studies. Regardless of the ML application area, there are core steps in every ML project that must be followed to get actionable insights from data.

Building the Right Team

Building the right team or providing the core team with access to the required domain expertise is a stage of analytical projects that is often overlooked with potentially important consequences. ML has its origins in computer science with increases in computing power and availability of cloud computing making ML approaches to data analysis possible. Consequently, there are many cases where the team performing the ML analysis consists solely of computer scientists. Whilst individuals with a background solely in computer science are undoubtedly skilled in the application of ML, they often do not possess the skills or domain knowledge needed to apply the methods in the health sector. Whilst the emphasis of analysis in many sectors is often solely on predictive ability, this is not the

case in the health sector, where there is critical importance on inference, causality, rigor, understanding potential sources of confounding and bias, underlying epidemiology, and reasons why a particular method can be used for prediction. By failing to take into consideration these additional factors, critical errors can result. Similarly, analytic teams that consist of clinicians or epidemiologists may not apply the ML algorithms in a rigorous enough manner, leading to overfitting and resulting in over-optimistic prediction performance. It is, therefore, important to ensure that an analytic team consists of, or has access to, all the skillsets for a particular application, and even then, it is necessary that the multi-disciplinary team members are able to effectively communicate with each other.

Establish Whether ML is Necessary

Not all business questions that involve data analysis require an ML approach. The first question the project team needs to answer is whether it is possible to follow simple if-else rules to make predictions with enough accuracy. If so, then complicated algorithms might not be necessary. Another question is the availability of high quality and relevant data in enough quantity. Is there enough labeled data for the ML algorithm to learn from and, if not, how expensive is it to acquire more labeled data? Necessity and feasibility of ML approaches must be considered before committing more resources to an ML project. A phased approach, where a small feasibility study is conducted, can shed light on the decision to go ahead with an ML project or to prioritize quality data collection.

Formulate the Business Question as an ML Question

Despite the proliferation of ML algorithms, there is a limited number of ML tasks these algorithms can perform.[34] Formulating the business question in terms of one of these tasks is the first step towards a successful ML application. Different tasks include classification, regression, measuring similarity of entities, clustering similar groups together, identifying potential links between entities, data reduction, and causal modeling.[34] After the business question is cast as an appropriate ML task, the team must think hard about the metric that will be used to evaluate the model performance. In a classification task, for example, one pitfall is to simply look at the percentage of observations the model correctly classifies. This can be misleading in situations where even a simple decision rule (e.g., predict that no patient will experience the event of interest in the next year) would yield a high accuracy, simply because the event to be predicted is very rare. A model performance metric needs to incorporate the cost of different types of error (e.g., false negatives and false positives) especially if these have very high economic or health costs. Ideally the ML model must improve upon the methods currently in use as measured by the appropriate metric, whether those methods are based on expert judgment or existing risk scoring instruments.

Prepare Data for Analysis

According to a widely quoted estimate, data analysts spend 80% of their time collecting and preparing the data for analysis.[35,36] Because ML algorithms need quality data, and often in large quantities, data preparation is a very labor intensive part of any ML project. Activities at this stage include dealing with missing variables, creating new variables from existing ones that can boost model performance (feature engineering), and processing data so that it is usable by ML algorithms. All these steps require an understanding of the data sources, data fields, and subject matter knowledge. The team must consider how exactly the model will be used and which variables will be available to make new predictions when the model is deployed.

After the data is prepared for analysis, it is then necessary to randomly separate the dataset into a training validation set which will be used to train the models and assess their performance for purposes of model selection, and a test set to get an estimate of the selected model's performance when applied to data it has never seen before.

Train Models and Communicate Results

For any given ML task there is a large number of models from which to choose. Before going with the most complex model, such as a deep neural network with dozens of layers, it is better to start with simpler models such as logistic regression or random forests. Mean and standard deviation of different models' performance on validation sets can then be compared to select the best model. It is imperative to automate all these steps, including data preparation, because they involve extensive experimentation to find the right mix of features and models, as well as fine tuning the process. Note that model building and data preparation is an iterative process. Once model selection is complete, the team can use the test set to estimate the model's performance on new data. A model's parameters must never be tweaked to increase its performance on the test set. Otherwise, the real-world performance estimate will be biased.

When a model is selected, the analyst needs to go beyond reporting the model's performance and be able to answer the "so what" question from the business perspective, whether it relates to drug discovery or identifying undiagnosed patients. Assumptions, methods, and other technical details should be clearly laid out for more technical audiences.

Maintain the Model

A model's performance depends on whether new observations to which it is applied have characteristics similar to observations on which it was trained. It is likely that over time the characteristics of patients, clinical sites, or the instances it is being asked to make predictions for will change, leading to erosion of the model's accuracy. To prevent this decline, a model's parameters must be

tuned as new data is available to make sure that the initial performance is maintained or improved upon. Repeating model training with new data instances is therefore usually necessary. A related problem is application of a model to a new setting. A model trained on data from one region, patient population, or disease area is unlikely to perform as well when applied to another.

Conclusions

Whilst adoption of ML in early stage development has been widespread, use in later stage development is relatively early in its evolutionary path. Use cases for ML are still being developed and understood. There is no doubt that ML approaches can yield benefits in terms of efficiencies, new insights, and actionable evidence. However, knowledge of appropriate use of ML methods and potential applications is not widespread in our industry, a factor which is likely to slow its adoption. Whilst there may be something of a misconception that ML can be "automated" and can produce almost "magical" results with little effort, this is not the case. ML is an analytical technique and is best thought of in the same manner as traditional statistical analysis. It requires a range of specialist knowledge and rigorous application with attention to detail in the medical and pharmaceutical industries. ■

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Disease Simulation in Drug Development
External Validation Confirms Benefit in Decision Making

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Introduction

Disease simulations offer a potential mechanism for extending the findings of clinical trials over longer time span and to broader populations than those considered in the clinical trials themselves. A flexible and transparent disease simulator is a cost-effective means of assessing the value of new target compounds, identifying key drivers, conducting "what if" analyses, and aiding in decision making at stage-gate reviews during early drug development.

For a disease simulator to be reliable, however, it is necessary to understand the model's predictive performance across different clinical settings, populations, and subgroups of interest. The robustness and generalizability of a developed model should be verified in one or more external validation studies by comparing the simulation outcomes against observed clinical data from other patient registries, clinical trials, or literature external to those used for model development.[1] In external validation, a model is used to simulate a real scenario, such as a clinical trial, and the predicted outcomes are compared with the real-world outcomes. A key to developing confidence in a model is to perform multiple validations on model components, such as population creation, disease incidence/progression, and occurrence of clinical outcomes.

One therapeutic area which benefits from disease simulation is Alzheimer's disease (AD), in which the vast majority of clinical trials in recent years have been unsuccessful. The clinical and economic value of potential therapies in development can be evaluated using disease simulation; from interventions targeted to attack AD earlier in its progression (during prodromal stage) through the most severe stages of AD.

In this article, we describe two external validation tests of the Alzheimer's Disease Archimedes Condition Event (AD ACE) simulator as an example; the first against the National Alzheimer's Coordinating Center (NACC) dataset, and the second compared to results of the BAN2401-G000-201 trial (Study 201), a recent clinical trial to evaluate safety,


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tolerability, and efficacy of an amyloid-targeted treatment (BAN2401) in subjects with early AD. The two selected sources were independent from the sources used to build the AD ACE simulator.

Disease Simulation with the AD ACE

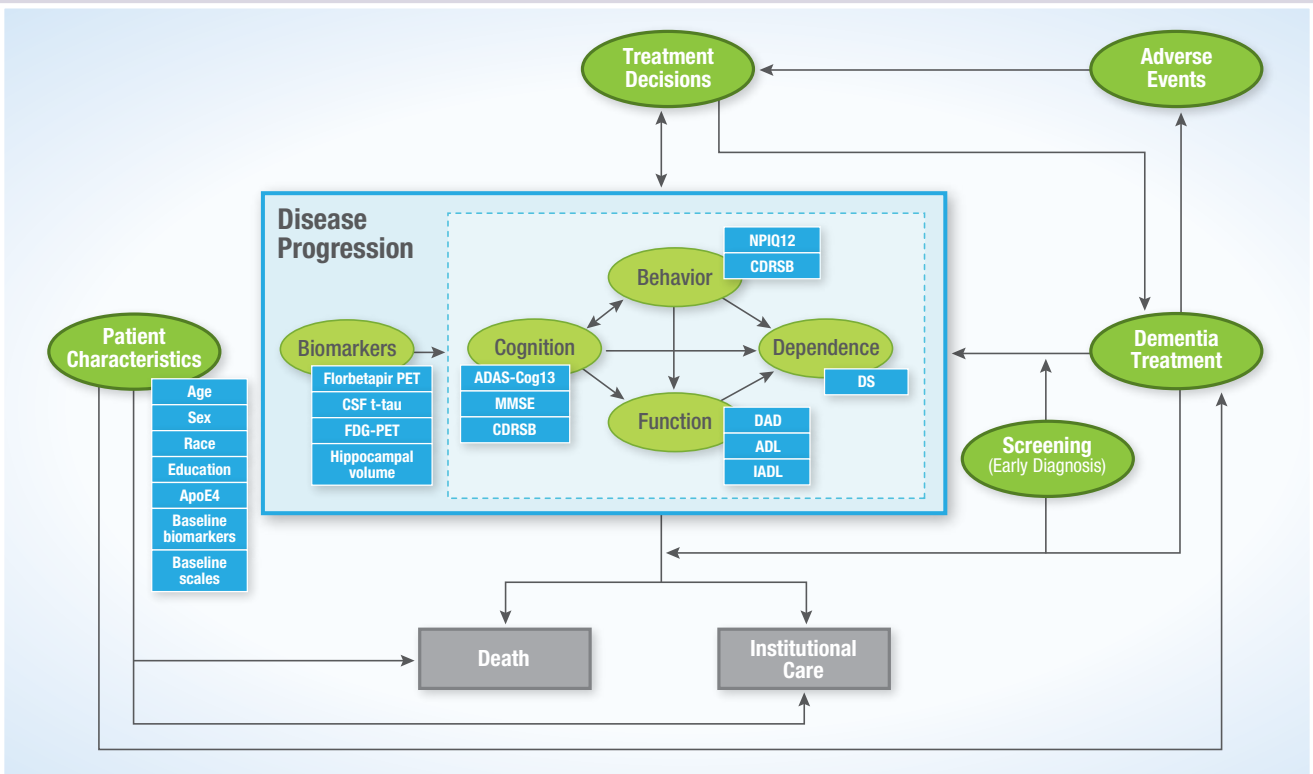
The AD ACE is a discretely integrated, condition event (DICE) simulation of AD.[2] The simulator incorporates measures of the underlying pathophysiology of AD, including measures of amyloid PET (AV45) and tau (CSF t-tau) levels and their connections to clinical presentation of AD, including cognition and behavioral scales (Figure 1). The relationship between changes in these measures over time are quantified using predictive equations derived from long-term observational data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) to predict natural history of individuals with normal cognition through to severe AD.[3] The AD ACE can evaluate the impact of disease-modifying treatments (DMTs) and symptomatic treatments on both the clinical and economic consequences of AD. It simulates at the level of individual patient profiles, including explicit quantification of intra- and inter-patient heterogeneity.

External Validation Against NACC Dataset

The National Alzheimer's Coordinating Center (NACC) maintains a database of participant information collected from the 29 Alzheimer's disease centers funded by the National Institute on Aging (NIA). It is unique in the United States (U.S.) for its size and capacity to support collaborative research in AD. The standardized Uniform Data Set (UDS), which collects prospective and longitudinal clinical data, includes over 38,000 subjects as of June 2018. The UDS provides a standard set of measures collected longitudinally to characterize participants with mild AD and mild cognitive impairment (MCI) in comparison with non-demented controls.

Simulated measures of cognition (i.e., CDRSB and MMSE) from the AD ACE were compared to observed mean trajectories from NACC in three subgroups: 1) normal cognition or subjective memory complaint (CN-SMC), 2) MCI, and 3) mild AD. The NACC subgroups were defined based on reported baseline cognition level and observed trajectories were computed for each subgroup based on all NACC patients with at least three visits (including baseline visit). A total of 385 patients were identified in NACC for inclusion in the external validation (40 CN-SMC, 125 MCI, 220 mild AD). Population average trajectories were computed for each subgroup independently, adjusting each visit timing to the nearest six-month timepoint. No imputation was performed for missing data, so the population average trajectories included different sets of patients at each time point.

Figure 1. AD ACE Model Diagram

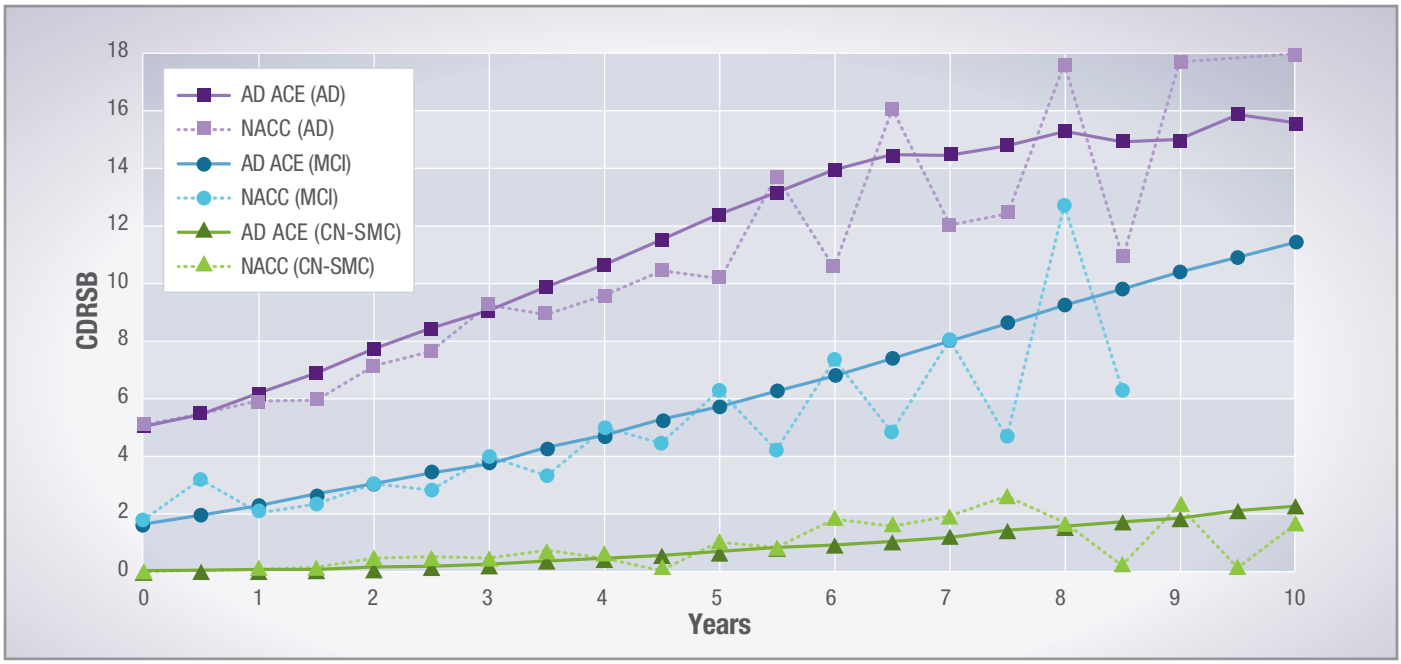


ADAS-Cog13 = Alzheimer's Disease Assessment Scale-Cognitive Subscale 13; **ADL** = Activities of Daily Living; **APOE4** = Apolipoprotein E4; **CDRSB** = Clinical Dementia Rating Sum of Boxes; **CSF t-tau** = Cerebrospinal Fluid Total-tau; **DAD** = Disability Assessment Scale for Dementia; **DS** = Dependence Scale; **FDG-PET** = Fluorodeoxyglucose–Positron Emission Tomography; **Florbetapir PET** = Florbetapir Positron Emission Tomography; **IADL** = Instrumental Activities of Daily Living; **MMSE** = Mini-Mental State Examination; **NPI-Q12** = Neuropsychiatric Inventory Questionnaire 12

Individual baseline ADNI patient profiles (1,735 total) were then filtered in the AD ACE based on the range of cognition scores observed in the NACC for each subgroup. The filtered subgroups in the AD ACE were well-matched with the NACC subgroups in terms of mean age and cognitive levels (CDRSB and MMSE) at baseline (Year 0 in Figures 2 and 3). The simulations sampled 500 patients from each subgroup in the AD ACE and simulated each patient over a 10-year time horizon outputting all measures of disease progression each six months. No modifications or fitting was performed in the disease simulation for these analyses.

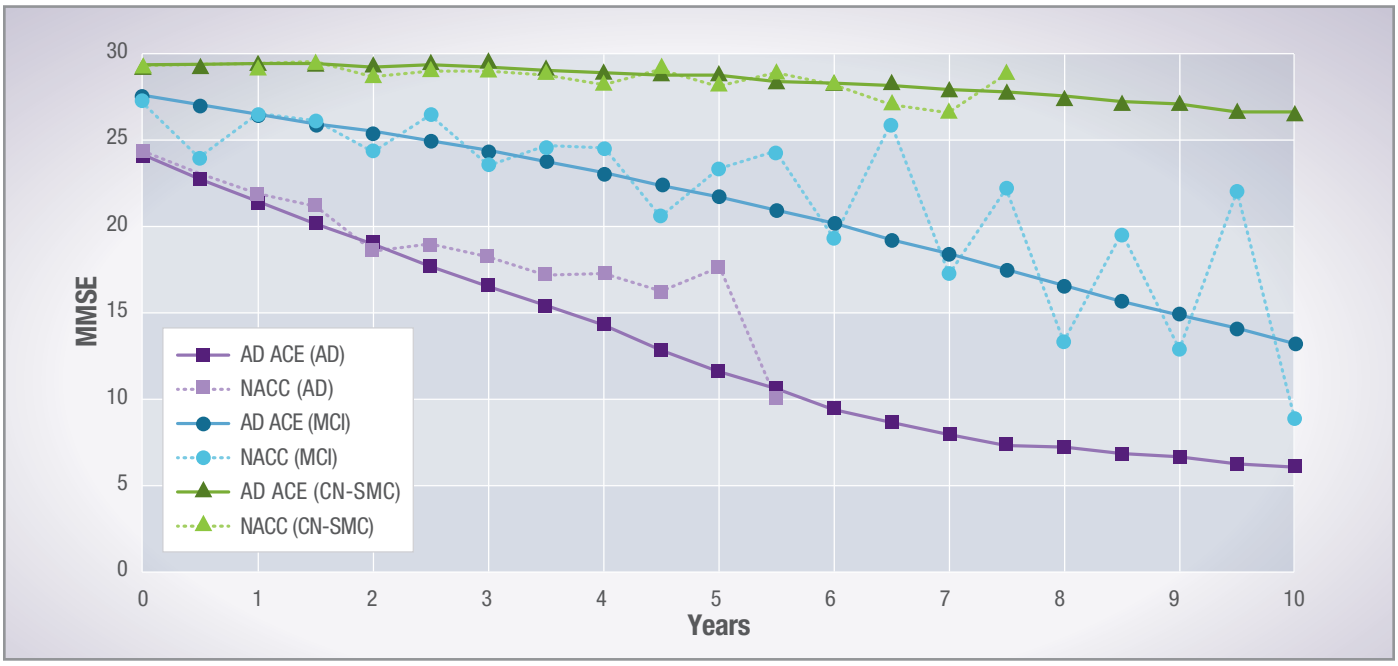
The simulated trajectories for CDRSB and MMSE agree well with the mean trajectories from NACC in all subgroups (Figures 2 and 3). The observed NACC trajectories show greater variance at late times as patient counts decrease

Figure 2. Mean CDRSB Trajectories for NACC vs. AD ACE for Different AD Disease Severity Levels



CN = Cognitively Normal; SMC = Significant Memory Concern; MCI = Mild Cognitive Impairment; AD = Alzheimer's Disease; MMSE = Mini-Mental State Examination; CDRSB = Clinical Dementia Rating Scale-Sum of Boxes; NACC = National Alzheimer's Coordinating Center; AD ACE = Alzheimer's Disease Archimedes Condition Event

Figure 3. Mean MMSE Trajectories for NACC vs. AD ACE for Different AD Disease Severity Levels



CN = Cognitively Normal; SMC = Significant Memory Concern; MCI = Mild Cognitive Impairment; AD = Alzheimer's Disease; MMSE = Mini-Mental State Examination; CDRSB = Clinical Dementia Rating Scale-Sum of Boxes; NACC = National Alzheimer's Coordinating Center; AD ACE = Alzheimer's Disease Archimedes Condition Event

and the population of patients at each time point becomes less consistent.

External Validation Against BAN2401-G000-201 Trial (Study 201) Results

Eisai and Biogen recently announced positive topline results from the Phase II study with BAN2401, an anti-amyloid antibody, in 856 patients with early AD.[4] The BAN2401 study 201 achieved statistical significance on key endpoints evaluating efficacy after 18 months of treatment in patients receiving the highest treatment dose (10 mg/kg biweekly) as compared to placebo on reduction of amyloid PET (positron emission tomography) standardized uptake value ratio (SUVR) accumulated in the brain (-0.30 adjusted mean change from baseline) and on slowing progression in key cognition scales (ADCOMS 30%, CDRSB 26%, ADAS-cog13 47%). Dose-dependent changes from baseline were observed across the PET results and the clinical endpoints.

To initiate the external validation of AD ACE against the reported BAN2401 study 201 results, a set of 610 ADNI patient profiles were initially selected in the AD ACE

Figure 4. Mean Change from Baseline in CDRSB for Different Placebo Populations

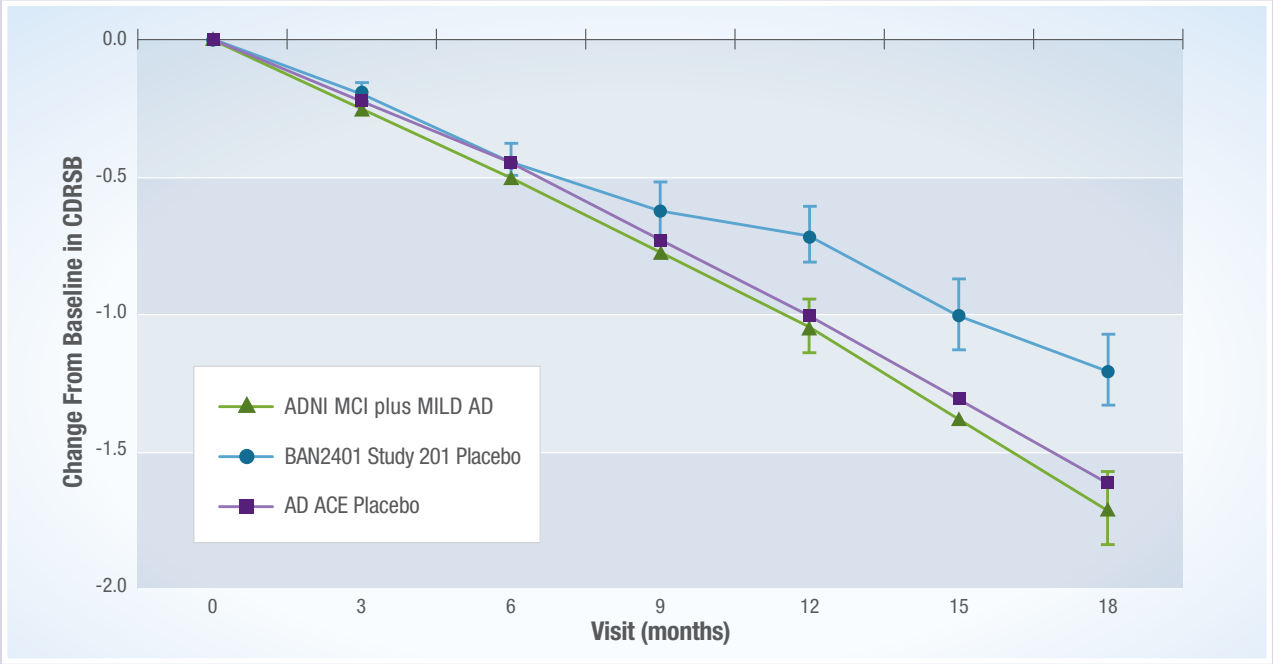
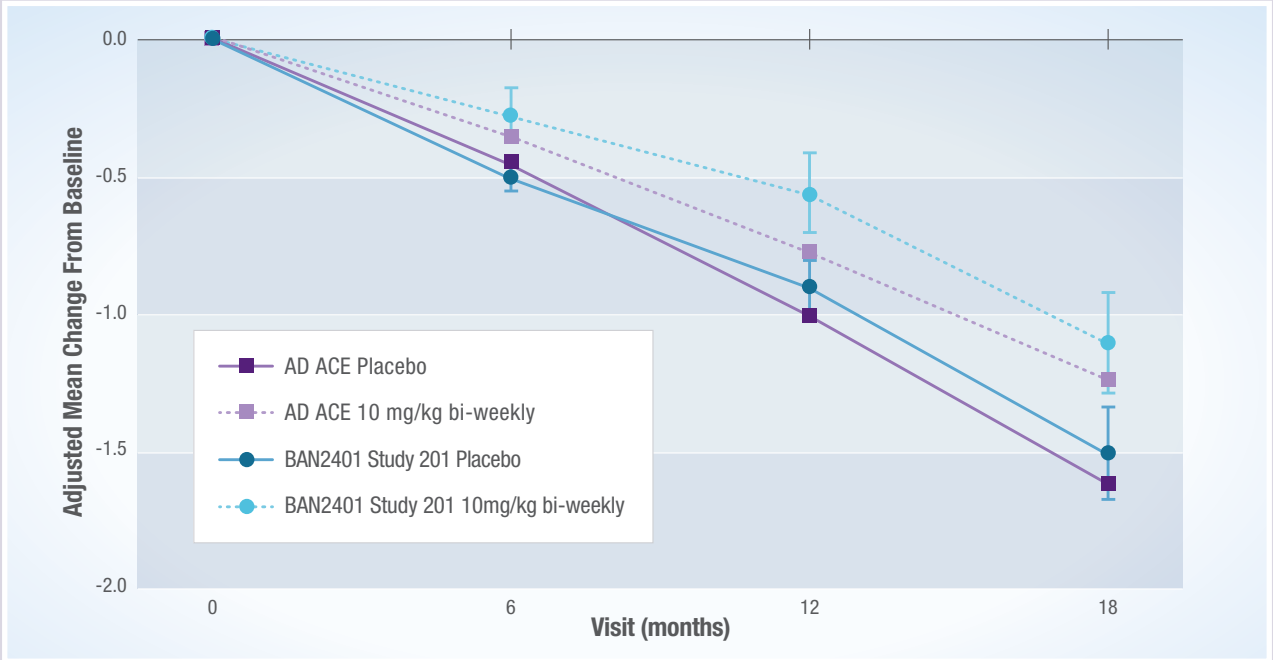


Figure 5. Adjusted Mean Change from Baseline in CDRSB for BAN2401 Study 201 vs. AD ACE



based on reported inclusion criteria in the BAN2401 study 201. Mean demographic and baseline characteristics in the filtered AD ACE profile were closely aligned with the placebo and BAN2401 arms of the trial as shown in Table 1. Next, we sampled 1,000 patients from the filtered ADNI profile and simulated each patient with and without treatment over 18 months and reported all measures of disease progression each six months. In the treatment arm, the baseline amyloid PET SUVR was adjusted by -0.30 after treatment initiation to mimic the 10 mg/kg bi-weekly regimen in the trial. No modifications or fitting was performed in the disease simulation for these analyses.

For the placebo arm, the AD ACE predicted a change of 1.61 points in CDRSB after 18 months (see Figure 4), which is consistent with the rate of progression reported for the placebo arm of BAN2401 Study 201 (1.2±0.1) and within the confidence bounds of what was reported for the ADNI MCI plus mild AD placebo population (1.7±0.1). For the treatment arm, the cognitive decline in CDRSB over 18 months was slowed by 23% in AD ACE compared to the 26% reported in the trial results (see Figure 5). The AD ACE also predicted a slowdown in cognitive decline on ADAS-cog13 consistent with, but lower, than what was reported in the trial results (30% vs 47%).

Discussion

Disease simulation can provide valuable insights during drug development in AD. For a simulation to inform decision-making, however, potential users need to know whether a model is reliable or generalizable to the setting and population of interest. External validation is essential in ensuring confidence in the simulator, and consequent results, being used for decision making.

In this article we presented the results of two external validations of the AD ACE – against a well-known AD dataset and a recent clinical trial. The results of the external validations indicated that AD ACE could closely match cognitive declines observed in both the NACC dataset and BAN2401 study 201. Specifically, the NACC validation showed generalizability of AD ACE to different populations by comparing model results with real-world results, while the BAN2401 study 201 validation demonstrated predictive validity of AD ACE by comparing model results with observed outcomes in a recent trial.

Table 1. Baseline Characteristics of Individuals in BAN2401 Study 201 (Placebo and BAN2401 arms) vs. AD ACE (Mean ± Standard Deviation)

	Placebo (N=238)	BAN2401 (N=587)	AD ACE (N=610)
ADAS-cog13	22.6±7.7	22.2±7.4	22.96±7.66
CDRSB	2.89±1.45	2.95±1.37	2.63±1.64
MMSE	26.0±2.3	25.6±2.4	25.95±2.16
PET SUVR	1.40±0.16	1.41±0.16	1.37±0.14
Age	71.1	71.4	74.1±7.2
Age Range	50 - 89	50 - 90	54 - 90
% Male	42%	54%	57%
% MCI	65%	64%	64%
% APOE4 +	71%	72%	73%
CDR Global = 0.5	84%	86%	89%

ADAS-cog13 = Alzheimer's Disease Assessment Scale-Cognitive Subscale 13; **CDRSB** = Clinical Dementia Rating Scale-Sum of Boxes; **MMSE** = Mini-Mental State Examination; **PET SUVR** = Positron Emission Tomography Standardized Uptake Value Ratio; **MCI** = Mild Cognitive Impairment; **APOE4** = Apolipoprotein E4

These results help provide context for appropriate applications of the AD ACE, but in a broader sense, they support the strength of using disease simulation to help make impactful decisions during the drug development process. While simulation is not always the answer, results like what we see from the external validation of the AD ACE clearly show that it can definitely be part of the equation for key stakeholders when evaluating the future of life changing medical treatments. ■

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Clinical Trial Simulation in Early Market Access Planning

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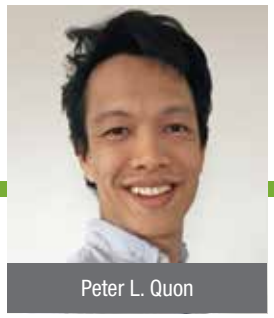
Introduction

Health technology assessments (HTAs) of a new treatment often require the manufacturer to justify its economic value through analyses that make inferences from the trial data to predict long term outcomes, costs, and quality of life. When challenges arise in the clinical data needed to support market access, the opportunity to address those issues unfortunately no longer exists. These challenges can be particularly acute in therapeutic areas in which single arm studies or very long duration trials are necessary. This risk can be mitigated with an improved understanding of the interaction between the potential trial outcomes and market access needs.

In this article, we discuss how clinical trial simulation (CTS) can support early market access planning by predicting a range of feasible trial results of a new treatment that can be fed into an economic model, making it possible to anticipate challenges to the economic value story. By understanding these challenges at the trial design phase, adjustments to the trial protocol and preparations for additional evidence generation can be made to improve the chances for a successful launch.

CTS Enables Earlier Integration of Market Access Strategy

To better prepare for HTAs' assessments of economic value, manufacturers are beginning to integrate market access planning throughout the product development lifecycle to allow more time to build out the economic value story. They are undertaking activities well in advance of launch, such as systematic literature reviews of economic models in the same indication and building economic models using early phase trial data to predict cost-effectiveness drivers and challenges. However, these approaches are limited by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their inability to evaluate and predict trial outcomes in new therapeutic areas where data or prior modeling may be scarce. Moreover, it may be challenging to understand the implications of heterogeneity in treatment response or other trial outcomes on economic modeling without patient level data. As an example, a common challenge in HTA reviews is the uncertainty associated with statistical extrapolations of survival curves, and so to get an early sense of this challenge, manufacturers may produce parametric fits from published curves or earlier phase trial data. However, both sources may not fully represent the heterogeneity seen in a later phase trial or reasonably match the pivotal trial population, which are needed to understand the limitations of extrapolations or the planning of subgroup analyses. Another increasingly common question is whether indirect treatment comparisons (ITC) are able to address patient heterogeneity (for example in NICE TA440[1]). With simulated patient-level data, early economic analyses can more accurately test statistical extrapolations and ITC approaches such as matching adjusted indirect comparisons (MAIC).

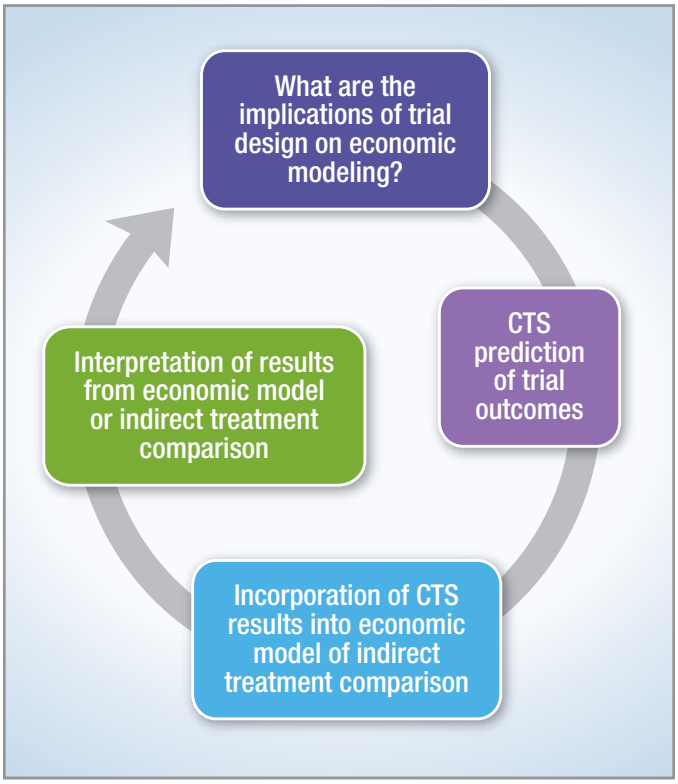
Market access planning should begin when trials are being designed, where there are still opportunities to provide input to the protocol and data collection or time to explore other routes of evidence generation. However, this requires a good understanding of the implications of trial design options and uncertainties on outcomes relevant to an economic model. This can be achieved through CTS, which mimics patient outcomes longitudinally within the context of a trial using existing data. CTS yields simulated patient level data which is then analyzed using standard statistical techniques and can be fed into an economic model or an indirect treatment comparison. This yields a complete integration between the trial design and the economic value assessment (Figure 1).

> Market access planning should begin when trials are being designed, where there are still opportunities to provide input to the protocol and data collection or time to explore other routes of evidence generation.

Existing Data Can Inform CTS Prior to the Start of a Trial

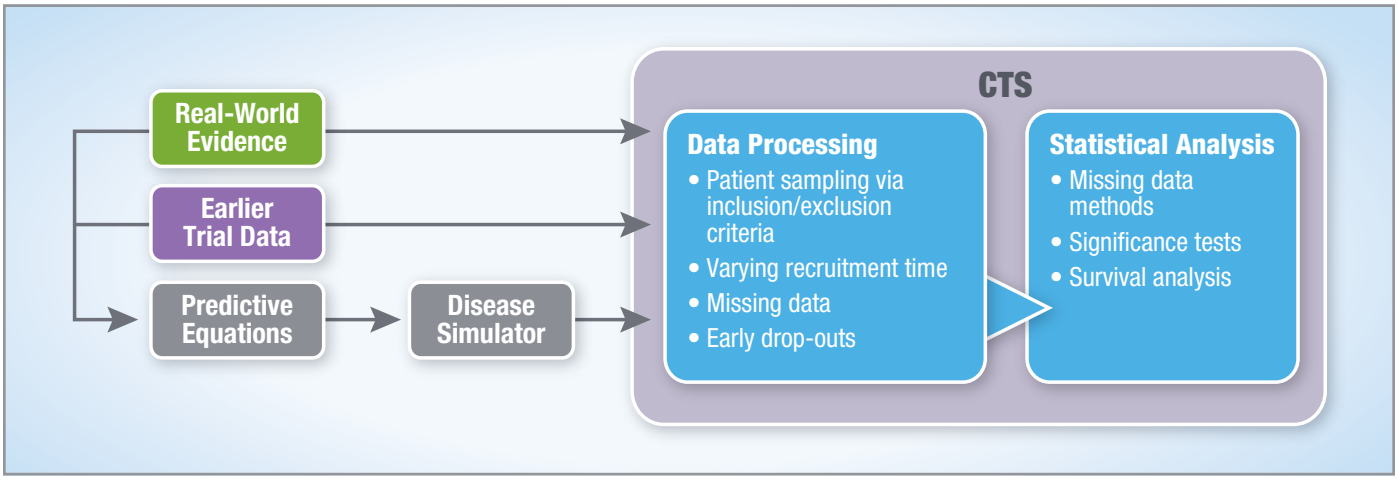
CTS requires a longitudinal, patient-level dataset of patients that, at a minimum, contains a baseline observation and an event observation. The dataset can be derived from various sources including prior clinical trials, real-world evidence (e.g., claims data), and disease simulator output (Figure 2). Clinical trials accessible to the manufacturer are the most relevant data and can be specific to the trial setting, but offer the least opportunity for exploration beyond the manufacturer's own research experience, such as new therapeutic areas or populations. Also, trial data, especially early phase trial data, generally may not involve long-term follow up. Real-world evidence, on the other hand, may include long-term data and offer a broader pool of patients that can cover therapeutic areas in which the manufacturer may not have experience; however, the form and granularity of data may not meet the level expected of a trial, limiting the aspects of the trial which can be explored. Moreover, data on early decline or disease progression are generally difficult to find. Disease simulators can offer the most flexibility and predictive power, and even serve as a bridge between trial data and real-world evidence, but, construction of disease simulators can take time and must be carefully validated before being used for decision making (see *Disease Simulation in Drug Development – External Validation Confirms Benefit in Decision Making* in this issue of *The Evidence Forum*).

Figure 1. Linking Trial Design to Economic Analysis Via CTS



Disease simulators use predictive equations based on trial or observed data to model the course of key markers over time and any interconnected clinical relationships to predict outcomes. As an example, previous Evidera CTS studies in Alzheimer's Disease (AD) have relied on simulated patient data from a disease simulator, the Alzheimer's Disease Archimedes Condition-Event (AD ACE). The AD ACE uses predictive equations derived from the Alzheimer's Disease Neuroimaging Initiative (ADNI) and Assessment of Health Economics in Alzheimer's Disease (AHEAD) to estimate the progression of AD in terms of multiple interacting trajectories for key biomarkers, cognition, behavior, function, and dependence markers.[2] By coupling the simulated longitudinal patient level data from a disease simulation with CTS, we can understand the interaction between trial operations and disease progression and the

Figure 2. Flow of Data for CTS



impact on the observed treatment effect. The data from the disease simulation can undergo additional processing to mimic data derived from an actual trial, including missing data, varying times of recruitment, and early dropouts (Figure 2). As an example of the importance of understanding the effect of trial operations on outcomes, a recent AD study suggested the observed treatment effect of a disease modifying drug can be influenced by the number of patients in a trial that are prone to faster disease progression and a higher likelihood of dropping out early.[3]

CTS Employs Robust Statistical Methods to Produces Trial-Like Data and Outputs

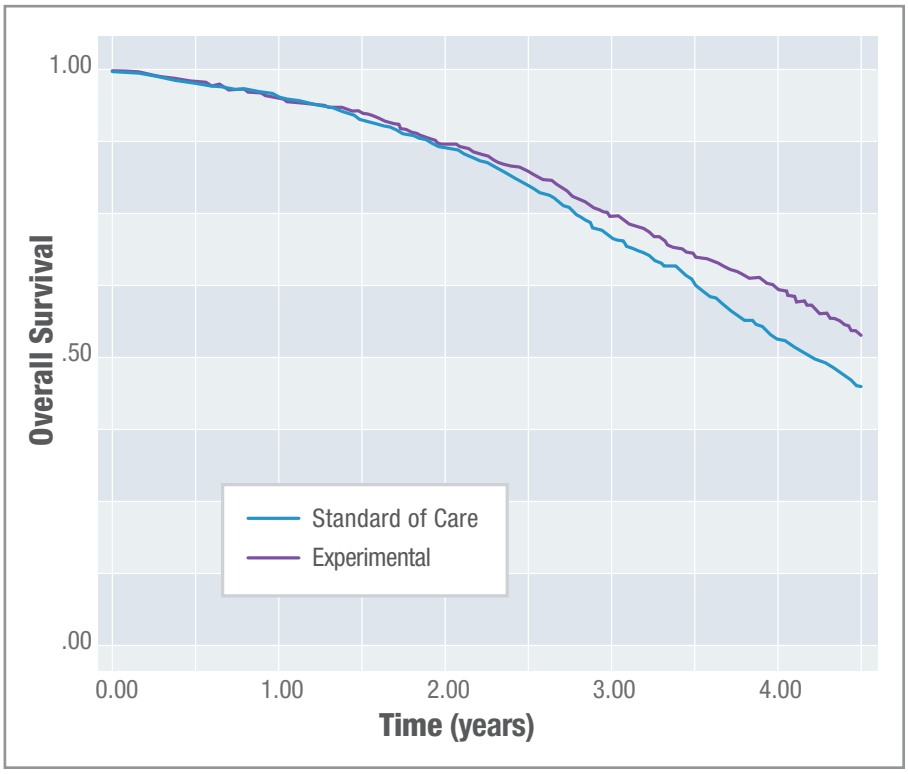
CTS can perform most standard statistical methods used in trial analyses. Survival analysis is among the methods, and the generation of the Kaplan-Meier (KM) curves allows for estimation of median survival time, hazard ratios, and evaluation of the overall difference between curves with log-rank test. This analysis coupled with simulation makes it applicable in the evaluation of cancer trial designs, which are becoming more challenging to show efficacy, as crossover or switching to other effective treatments in market can dilute the overall survival (OS) signal. For example, Evidera conducted a CTS study examining the effect of subsequent life-extending therapies on OS in a non-metastatic prostate cancer trial of a hypothetical treatment with a OS hazard ratio of 0.70.[4] Coupled with a disease simulator in prostate cancer,[5] the CTS of a scenario in which 75% of patients continued onto an effective subsequent treatment (similar OS hazard ratio as the initial treatment) produced OS KM curves that showed separation at around two to three years. The difference became significant at about four years (Figure 3).

As the level of subsequent treatment use lowered, time to show benefit in OS shortened as expected.

CTS Can Benefit Planning of Evidence Generation for Optimal Market Access Success

Given CTS's ability to provide trial-like results, it can be used to inform early economic models or comparative effectiveness such as indirect treatment comparisons. In a similar fashion to how early economic models are used, using CTS to conduct early comparative effectiveness assessments can help identify challenges to market access. For example, the method of extrapolation is often scrutinized by HTAs; as such, the process to determine the most appropriate approach can be time consuming and

Figure 3.
Example Prediction of Overall Survival Accounting for Subsequent Treatments



require the input of various experts in health economics outcomes research (HEOR), medical affairs, payer affairs, and outside clinicians. With CTS generating potential KM curves to base extrapolations and accompanying statistics, the discussion with, and preparation of, various stakeholders can take place earlier and facilitate clinical input to the economic analysis plans.

Discussion

With the number of factors outside the trial data to be considered in an economic analysis, there is no guarantee that a trial meeting its primary end points translates to a positive economic evaluation, which is why manufacturers are integrating market access planning throughout the product development lifecycle. CTS can be a tool to enhance this integration by providing the means for clinical operations and market access operations to more effectively collaborate. CTS allows the relationship between trial design and market access needs to be understood earlier in the process, when there is still the opportunity to address any potential issues. This can be particularly important in new therapeutic areas where prior information is limited; when there may not be a track record of HTA successes to follow; or, more novel trial designs are being considered. CTS can help understand the implications of trial designs on economic modeling, identify potential challenges, form constructive feedback at the trial design phase, and assist in the planning of studies for additional evidence generation to support market access. ■

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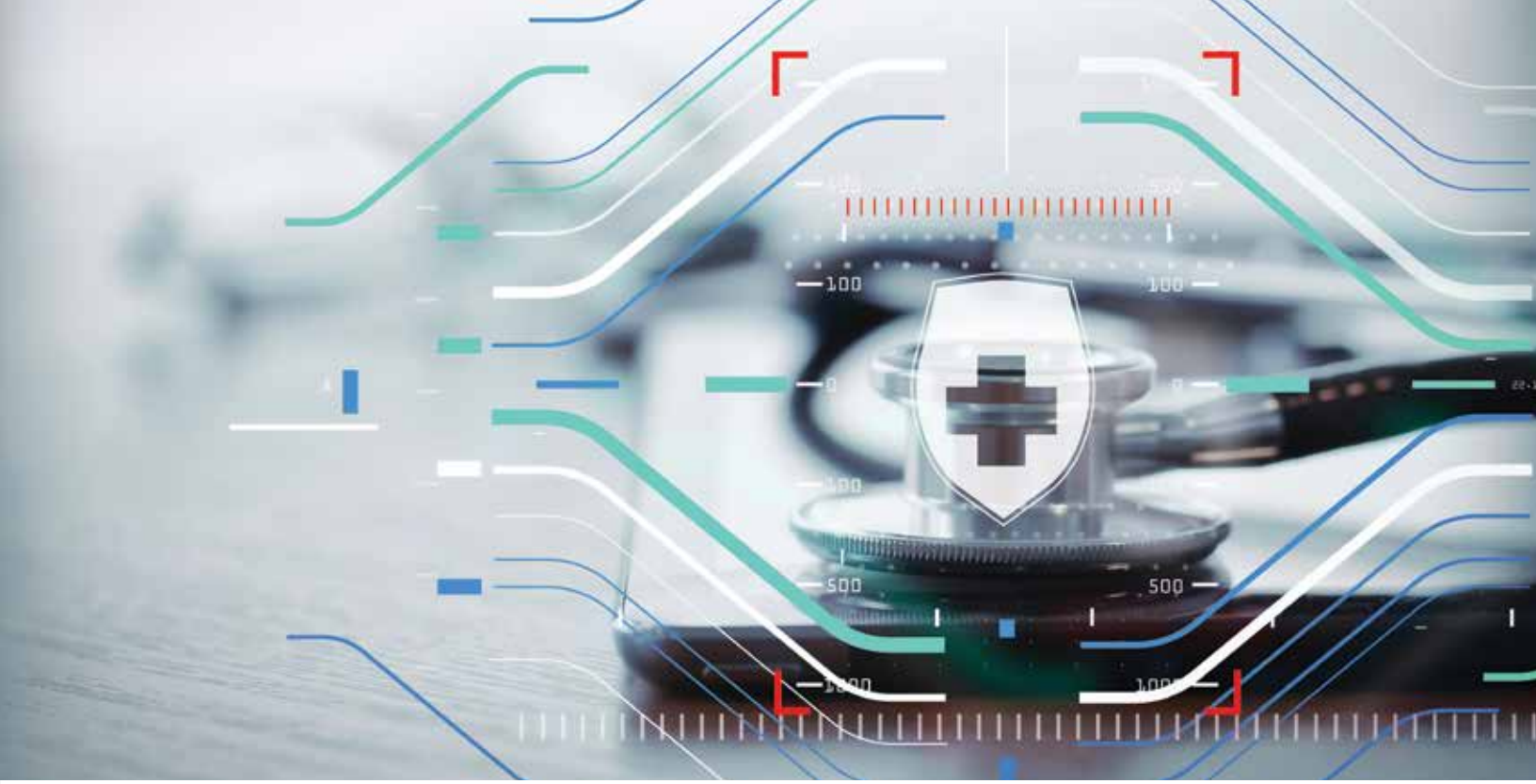

New Trends in Drug Safety and the Growing Role of Real-World Evidence

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Introduction

A renewed focus on drug safety has emerged with the increased number of approved drugs, greater availability of information, and more direct involvement of patients in their treatments. Major drug safety issues in the past several decades (e.g., thalidomide in the '60s, diethylstilbestrol in the '70s, cerivastatin, rofecoxib, and benfluorex in the 2000s) have contributed to an evolution of the regulatory framework for drug safety, particularly in the post-approval period, supported by scientific developments and technological innovations that have enhanced traditional passive pharmacovigilance activities with active surveillance and pharmacoepidemiological studies to bolster the precision and granularity of drug safety information.

The current period is marked by a focus on accelerated approvals of cancer drugs, immunotherapies, and orphan indications, and an increase in the use of biomarkers and surrogate endpoints in an environment where the amount of and accessibility to data seems to be exploding. Between 2001 and 2010, nearly one-third of drugs approved by the U.S. Food and Drug Administration (FDA) had major safety issues uncovered over four years, on average, after approval.[1] With this backdrop, we explore the recent developments of drug safety from the perspective of multiple stakeholders to bring a clearer global picture of:

- where we stand and where we go in terms of regulations, data sources, and methods
- what is needed to ensure state-of-the-art real-world evidence (RWE) generation in drug safety.

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Shifts in Regulatory Thinking

The Evolving Focus

The focus around drug safety has moved through the different steps represented in Figure 1.

- **Passive surveillance** and signal detection based on continuous monitoring of spontaneous reports of adverse drug reactions sent by physicians and compiled by biopharma companies and regulatory authorities.[2] Although signal detection approaches have been refined with adoption of metrics such as disproportionality measures,[3,4] this approach remains reactive and hypothesis-generating.
- **Risk management planning and evaluation** was originally applied beginning in the late '80s to specific drugs and evolved towards current Risk Evaluation and Mitigation Strategies (REMS) in the U.S. and the Good Pharmacovigilance Practice (GVP) in Europe and was formalized by the ICH-E2E guideline.[5] Risk management planning led to post-authorization safety studies, required by regulatory authorities or voluntary, to detect and/or monitor risks associated with newly-approved drugs and evaluate the effectiveness of risk minimization measures.
- **Active surveillance** became possible with the wider availability of real-world data sources and methodological innovation. It can be complemented with subsequent investigation to further define the magnitude of any new or known risk, and characteristics of patients that might alter the benefit-risk equation. A major example is the Sentinel System launched by the FDA to develop a systematic approach to leverage electronic healthcare databases to enable active post-marketing safety surveillance.[6] Another example is the EU-ADR project, a large European initiative based on a public-private partnership to enable analyses across different European electronic medical records data sources to improve signal detection.[7]

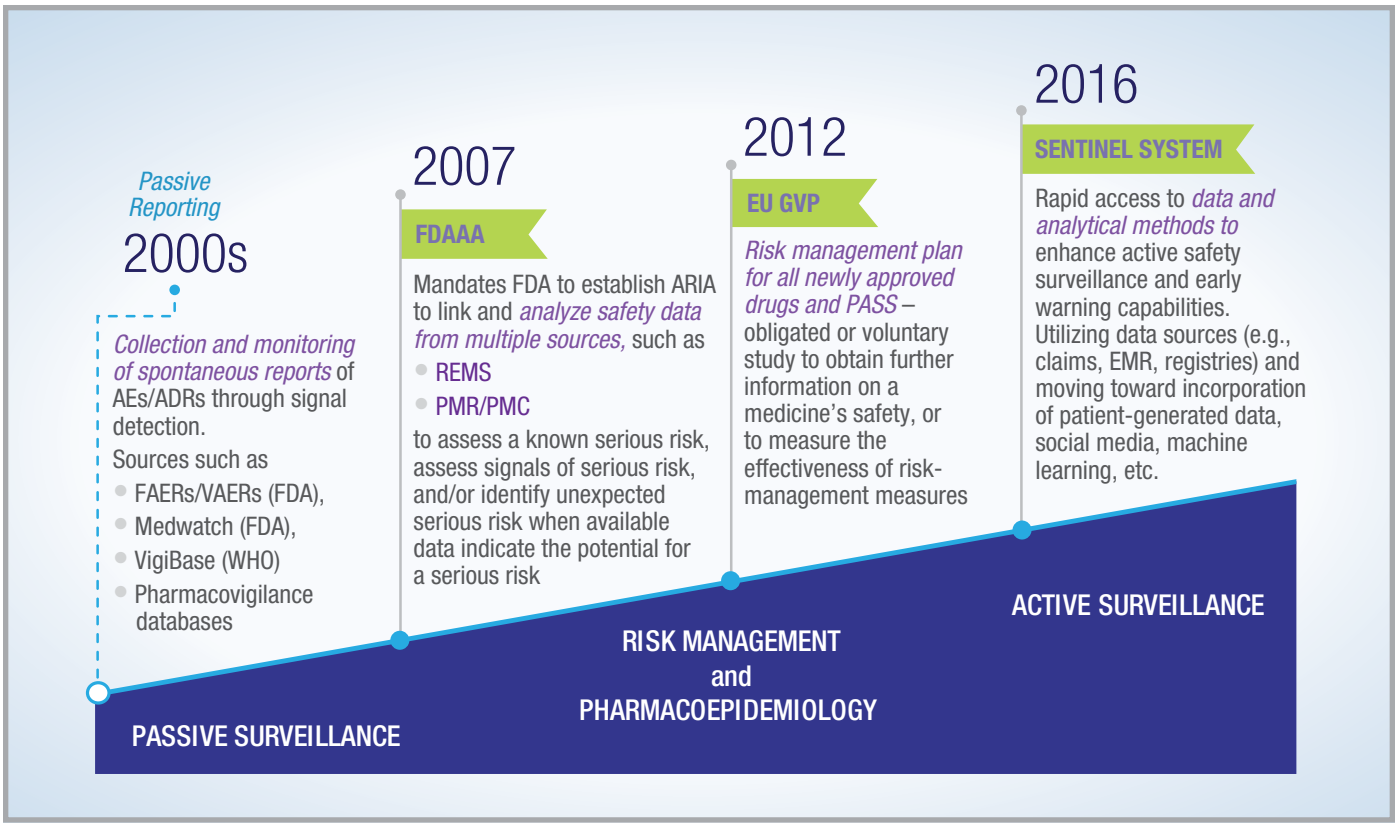
An Expanding Scope

Increased Role of Real-World Evidence in Drug Safety

Post-authorization safety studies (PASS) in Europe, and post-marketing requirements (PMR) or commitments (PMC) in the U.S., have become more frequent. Figure 2 shows the number of PASS currently registered in the EU Post-Authorization Studies (PAS) Register by category.

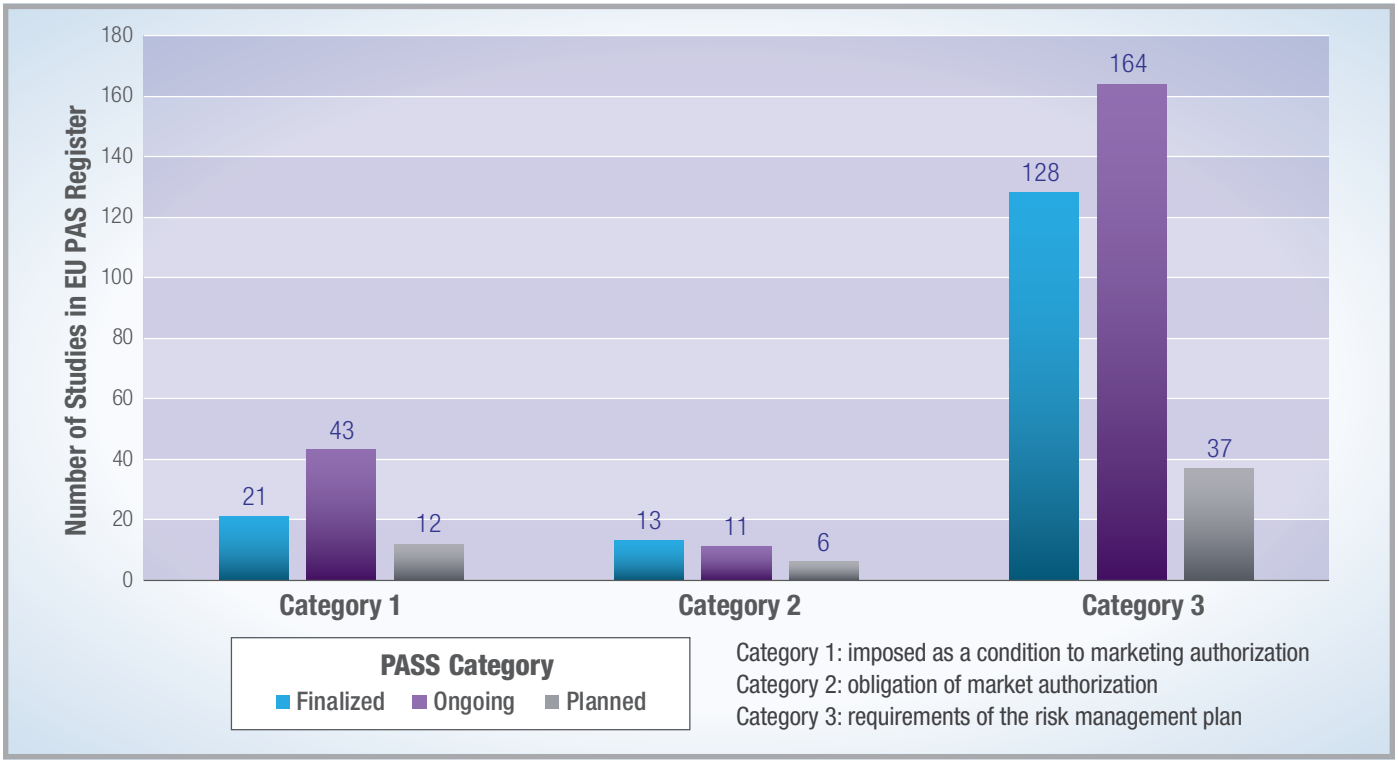
The European GVP acknowledges RWE approaches for PASS (for both primary or secondary data).[8,9] Most PASS

Figure 1. An Overview of the Regulatory Focus around Safety Surveillance and Evaluation over Time



ADR = Adverse Drug Reaction; **AE** = Adverse Events; **ARIA** = Active Post-Market Risk Identification and Analysis; **EMR** = Electronic Medical Records; **EU** = European Union; **FAER** = FDA Adverse Event Reporting System; **FDAAA** = Food and Drug Administration Amendments Act; **GVP** = European Union Good Pharmacovigilance Practices; **PASS** = Post-Approval Safety Studies; **PMC** = Post-Marketing Commitments; **PMR** = Post-Marketing Requirements; **REMS** = Risk Evaluation and Mitigation Strategies; **VAER** = Vaccine Adverse Event Reporting System

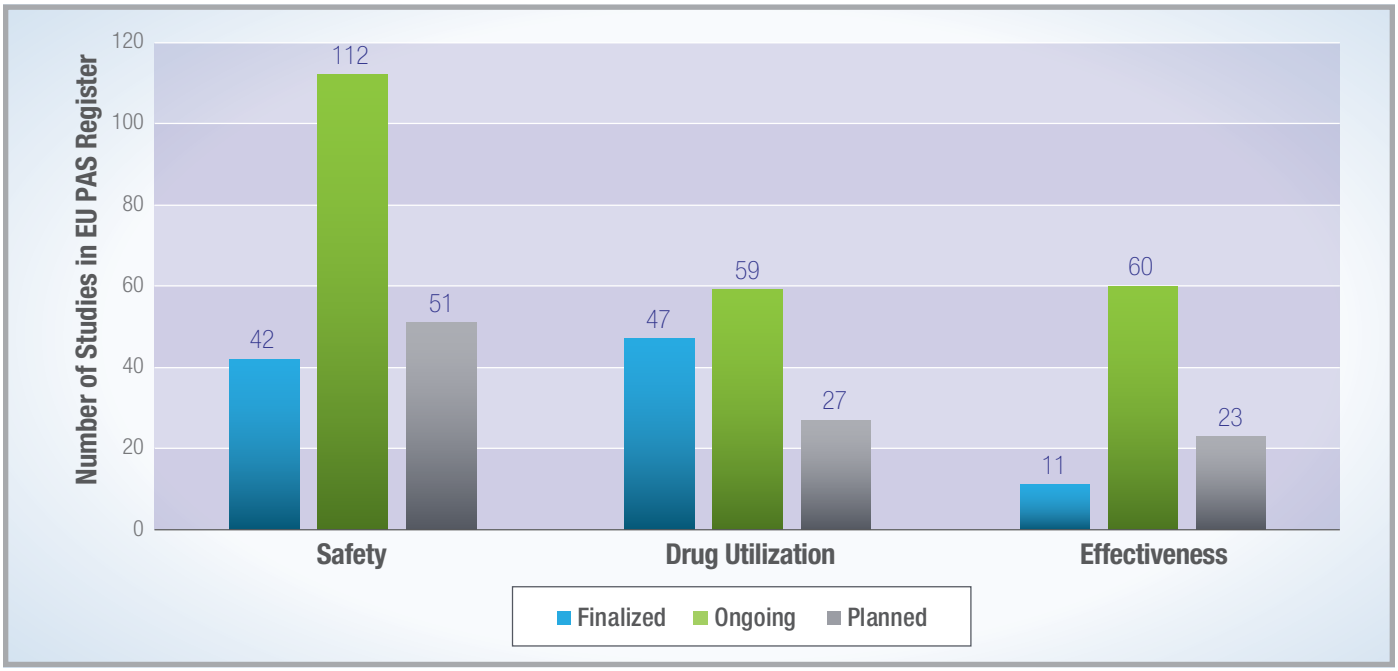
Figure 2. Status of PASS in the EU PAS Register by Study Category as of April 2018



are observational studies,[10] and increasingly introduce real-world utilization (in particular, to describe exposure in groups not exposed in clinical trials) and effectiveness outcomes on top of safety outcomes. A recent article by Carroll et al. focused on non-interventional, post-authorization studies (PAS) in the EU PAS Register showed that many of the studies (65%) covered safety objectives, followed by drug utilization objectives in 42%, and effectiveness objectives in 30%.[10]

In the U.S., the use of RWE for regulatory decision-making has been acknowledged and defined in the 21st Century Act of December 2016.[11] Although specific guidance is under development, the Cures Act provides sponsors with an array of study design options for the post-approval setting.

Figure 3. Type of PAS Registered in the EU PAS Register by Study Status (Finalized, Ongoing, or Planned) as of October 2016
(extracted from Carroll et al, 2017[10])



> "Real-world evidence for drug safety has been around for more than 20 years, but it has now become a hot topic, with much more recognition, emphasis, and requests by the regulatory authorities."
>
> —***Beth Nordstrom**, PhD, MPH, Senior Research Leader, Real-World Evidence, Evidera*

The FDA has integrated RWE as an important part of the activity in the Center of Drug Evaluation and Research (CDER) Drug Safety Priorities 2017 report and stated an expectation that RWE will begin to play a greater role in regulatory decisions.[12] This is already the case with the use of Sentinel data via the Active post-market Risk Identification and Analysis (ARIA) system that is now used in FDA regulatory decisions.

An increasing number of public-private initiatives has contributed to greater consideration of RWE. The Sentinel System has provided opportunities for partnerships between the FDA and data providers as well as healthcare centers. For example, the Innovation in Medical Evidence Development and Surveillance (IMEDS) collaboration allows public and private partners to access Sentinel data while ensuring data security and integrity.[12] In Europe, the Innovative Medicines Initiative (IMI) is the biggest public-private partnership on drug development. Recently, IMI issued a call for proposals on several topics, including medicine safety in pregnancy and during breastfeeding, and predicting drug safety early in development. These projects will be funded jointly by the EU's Horizon 2020 program and the European Federation of Pharmaceutical Industries and Associations (EFPIA). Currently, public-private partnerships govern most of the innovative projects aimed at pooling data sources and/or delivering standardized methods.

Beyond Europe and the U.S., which have been followed closely by Canada and Australia, Asian countries such as South Korea, India, Japan, and mainland China now request post-marketing real-world evidence to observe drug effects in routine practice conditions and in larger and more diverse populations.[13] Although the availability of electronic health-care databases is increasing, the trend in these countries is to request primary data collection of large cohorts of exposed patients with a prospective follow-up.[14] In Latin America, Mexico also typically requires post-marketing studies as part of their market authorization process.[13]

Expanding to New Populations

Understanding the safety of drugs in populations usually excluded from clinical trials is an important concern of regulators and biopharma companies. Regarding pregnancy and breastfeeding, the FDA issued guidance for industry in 2002 to establish pregnancy exposure registries[15] and the European Medicines Agency (EMA) introduced the need for post-authorization data in 2005.[16] More recently, the Pregnancy and Lactation Labeling Rule (PLLR) issued by the FDA in 2015 brought more emphasis on evidence supporting the label and benefit-risk evaluation in pregnancy, including the existence of a pregnancy registry, and the impact of the underlying disease.[17] A recent study shows that the PLLR so far has had an impact on methodological requirements for pregnancy registries.[18]

There is an increased acknowledgment of the specific challenges of assessing drug safety in children (e.g., long-term outcomes such as impact on growth and development), especially in chronic and rare diseases. The 21st Century Cures Act acknowledges these challenges by promoting pediatric research, supporting, amongst others, the implementation of the 2013 National Pediatric Research Network Act.[11]

Increased development of therapies for rare diseases, often under special regulatory requirements, has also contributed to a need for active surveillance. The FDA has announced an Orphan Drug Designation Modernization Plan and established an Orphan Products Council. The European Union and other countries have followed.[19] The 21st Century Cures Act has also brought focus on regenerative advanced therapies and pathways for early approval.[11] As the need for continuous safety data generation is high for these drugs, and their use is limited to small patient populations, rare disease/orphan drug registries provide a good solution for long-term safety studies.

Real-World Data Definition According to the 21st Century Cures Act

Data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than randomized clinical trials (RCTs) and covering:

- Large simple trials or pragmatic clinical trials
- Prospective observational or registry studies
- Retrospective database studies
- Case reports
- Administrative and healthcare claims
- Electronic health records
- Data obtained as part of a public health investigation or routine public health surveillance
- Data gathered through personal devices and health

The Era of Patient Centricity

Patients were allowed to report adverse drug reactions in the early 2000s in the U.S. and as late as 2010 in the EU,[20] and were then invited to participate in the decision-making process through the Patient Representative Program[sm] at the FDA and later in scientific advisory groups at the EMA. Patient surveys also became a key source of data to assess the effectiveness of risk minimization measures in Europe and for REMS in the U.S. More recently, the 21st Century Cures Act has expanded the focus on patient centricity by introducing "Patient-Focused Drug Development" and developing a plan to issue guidance on how to include the patient experience in drug development and regulatory decision-making.[11]

The inclusion of patient centricity in drug development can involve a multitude of activities. One aspect is the use of patient-reported outcomes (PROs) to collect patient experiences, however, this remains infrequent with a recent study showing only 6 out of 30 registries collected data on measures of quality of life.[21] Drug safety studies could benefit from more patient-reported feedback, such as quality of life studies which can help understand the impact of the disease, treatment, and safety events on patients' lives. One illustration is the Fabry Outcome Study, a long-term registry of patients with Fabry Disease with or without specific treatments, which includes a number of pediatric and adult PROs.[22]

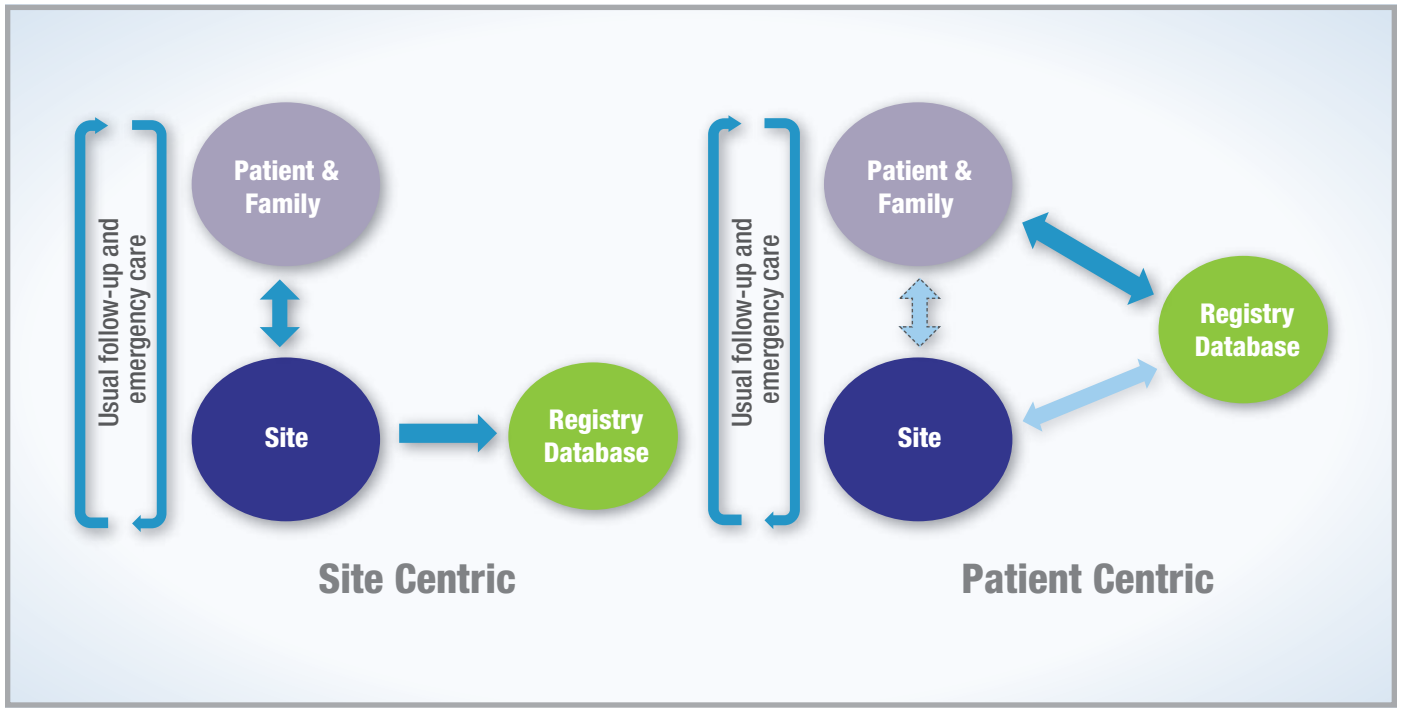
How to collect data with minimal burden to patients is another important aspect of patient centricity. As an example, rare disease registries pose specific operational challenges related to the need to include and retain small numbers of patients, often children, scattered geographically, sometimes far away from research sites, with a low number of patients per site. One solution is to build a patient-centric registry, with one single reference site, where this site, the patients, their caregivers, and primary care providers can access an electronic data collection platform and record study-specific data.[23] (See Figure 4.)

New Conditions of Market Approval and Access

Accelerated regulatory processes (e.g., adaptive pathways, conditional market approval) and early access programs now allow patients with no other therapeutic options or who are ineligible for clinical trials to access new drugs more rapidly. In these programs, regulatory decision making is based on more limited clinical evidence than usually required. In some cases (e.g., regenerative medicine advanced therapy [RMAT] designation in the U.S.), preliminary clinical data could potentially arise from real-world evidence, for example in the case of one-arm clinical trials with observational historical or synthetic control arms. In return, the market authorization holder (MAH) is expected to continue generating evidence on the marketed drug or from patients in the early access program. Safety data are particularly sought after to clarify the benefit-risk ratio over time, due to the limited number of patients exposed during clinical trials.[24, 25]

As an example, pazopanib was initially conditionally approved by the EMA for renal cell carcinoma. During the conditional approval period, a post-marketing study was required to better understand the hepatotoxicity profile of the drug.[26] In addition, during the regulatory process,

Figure 4. The Traditional Site-Centric Model Versus the Patient-Centric Model



a named patient program in soft tissue sarcoma was launched. A chart review study of the effectiveness and safety of pazopanib was conducted in patients included in the named patient program and confirmed the effectiveness and safety results from clinical trials.[27] Pazopanib now has full European market approval in both indications.

> "There is an increasing trend towards integration of real-world evidence within the standard clinical development programs. This is most obvious in the case of conditional approval and adaptive pathways, where real-world evidence plays a major role towards helping to obtain full approval, for example by providing pre-marketing comparison data and post-marketing confirmatory effectiveness and safety data."
>
> —***Patrice Verpillat**, MD, MPH, PhD, Head of Global Epidemiology, Merck KGaA, EFPIA Observer at ENCePP Steering Committee, Darmstadt, Germany*

Rapidly Evolving Technologies and Methods

Data Sources

Electronic Databases: Expansion in Number and Size

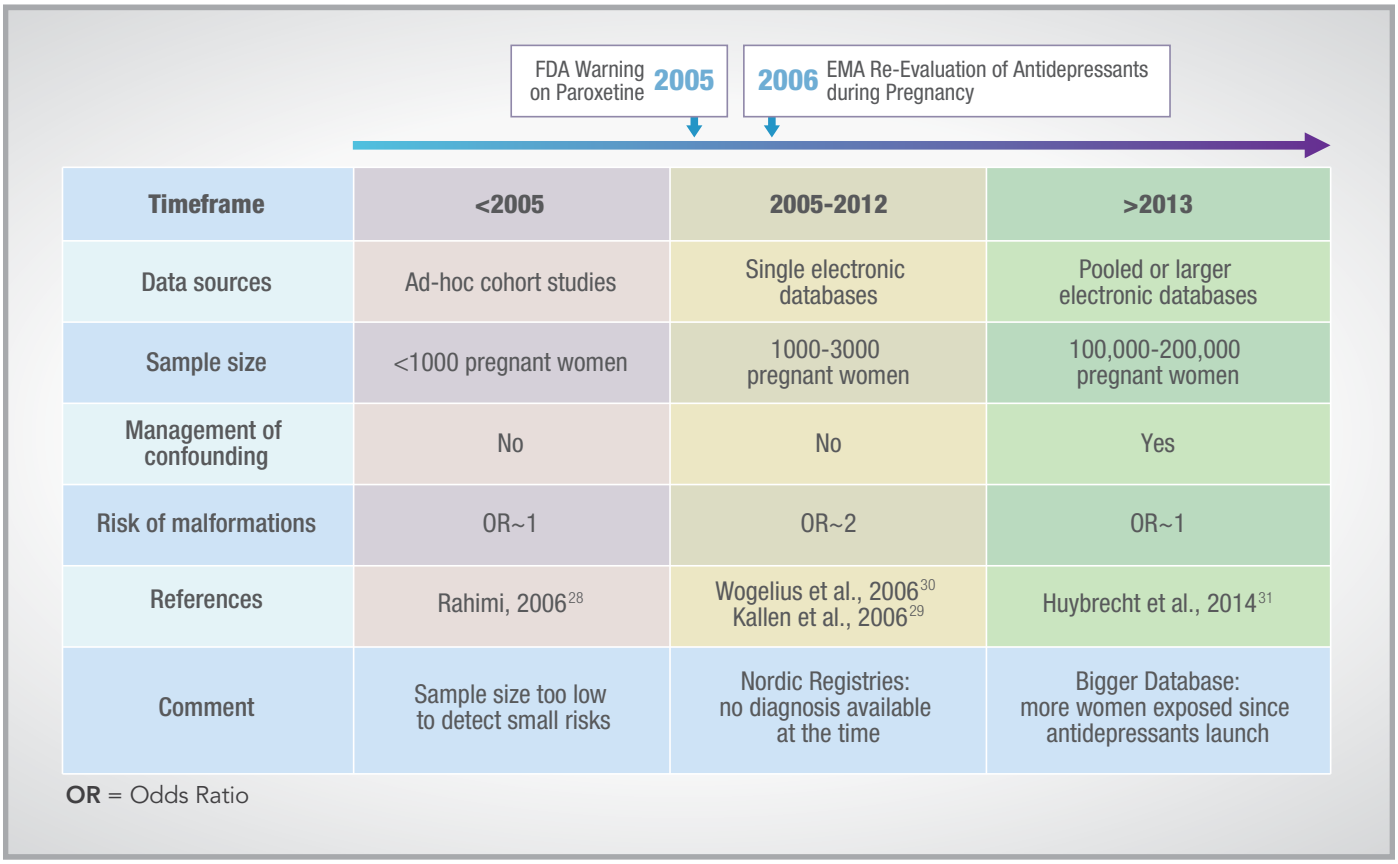
Epidemiology and pharmacoepidemiology investigations for drug safety are evolving with the greater availability and expanded content of existing data sources such as electronic medical records (EMR) databases and claims databases. One example of this evolution is the exposure to antidepressants during pregnancy and the risk of birth defects. Before the generalized use of large electronic data sources, the ad hoc studies performed were too small to be able to detect risks of malformation below 1 percent.[28] As large databases started being used, methods improved, and risks were shown to increase, but with major caveats such as the absence of adjustment on the underlying disease,[29,30] often due to a lack of information (e.g., Danish and Swedish national registers in the early 2000s, although these were the first examples of linkage of different data sources via the patient anonymized number). The use of a big U.S. database and the application of propensity scores changed the conclusions regarding the risk of birth defects associated with antidepressants.[31] This illustrates that access to novel data sources must be accompanied by a strong study design and reliable methods.

Figure 5. Data Sources by Drug Safety Objective

	Signal Detection	Active Surveillance	Drug Utilization	Risk Assessment Descriptive/Comparative + Effectiveness	Risk Minimization REMS/Effectiveness of aRMM
Registries		✖	✖	✖	
Other Primary Data Collection (including PROs)			✖ In some circumstances	✖	
Electronic Healthcare Databases	✖ Linked/ pooled databases	✖	✖	✖	✖ In some circumstances
Patient Surveys					✖
Physician Surveys					✖
Spontaneous Reports	✖				
Social Media	✖		?	?	

aRMM = Additional Risk Minimization Measures

Figure 6. Antidepressants and Risk of Birth Defects – Evolution of Data Sources, Methods, and Conclusions



Timeframe	<2005	2005-2012	>2013
Data sources	Ad-hoc cohort studies	Single electronic databases	Pooled or larger electronic databases
Sample size	<1000 pregnant women	1000-3000 pregnant women	100,000-200,000 pregnant women
Management of confounding	No	No	Yes
Risk of malformations	OR~1	OR~2	OR~1
References	Rahimi, 2006[28]	Wogelius et al., 2006[30] Kallen et al., 2006[29]	Huybrecht et al., 2014[31]
Comment	Sample size too low to detect small risks	Nordic Registries: no diagnosis available at the time	Bigger Database: more women exposed since antidepressants launch

OR = Odds Ratio

The number of available data sources is still increasing, for example with the opening of the French national claims database (Système National des Données de Santé or SNDS) to private researchers in 2017.[32] The content of databases is also increasing, with new linkages developed between different data sources via anonymized patient identifiers (e.g., linkage between primary care medical records, hospital data, and death registries in the Clinical Practice Research Database, or between outpatient claims and inpatient data in the SNDS). The latest trend is now to pool several databases from several systems or countries together to increase the size of the populations.[33]

> "Drug safety in pregnancy is often an area where only collaboration between databases allows the identification of a sufficient number of exposed pregnancies to assess the safety of a new drug with acceptable uncertainty, assuming no systematic errors."
>
> —***Sonia Hernandez-Diaz**, MD, MPH, DrPH, FISPE, Professor of Epidemiology, Director, Pharmacoepidemiology Program, Harvard School of Public Health*

> "There is a trend towards using multiple databases (in parallel and via linkage) to expand the patient population and/or deepen the data available on the patients of interest."
>
> —***Matthew Reynolds**, PhD, Vice President, Epidemiology, Evidera*

Patient Networks, Social Media, and Wearables: New Sources of Data

Social media can comprise several entities, including patient networks, forums, blogs, and social networks such as Facebook and Twitter. Data derived from such sources are by nature unstructured and unsolicited. With some similarity in this respect to passive surveillance using spontaneous adverse events reporting, an early application of social media data for safety focused on signal detection. An example is the exploration by the FDA of the potential of Facebook and Twitter for safety signal detection by checking signals based on these social networks' data against known signals.[34]

PatientsLikeMe, a web-based network on which patients can connect with others with the same condition and share

their experiences, is an example of a patient network. In 2008, PatientsLikeMe launched a drug safety initiative facilitating direct patient reports of adverse events to the FDA, adding to the FDAERs spontaneously reported events. Since 2015, the network has been in a structured collaboration with the FDA covering several research topics, with the aim of clarifying if data from such patient networks can help with earlier identification of adverse events or support the implementation of REMS.

Remote access to patients for healthcare research has been facilitated by the development of wearable devices, such as smartphones equipped with specific applications, but also watches, clothes, glasses, etc. As long as the wearer agrees to share personal data via the device, a great amount of data can be collected, whether actively by the patient (e.g., answering questionnaires) or passively (e.g., heart rate, sleep rhythms, typing speed).

> "Although there will inevitably be some push back at first, data collected from wearables will be used more and more to assess exposures and safety risks, and for signal detection. This is open to creativity."
>
> —***Javier Cid**, MD, DrPH, MBA, Senior Research Scientist, Real-World Evidence, Evidera*

New Approaches to Existing Data Sources

Registries

Some research questions still require bespoke studies and data collection. Registries are often used to generate safety data for rare diseases, orphan drugs, or pregnancy. They can be exhaustive (including all the patients treated with a given drug; registry is a condition for prescription) or not (e.g., pregnancy registry with or without a non-exposed arm; inclusion on a voluntary basis). It is estimated that between 2005 and 2013, a registry was required in almost 10 percent of newly approved drugs to provide additional data on safety. Most of these drugs were approved under exceptional circumstances or orphan designation.[21]

Registries often have long follow-up and require strong operational organization to ensure adequate recruitment and retention. These can now be supported by new technologies. For example, the recruitment in pregnancy registries has been augmented by leveraging social networks and other communication platforms, enabling more rapid recruitment and improved patient diversity.[35]

> "Different technological approaches to recruitment must be used to achieve recruitment goals more quickly."
>
> —***Doug Eckley**, Executive Director, Peri- and Post-Approval Research Operations, Evidera*

The Case of EMRs

To date, EMRs have been most easily used when compiled into databases. Such databases can be found in Europe (e.g., UK, Netherlands) but are less frequent in the U.S. EMR databases contain mostly structured data for clinical information, such as vital signs, lab test, or drug prescriptions that can be used for safety research. Current EMR databases are more often focused on outpatient care. Unstructured data contained in clinical narratives have generally required a chart review protocol involving the support of trained research staff, but new methods of text mining have opened new possibilities to analyze free text.

In parallel, the possibility of automated digital data extraction from the EMRs with direct exportation into a study database is developing. Challenges to such automation include variations in record structure and format. Feasibility of this approach includes assessment of extent of EMR coverage, access to individual EMR platforms, understanding the format of the data and technical requirements, checking on the authorization needed, and the respect of data privacy.[36] This approach can be particularly interesting when hospital prescription data are needed.

New Methodological and Analytical Approaches to Match New Data Sources

Common Data Models and Software Platforms

Common data models (CDMs) have been developed with four main objectives: standardize, analyze, visualize, and optimize the use of multiple databases for pooled analyses. CDMs will bring the expected benefits only if built and designed based on the anticipated objectives of the analyses, and if the quality of all the processes (including data protection, transparency, and reproducibility) is ensured.[37]

For example, the FDA Sentinel System developed its own CDM, which is in turn used by the CNODES (Canadian Network for Observational Drug Effects Studies) project which aims at pooling the provincial claims databases throughout Canada,[38] and by the AsPEN (Asian PharmacoEpidemiology Network).[39]

Another CDM is the OMOP (Observational Medical Outcomes Partnership).[37] The OMOP model is used, for example, by the EMIF (European Medical Information

What about Data Privacy?

- The expansion of new data sources leads to a reinforcement of the legislation around data privacy, in particular in Europe with the General Data Protection Regulation (GDPR) enforced on the 28th of May 2018.
- The GDPR aims to protect EU citizens' personal data in general and also addresses healthcare research.[27] The GDPR applies to any data treatment involving European subjects, whether or not the sponsor is based in the EU.
- Safety studies, especially when requested by regulatory authorities, can most often demonstrate a clear public health interest and thus justify the collection and treatment of personal data, provided a rigorous framework is applied to protect them.
- Primary data collections involve informed consent and usually already comply with the GDPR.
- However, the use of new types of data will be more closely scrutinized and some new modes of data protection and consent will emerge, especially for data initially collected for other purposes and only recently used for healthcare research (e.g., data from social media).

Framework) project, part of the IMI, which aims to develop a common information framework of patient-level data that will link up and facilitate access to diverse medical and research data sources.[40] The challenge of putting together several European databases is even greater due to the diversity of data collected (e.g., Danish hospital data, Spanish primary care electronic medical records, Italian administrative data). The OMOP model is also used by the Observational Health Data Sciences and Informatics (OHDSI). This collaborative program develops and provides open-source solutions to standardize, analyze, and visualize data from different databases.[41]

Some pharma companies have now started putting together their own data platforms with the perspective to analyze both external sources of data as well as internal sources from their own clinical trial and observational studies.

Natural Language Processing (NLP)

In pharmacoepidemiologic research, natural language processing (NLP) is used to identify events/outcomes/risk factors in unstructured data such as clinical text from labels,

> "There is pressure for data to be analyzed and results delivered even more quickly. Common data models allow streamlined programming and analytics for pooled database analyses, which are necessary for fast accrual of patients on newly approved drugs."
>
> —***Beth Nordstrom**, PhD, MPH, Senior Research Leader, Real-World Evidence, Evidera*

electronic medical records (EMRs), or social media data. NLP technology has improved in recent years and can be more widely applied. The main applications of NLP in drug safety are:

- **Identification of adverse events for signal detection**: within the WEB-RADR initiative (part of IMI projects and issued from a private-public European partnership), NLP was applied to social media such as Twitter to extract data on drug usage and health events, create drug-event pairs, and analyse their occurrence via disproportionality analyze, thus potentially contributing to signal detection.[42]
- **Definition of outcomes in pharmacoepidemiologic studies**: for example, Lin and colleagues demonstrated the new possibility to directly identify arthralgias in EMRs, and to compare the risk of arthralgias related between two drugs in patients with inflammatory bowel diseases.[43] Validation of such methods is needed, but work to date tends to highlight the accuracy of NLP definitions.[44]
- Other applications include identification of drug-drug interactions.[45]

Machine Learning

In machine learning, the computer can learn from existing data and apply that knowledge to new data to develop insights. In the field of drug safety, machine learning is at the pilot testing stage for performance, however, the main foreseen applications include:

- **Predictive models of adverse events occurrence for new drugs, or unknown adverse events, based on the current knowledge and using large datasets.** This could lead to a new era of predictive safety in which, for example, post-approval safety requirements are predicted on sophisticated analysis of likely risks prioritized for interrogation. For example, Bean et al. could validate their predictive model of new adverse events of marketed products against electronic medical records and show new unknown associations.[46]

- **Management of confounding in pharmacoepidemiologic studies via the propensity scores.** A most recent version of the propensity score is the high-dimensional propensity score (HDPS). The HDPS is typically a method that can be automated (in particular the covariates identification and prioritization), and there are attempts at machine learning extensions of the HDPS.[47]

NLP and Machine Learning in Practice?

Innovative methods are building the future but some of these methods and technologies are for the moment limited to pilot-testing before they are deemed reliable enough to be used by the regulatory authorities. In the meantime, the priority is for biopharma to implement current post-marketing commitments and comply to regulatory obligations. We are at a technological turning point, and choices need to be made between implementing post-marketing commitments in the traditional way or daring to try new approaches. The trend currently is that innovative methods are tested and implemented by regulatory authorities, non-profit organizations, and public-private partnerships in a research perspective. Some pharma companies are also investing in research in these areas but are still in the pilot testing phase. When it comes to implementing post-marketing commitments, pharma companies and regulatory authorities are usually in agreement to use standard recognized data sources and methods until newer approaches are validated.

Current and Emerging Needs

Validated Systems and Methods

Safety studies require the use of efficient technologies and methods to optimize the internal and external validity by minimizing biases and ensuring transparency and reproducibility. For a primary data collection study, the use of validated 21 CFR part 11-compliant electronic code of federal regulations (eCFR) systems with electronic audit trails is a minimum to ensure the traceability and quality of data collection. In new patient-centric study models, eCFR platforms must be able to collect and combine data from physicians, patients, and caregivers. They need to integrate with central databases containing other data such as from EMRs or wearables.

In electronic databases, using validated algorithms to define inclusion criteria or outcomes/events of interest is highly recommended. If validated algorithms are not available, a validation step must be planned.[48,49] A major example is the definition of pregnancy and pregnancy outcomes in electronic databases, which can be quite complex according to the database type. So far, algorithms have been developed separately for different databases; this can be justified by the different types of data and structure across them. However, there are now attempts at creating standardized algorithms across databases to allow for comparability or pooling.[50]

Using these systems and methods will deliver their full value only if reported in a transparent manner, with enough information to ensure reproducibility. This is fully part of the validity and credibility of a study. In the case of a database analysis, where so many design decisions are made that can all influence the results, it is key to follow the guidelines issued by ISPOR in 2017.[49]

Sufficient Real-World Exposure Time Needed to Assess Safety Outcomes

Real-world safety data can only be collected if the drug of interest is prescribed in routine practice. Keeping up to date with the market access status is key to assess the feasibility, sample size, and timelines of the study. This may be frustrating to the regulator and to the market authorization holder but needs to be considered in plans for safety evidence generation.

In pregnancy studies, this constraint now tends to be addressed by planning both an observational pregnancy registry and database study.[51] The registry allows for real-time assessment of exposure and signal detection after drug launch (although on a limited population), while the database analysis allows it to generate a helicopter view of the drug's safety profile in larger populations and with a defined denominator.

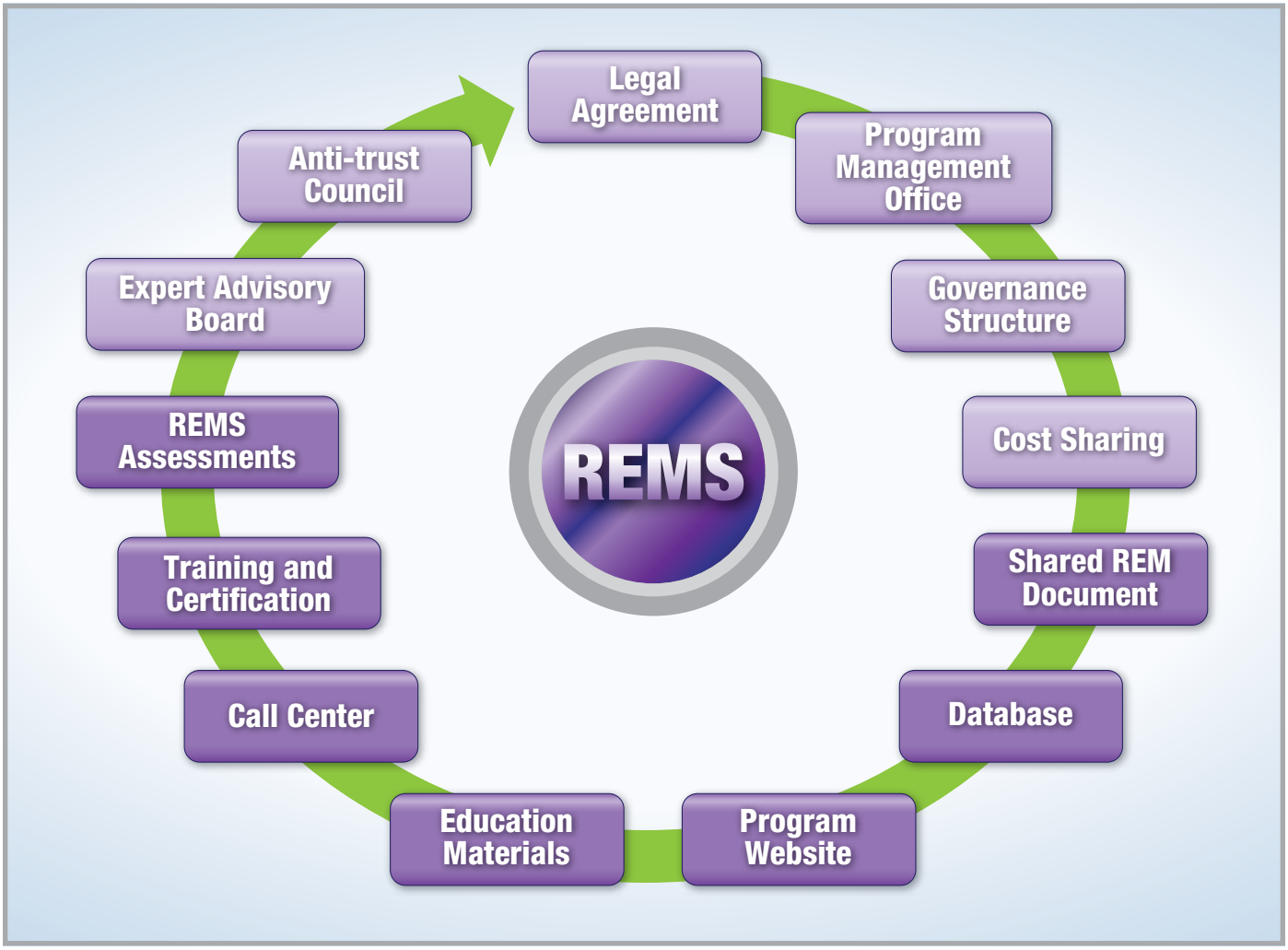
> "Regarding pregnancy studies, we are at a transition between the registry and the database era. At the moment, the optimal approach is a combination of both."
>
> *—**Deborah Covington**, DrPH, FISPE, Senior Research Leader, Real-World Evidence, Evidera*

Organizational Optimization: Shared REMS, Registries, or RWE Platforms

A current trend initiated by the regulatory authorities is sharing projects between different MAHs of the same product. For example, the FDA very recently issued a guidance on shared REMS that reinforces the injunction for MAHs to pool resources.[52] Expectations are to share the costs between the MAHs and maximize the collection, reporting, and use of data. Another expectation is to decrease the strain on the healthcare system and optimize the participation of healthcare providers and patients. This requires an externalized, rigorous, and centralized organization with a clear definition of all the practical aspects of the collaboration between MAHs.

Another example is registries. Due to their higher cost and similar designs, registries are good candidates for pooling resources, whether across several MAHs of the same product that will be requested to merge their registries into one shared registry; or, within the same company, that

Figure 7. Shared REMS Components



could, in case of several registries in different therapeutic areas, invest in a platform allowing the optimization of human and technical resources. Beyond savings, such platforms can increase the collaborations between therapeutic areas or regions within the same company by facilitating experience sharing and learning.

> "One success factor for shared REMS is the coordination by a dedicated project management office that will manage all the organizational aspects, including the decision-making process, but also the relationships between the different market authorization holders."
>
> —***Robin Kinard**, Senior Director, Risk Management Programs, Peri- and Post-Approval Research Operations, Evidera; and, **Kristin Veley**, PharmD, MPH, Research Scientist and Director, REMS and Pregnancy Registries, Real-World Evidence, Evidera*

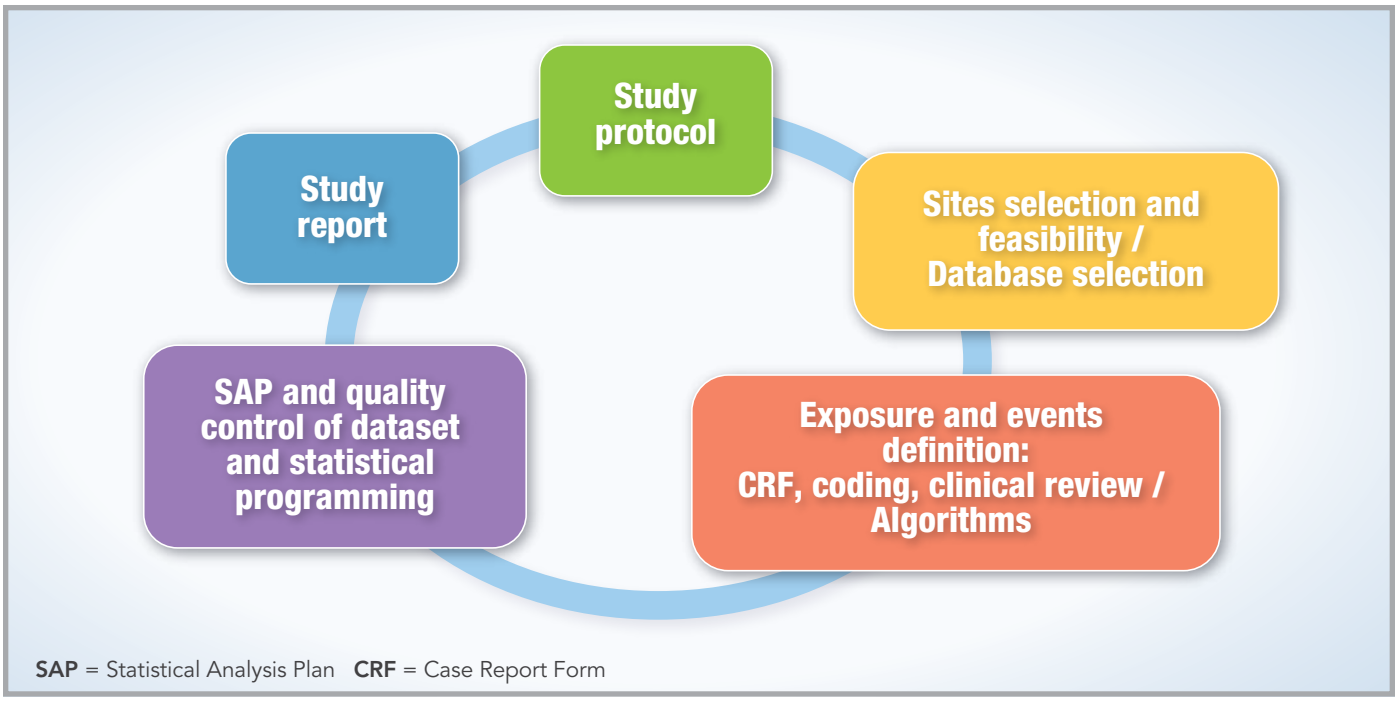
Faster Turnaround Time

The need for rapid analyses to increase the reactivity of the public health response by the regulatory authorities has been clearly highlighted by the EMA.[53] The FDA also used this argument when presenting and justifying their new initiatives towards active surveillance systems and common data models.[54] The objective is to reduce the time to detect issues and launch corrective actions. However, quickness should not reduce quality. Accuracy, transparency, and reproducibility are needed for credible drug safety studies.

The need for faster turnaround contributed to the success of electronic healthcare databases, and timelines could be further reduced by the use of CDM and more technology-driven approaches.

For primary data collection studies (e.g., registries), optimization is possible via careful planning and organization, by clearly identifying the key points for enhanced quality procedures, and by not falling into the trap of increasing all the study procedures (e.g., on-site monitoring) beyond the acceptable for a non-interventional study.

Figure 8. Key Enhanced Quality Points for Non-Interventional Safety Studies



SAP = Statistical Analysis Plan **CRF** = Case Report Form

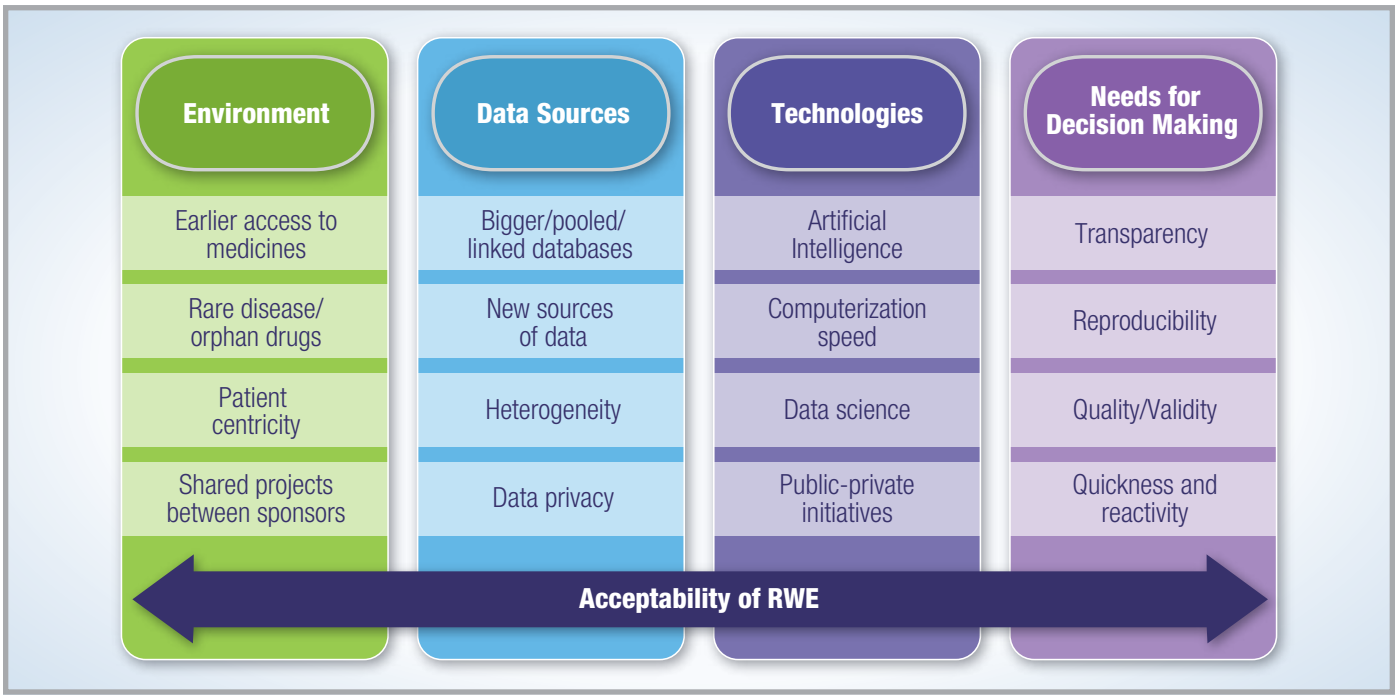
> "Close collaboration between the science, strategy, and operations is the only way to achieve the right balance between quality and speed in primary data collection within non-interventional safety studies."
>
> —***Javier Cid**, MD, DrPH, MBA, Senior Research Scientist, Real-World Evidence, Evidera*

Conclusion

In the last twenty years, generation of safety data outside of clinical trials has developed from a single-source, passive system to a holistic and proactive approach based on the combination of data generation systems and a multitude of data sources and designs. Within an evolving regulatory environment, RWE safety data has moved from supportive data to a key element in regulatory decisions.

Real-world data sources are increasing in number, size, and diversity. They are very well suited for new analytical

Figure 9. Summary of Trends in Drug Safety



technologies such as standardization, automatization, and artificial intelligence, thus increasing the granularity of the available information.

As the field expands, a thorough understanding of the safety landscape, possible study options, and available methods is crucial to implement a fit for purpose study design to ensure the continuous assessment of benefit/risk for patients. ■

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Acknowledgments

The authors would like to thank the experts quoted in this paper who have provided their personal views on the trends and evolution of drug safety.

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Evidera Presents at ISPOR Europe 2018

10-14 November 2018 – Barcelona, Spain

SHORT COURSES

Sat., Nov. 10, 8:00 AM–12:00 PM
MORNING SESSION

Conjoint Analysis - Theory & Methods

Heidenreich S

Introduction to Constrained Optimization Methods for Health Care Research

Tosh J

Using DICE Simulation for Health Economic Analyses

Caro JJ, Moller J

Sat., Nov. 10, 1:00 PM–5:00 PM
AFTERNOON SESSION

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

IJzerman MJ, **Marsh K**, Devlin N

WORKSHOPS

Mon., Nov. 12, 5:00 PM–6:00 PM

W7: Preference Research in HTA Agencies Europe - A Review of its Use in Approval, Reimbursement, and Pricing

Mühlbacher AC, **Marsh K**, van Til JA

Tue., Nov. 13, 3:30 PM–4:30 PM

W11: Challenges and Lessons Learned from Electronic Recruitment and Validation of Patients for Outcome Research Studies in Rare Diseases

Hadi M, Swinburn P, Waby J

ISSUE PANEL

Wed., Nov. 14, 3:00 PM–4:00 PM

IP26: Will Regenerative Medicines Change the Way We Evaluate Evidence, Fund Innovation, and Determine Value?

Epstein M, van Amerongen D, Maywald U, de Solà-Morales O

FORUMS

Mon., Nov. 12, 6:15 PM–7:15 PM

F2: Towards a Value Framework for Precision Medicine: Recommendations from the ISPOR Precision Medicine Special Interest Group

IJzerman M, Brizner D, Holtorf AP, **Faulkner E**

Tue., Nov. 13, 6:00 PM–7:00 PM

F9: Diagnostics Evidentiary Dinosaur Evolution: Conventional Health Economics and Market Access Approaches vs. Advanced Analytics as the New Norm?

Faulkner E, Poulios N, Redekop K, Zah V

PODIUM PRESENTATIONS

Mon., Nov. 12, 11:15 AM–12:15 PM

P1: METHODS IN CANCER STUDIES

P1: Value of Adjuvant Oncology Therapies: Methodological Challenges of Modelling Cost-Effectiveness of an Adjuvant Treatment in an Era of High-Cost Oncology Treatments

Kovacs V, Kiss Z, Tichy E, Benedict A

Tue., Nov. 13, 4:45 PM–5:45 PM

P12: PATIENT PREFERENCE STUDIES

PP3: Tuning into what Patients Say About Clinical Trials when Scientists and Clinicians are Not Listening? Implications for Recruitment

Halhol S, Booth A, Pan S, Cox A, Merinopoulou E

POSTERS

Mon., Nov. 12, 8:45 AM–1:45 PM
SESSION I

PCP: CONCEPTUAL PAPERS

PCP45: The Role of Crossover and Treatment Switching in Indirect Treatment Comparison in Immuno-Oncology

Ishak KJ, Muszbek N, **Altincatal A, Sarri G**, Schlichting M, Zhou J

PCP46: A Simple Decision Tree to Identify Potential Applications of Machine Learning as an Addition to Traditional Statistical Analysis in Health Economics and Outcomes Research

Cox A, Oguz M

PCP48: Stability of Results in Simulation Based Health Economic Models

Gal P, Kovacs V

PCP54: Overview of Methods for Assessing Comparative Evidence for Treatments Evaluated in Early Phase Trials in Oncology

Proskorovsky I, Stein D, Bobiak S, **Ishak KJ**

PCP56: Early Access Programs: Recommendations for Real-World Data Collection

Stein D, Soni M

PMU: MULTIPLE DISEASES

PMU1: Frequency of Reportable Adverse Events in Health-Related Social Media Posts

Booth A, Halhol S, Merinopoulou E, Oguz M, Pan S, Cox A

PSS: SENSORY SYSTEMS DISORDERS

PSS24: Estimation of the Long-Term Population Costs and Benefits for Five Different Varicella Childhood Immunization Strategies in Bulgaria

Dimitrova M, Zdrakova MM, Faivre P, **Gani R, O'Brien E, Sutton K**, Weiss TJ, Wolfson LJ

PSS65: Development of the Neurotrophic Keratopathy Questionnaire: Qualitative Research

Murray LT, McCormack J, Wiklund IK, Grobeiu ID, Van Nooten F

PSY: SYSTEMIC DISORDERS/CONDITIONS

PSY25: Systematic Literature Review of the Clinical Efficacy and Safety of Treatments for Patients with Waldenstrom's Macroglobulinemia

Gulea C, Lee J, Gorcyca K, Jeyakumaran D, Ren J, Buske C

PSY191: Health State Utilities Associated with Treatment for Transfusion Dependent B-Thalassemia

Matza LS, Paramore C, **Stewart KD, Syrad H**, Jobanputra M, Dietz A

PSY202: The Occupational Hazards of Measuring Risk Tolerance: Convergent Validity in Preference Elicitation

SriBhashyam S, Quartel A, Gershman A, Stadler K, **Marsh K**

Mon., Nov. 12, 3:45 PM–7:15 PM SESSSION II

PIN: INFECTION

PIN63: A Cost-Minimization Model to Evaluate the Impact of Ceftaroline Fosamil For the Treatment of Complicated Skin and Soft Tissue Infections in Hospitalized Adults in Spain

Soriano A, Grau S, **Rivolo S**, Remak E, Peral C, Kantecki M, Ansari W, Charbonneau C, Hammond J, Wilcox M

PIN111: Impact of Variation in Influenza Vaccination Schedules and Decision-Making Criteria on Patient Outcomes in European Countries

Gani R, Chapman R, Sutton K, Feng H

PIN116: Prioritizing Investments in New Vaccines Against Epidemic Infectious Diseases: A Multi-Criteria Decision Analysis

Gouglas D, **Marsh K**

PMD: MEDICAL DEVICES/DIAGNOSTICS

PMD177: Patient Preferences and Health State Utilities Associated with Dulaglutide and Semaglutide Injection Devices Among Patients with Type 2 Diabetes in Italy

Matza LS, Boye KS, **Stewart KD, Jordan J**, Biricolti G, Del Santo S, Norrbacka K, Perez M, Orsini Federici M, Gentilella R, Losi S

PND: NEUROLOGICAL DISORDERS

PND53: Model-Based Economic Evaluations of Treatments for Parkinson's Disease: A Systematic Literature Review

Folse H, Chandler C, Alvarez P, Uyei J, **Ward A**

PND121: Utilities Associated with Attributes of Migraine Preventive Treatments: Route of Administration and Adverse Events

Matza LS, Deger K, Vo P, Maniyar F, Bilitou A, Goadsby PJ

PND122: Health State Utilities Associated with Familial Chylomicronemia Syndrome (FCS), a Rare Genetic Disorder

Matza LS, Phillips GA, **Howell TA**, Ciffone N, Ahmad Z

PND125: The Association Between Utilities and Disease Severity for Parkinson's Disease: A Systematic Literature Review

Chandler C, Alvarez P, Folse HJ, Ward A

Tue., Nov. 13, 8:45 AM–1:30 PM SESSION III

PDB: DIABETES/ENDOCRINE DISORDERS

PDB63: Cost-Effectiveness Analysis of Empagliflozin Treatment in Patients with Type 2 Diabetes and Chronic Heart Failure Based on Subgroup of EMPA-REG Outcome in the United Kingdom

Reifsnider O, Kansal A, Franke J, **Lee J**, George JT, Brueckmann M, Kaspers S, **Brand S**, Ustyugova A, Linden S, Hau N

PDB119: Patient Preferences and Health State Utilities Associated with Mealtime Insulin Concentrations among Patients with Diabetes in Italy

Matza LS, Osumili B, **Stewart KD**, Perez M, **Jordan J**, Biricolti G, Romoli E, Losi S, Del Santo S, Spaepen E, **Parola G, Syrad H**, Boye KS

PGI: GASTROINTESTINAL DISORDERS

PGI39: Darvadstrocel in the Management of Complex Perianal Fistulas: The Role of Patient Registry Data Collection to Support Performance-Based Risk Sharing Agreements

Schmetz A, Petrakis I, Khalid JM, Minda K, Agboton C, **Rawson K**, Baumgart DC

PGI40: The Role of Performance-Based Risk-Sharing Agreements in Minimising Payer Uncertainty When Standard of Care is Not Clearly Defined; The Example of Crohn's Disease Related Complex Perianal Fistulas

Schmetz A, Kaur S, Petrakis I, Agboton C, Azzabi Zouraq I, Minda K, **Rawson K**, Campbell-Hill S, Baumgart DC

PHP: HEALTH CARE USE & POLICY STUDIES

PHP131: What Use is Distributed Ledger Technology in Real-World Practice? A Systematic Literature Review

Abogunrin S, Koufopoulou M, Arregui M, Lovelace M, Arisa O

PHP132: Can Blockchain Technology Improve the Quality of Clinical Trial Evidence? A Systematic Literature Review

Koufopoulou M, Arregui M, Lovelace M, Arisa O, **Abogunrin S**

PHP274: Italy's New Pharmaceutical Innovation Ranking System: Key Criteria for Successfully Achieving Innovative Status

Sligh S

PHP315: How Frequently is Patient Experience Formally Assessed in Health Technology Assessments? Results from a Systematic Literature Review

Sarri G, Kenny J, **Freitag A**, Mountian I, Szegvari B, Brixner D, Maniadakis N

Tue., Nov. 13, 3:30 PM–7:00 PM
SESSION IV

PCV: CARDIOVASCULAR DISORDERS

PCV116: Discontinuation and Health Care Resource Utilisation in Non-Valvular Atrial Fibrillation Patients Treated with Apixaban or Warfarin in England

Graham S, Raluy M, Donaldson R, Colby C, Carroll R, **Nordstrom B**, Stynes G, Hill N, Ramagopalan S, Alikhan R

PCV138: Treatment Patterns of Patients with Venous Thromboembolism Treated with Oral Anticoagulants in England

Carroll R, **Lambrelli D, Donaldson R, Schultze A, Nordstrom B**, Stynes G, Ramagopalan S, Alikhan R

PRM: RESEARCH ON METHODS

PRM5: Profiling of Disease Symptoms and Adverse Events: Does Social Media Augment Traditional Approaches?

Pan S, Halhol S, Booth A, Cox A, Merinopoulou E

PRM57: Assessments of Economic Value Using Five Different Oncology Value Frameworks (ASCO, ESMO, NCCN, MSKCC, ICER)

Ambavane A, Meier G, **Rivolo S, Gani R**

PRM84: Leveraging Hospital-Based EMR Systems for Real-World Evidence Generation: Opportunities and Challenges

Stein D, Carroll R, **Dhalwani N**, Ramagopalan S

PRM143: Exploring the Effects of Subsequent Life Extending Treatments on Cancer Trial Endpoints Using Clinical Trial Simulation

Stern S, Quon P, Kansal AR, Chavan A

PRM193: From Individual Patient to Population Preferences: Multinomial Logit Model vs Dirichlet Distribution

Tervonen T, Pignatti F, Postmus D

PRM242: Using Non-Randomised Evidence or Clinical Assumptions to Make Connections In Network Meta-Analysis – A Case Study In Relapsed/Refractory Multiple Myeloma

Guo Y, Rabar S, Rizzo M

PRM254: On Simulation of Time to Progression and Death Based on Aggregate PFS and OS Curves

Rakonczai P, Kapetanakis V, Ishak KJ

PRM260: Generation of Reconstructed Individual Patient Data from Digitized Curves in Cost-Effectiveness Model: A Discrete Optimization Approach

Prawitz T, Kapetanakis V, Rael M, Ishak KJ

PRM267: What is Driving NICE-Decision Making on Single-Arm Trials

Rizzo M, Rabar S, Guo Y, Deshpande S

PRM268: Evaluation of Real-World Data Collection and Evidence Generation From Early Access Programs

Stein D, Soni M

PRS: RESPIRATORY-RELATED DISORDERS

PRS11: Initiation of Triple Therapy in Newly Diagnosed COPD Patients

Merinopoulou E, Monteagudo M, **Booth A**, Miravitlles M, **Lambrelli D**

PRS16: Modeled Survival Gains of Patients with Cystic Fibrosis (CF) Aged ≥12 Years Heterozygous for F508DELCFTR and a Residual Function Mutation (F508DEL/RF) Treated with the CF Transmembrane Conductance Regulator Modulator (CFTRM) TEZACAFTOR/IVACAFTOR (TEZ/IVA)

Lopez A, Yang Y, Loop B, **Chandler C**, Liou T, Konstan M, **Pelligra C, Ward A**, Rubin J

PRS37: Economic Burden Associated with Chronic Obstructive Pulmonary Disease (COPD): A Systematic Literature Review

King D, Zhang S, **Iheanacho I**, Kenny J, **Rizzo M**, Ismaila A

PRS83: Patient Perspective on Medication Adherence in Asthma: A Systematic Review of the Literature

Amin S, **Leighton P, McHorney CA, Safikhani S**, Svangren P, Cabrera CS

PRS89: Measurement of Maintenance and Reliever Use in Asthma: A Systematic Review of The Literature

Amin S, **Leighton P, McHorney CA, Dias-Barbosa C**, Svangren P, Cabrera CS

PRS92: What Symptomatic Patients with Asthma and Chronic Obstructive Pulmonary Disease (COPD) Find Important in Their Maintenance Inhaler Therapy: A Focus Group Study

Hawken N, Hanania NA, Gilbert I, Martinez FJ, Fox KM, **Ross M, Duenas A, Cooper O, Kawata AK, Tervonen T**

PRS101: Impact of Chronic Obstructive Pulmonary Disease (COPD) on Quality of Life: Findings from a Systematic Literature Review

King D, **Iheanacho I**, Zhang S, Kenny J, **Rizzo M**, Ismaila A

Wed., Nov. 14, 8:45 AM–1:15 PM
SESSION V

PCN: CANCER

PCN155: Cost-Effectiveness of CPX-351 Versus 3+7 among Patients <60 Years of Age in the Treatment of High-Risk Acute Myeloid Leukemia (AML) in the United Kingdom (UK)

Kansal A, Reifsnider O, Khankhel Z, Todorova L, **Dorman E, Coughlan A, Hoog M**, Villa K

PCN280: Impact of Suboptimal Clinical Evidence on Health Technology Assessment Recommendations

Zou D, Desrosiers N, **Wu S, Prawitz T, Tervonen T, Marsh K, Caro JJ**

PCN362: Understanding Patient and Clinician Perceptions of Cell and Gene Therapy in Oncology Using Qualitative Analyses of Social Media Data

Merinopoulou E, Cooper O, Hareendran A, Booth A, Faulkner EC, Spinner DS, Bruno A, Arjunji R

PCN373: Understanding Patient Perspectives of Renal Cell Carcinoma Using Social Media: a Qualitative Analysis

McDonald L, **Merinopoulou E, Cox A**, Malcolm B, Mehmud F, Ramagopalan S

PCN385: Quality of Life of Patients Living with Metastatic Colorectal Cancer (MCRC): European Organization for Research and Treatment of Cancer (EORTC) Questionnaire Results from a Real-World European Survey

Benedict A, Rakonczai P, Muszbek N, Maravic Z

PMS: MUSCULAR-SKELETAL DISORDERS

PMS76: Healthcare Resource Utilisation Associated with Refractory Myasthenia Gravis (MG) in Comparison to Non-Refractory MG Patients in England: A Retrospective Cohort Study

Graham S, MacLachlan S, Exuzides A, Buus R, Harris L, Jacob S

PUK: URINARY/KIDNEY DISORDERS

PUK24: Hyperkalaemia in Chronic Kidney Disease: Patient Treatment Experience with Renin-Angiotensin-Aldosterone- System Inhibitors in Primary Care in England

Simpson A, Zakin L, Vrouchou P, Moore-Ramdin L, **Rubino A**

Upcoming Presentations

ISOQOL 2018 25th Annual Conference

October 24-27, 2018; Dublin, Ireland

WORKSHOPS

Clinical Outcome Assessment in a Multi-Cultural Context: Measurement Challenges and Solutions

Eremenco S, Hudgens S, **Martin M**, McLeod L, Regnault A

Concept Elicitation for the Development of Clinical Outcome Assessments (COAs) - Qualitative Approaches for Data Collection, Analyses and Reporting

Hareendran A, Skalicky A, Magasi S

POSTERS

Development of a Patient Reported Measure of Quality of Care Transitions: Evidence of Structural Validity

Anatchkova M, Atkinson M, Santry H, Erskine N, Kiefe C

The American Neurogastroenterology and Motility Society Gastroparesis Cardinal Symptom Index-Daily Diary (ANMS GCSI-DD): Assessing Qualitative Validity and Electronic Usability in Patients with Idiopathic or Diabetic Gastroparesis

Revicki DA, Gleeson S, Speck R, Puelles J, Kuo B, Camilleri M, Parkman HP

Clinical Trials on Alzheimer's Disease 2018

October 24-27, 2018; Barcelona, Spain

POSTER

Validating Simulated Cognition Trajectories Based on ADNI Against Trajectories from the National Alzheimer's Coordinating Center (NACC) Dataset

Tafazzoli A, Weng J, Sutton K, Litkiewicz M, Chavan A, Krotneva M, Kansal A

ACPE 2018

Oct 27-29, 2018; Xi'an, China

POSTER

Feasibility Assessment for an Observational Study Evaluating Effectiveness/Safety of a Fifth-Generation Cephalosporin Antibiotic in Community-Acquired Pneumonia (CAP) Patients in China

Gu Y, **Stein D, Soni M, Simeone JC**

28th Alzheimer Europe Conference

October 29-31, 2018; Barcelona, Spain

POSTER

Identifying Patients at Higher Risk of Initiating Cognitive Decline for Evaluating Amyloid-Targeted Treatments

Tafazzoli A, Kansal A, Weng J, Ishak J

Recent Presentations

AMCP 2018 NEXUS

Oct 22-25, 2018; Orlando, FL, USA

POSTERS

A Cost-Consequence Analysis of Bictegravir/Emtricitabine/Tenofovir Alafenamide (BIC/FTC/TAF) Compared with Other Antiretroviral Regimens in a Simulated Model of Adult HIV Patients

Dejesus E, **Folse H**, Altice F

Budget Impact Analysis of Moxetumomab Pasudotox-TDFK for the Treatment of Patients with Relapsed or Refractory Hairy Cell Leukemia in the United States

Tafazzoli A, Kempster J, Pavilack M, **Deger K**, Ma W, Olufade T

UEG Week 2018

Oct 20-24, 2018; Vienna, Austria

POSTERS

Efficacy of Tofacitinib and Biologics as Induction and Maintenance Therapy for Moderately-to-Severely Active Ulcerative Colitis: A Systematic Review and Network Meta-Analysis

Rubin D, Ashaye AO, Zhang Y, **Fahrbach K, Freitag A**, Kayhan C, Lohan C, Cappelleri JC, DiBonaventura M

Vedolizumab Outcomes in Real-World Bio-Naive Ulcerative Colitis and Crohn's Disease Patients (EVOLVE) in Canada: Treatment Patterns, Clinical Effectiveness and Safety

Bressler B, **Bassel M, Stein D, Soni M**, Radulescu G, Greenup A-J, Khalid JM, Demuth D

ESMO 2018 Congress

Oct 19-23, 2018; Munich, Germany

POSTER

Advanced Melanoma Treatment Patterns in the Modern Era: United Kingdom (UK) Real World Retrospective Chart Review Study

Sacco JJ, Corrie PG, Oladipo O, Payne M, Larkin J, Talbot T, Wagstaff J, Cheetham S, **Stein D, Soni M, Coombs C**, Amadi A, Wang M, Ellis J

ISPOR Summit 2018

Oct 19, 2018; Washington, DC, USA

SPEAKERS

Novel Approaches to Value Assessment, Beyond Cost-Effectiveness

Johnson R, **Caro JJ**, Phelps C, DuBois R, Reed S

Practical Next Steps in Improving Value Measurement and Use

O'Brien J, Schrandt S, **Luce B**, McElwee N

American Society for Reproductive Medicine 2018 Scientific Congress

Oct 6-10, 2018; Denver, CO, USA

POSTER

A Meaningful Response on the Uterine Fibroid Symptom and Health-Related Quality of Life Questionnaire (UFS-QOL)

Coyne KS, Harrington A, **Currie BM**, Mo Y, Gillard P, Spies JB

ACG 2018

Oct 5-10, 2018; Philadelphia, PA, USA

POSTERS

Documenting the Journey of Patients with Eosinophilic Esophagitis and its Impact on Their Caregivers

Pokrzywinski RM, Harding G, Brooks A, Todorova L, Williams J

Efficacy of Tofacitinib and Biologics as Induction and Maintenance Therapy for Moderately-to-Severely Active Ulcerative Colitis: A Systematic Review and Network Meta-Analysis

Rubin DT, Ashaye AO, Zhang Y, **Fahrbach K, Freitag A**, Kayhan C, Lohan C, Cappelleri JC, DiBonaventura M

Vedolizumab Outcomes in Real-World Bio-Naive Ulcerative Colitis and Crohn's Disease Patients (EVOLVE) in North America

Yarur A, **Bassel M, Stein D, Kim H**, Radulescu G, Lopez C, Lissoos T, Demuth D, Bressler B

The American Neurogastroenterology and Motility Society Gastroparesis Cardinal Symptom Index-Daily Diary (ANMS GCSI-DD): Psychometric Evaluation in Patients with Idiopathic or Diabetic Gastroparesis

Revicki DA, Speck R, Gleeson S, Puelles J, Kuo B, Camilleri M, Parkman HP

World CB & CDx

Oct 4-5, 2018; Boston, MA, USA

ISSUE PANEL

Overcoming Hurdles in Reimbursement & Access for Diagnostic Enabled Therapeutics

Lerner P, Matthews C, **Spinner D**

Cell & Gene Meeting on the Mesa

Oct 3-5, 2018; La Jolla, CA, USA

ISSUE PANEL

Navigating Acceptance, Uptake and Affordability Across the Lifecycle: What Does Good Look Like?

Faulkner E, Jacques L, Keith P, Philip R, Pinilla-Dominguez P, Powell R

EASD 2018 Annual Meeting

Oct 1-5, 2018; Berlin, Germany

POSTER

Time to Treatment Intensification with GLP-1 Receptor Agonists for Patients with Type 2 Diabetes in the UK: Medical Record Review Study

Norrbacka K, **Stein D, Matza LS, Jordan JB**, García-Pérez L-E, Wasi Hassan S, Boye KS

ASGCT Value Summit

Sept 24, 2018; Washington, DC, USA

SPEAKER

Considerations for High Risk Pools for Regenerative and Advanced Therapy

Faulkner E

HFSA 2018 22nd Annual Scientific Meeting

Sept 15-18, 2018; Nashville, TN, USA

POSTER

Improving the Efficiency of Heart Failure Care

Rathman L, Pointer S, Small R, Needles A, **Yeomans K**, Bharmi R, Roberts J

EADV 2018 Congress

Sept 12-16, 2018; Paris, France

EPOSTER

Qualitative Assessment of Patient-Reported Outcome Measures Among Patients with Moderate to Severe Plaque Psoriasis of the Scalp

Wang Y, **Coyne K**, Sofen H, Santanello N, **Currie B**, Zhang Z, Nograles K

ISPOR 2018 Asia Pacific

Sept 8-11, 2018; Tokyo, Japan

ISSUE PANEL

Better the Devil You Know? QALYs and their Alternatives in Drug Reimbursement Decision-Making

Kim H, Sculpher M, **Caro JJ**, Liew D

WORKSHOP

Response Based Cost-Effectiveness Modeling in Immuno-Oncology

Caro JJ, Muszbek N, Zhuo J

ESC 2018 Congress

Aug 25-29, 2018; Munich, Germany

POSTER

Hyperkalemia in Chronic Kidney Disease: Incidence, Prevalence and Impact on RAAS Inhibitors treatment in Primary Care in Scotland

Simpson A, Zakin L, Moore-Ramdin L, Vrouchou P, **Rubino A**

ICPE 2018

Aug 22-26, 2018; Prague, Czech Republic

SYMPOSIUM

Patient-Focused Benefit Risk Assessment: Why, When and How Should Epidemiologists Get Involved

DiSantostefano RL, Russo L, **Marsh K**, Cave A, Hauber B, Andrews E

WORKSHOPS

Quantitative Benefit-Risk Assessment

Ataher QS, Postmus D, Hillege HL, **Tervonen T**

Selection of Databases for Pharmacoepidemiology Research

Reynolds MW

ORAL PRESENTATIONS

Long-Term Clinical Outcomes Following a Myocardial Infarction among the General Population in England

Schultze A, Shah R, Tershakovec A, Hammad TA, **Tervonen T**, Pinto CA, **Lambrelli D**

Use of Real-World Evidence in Personalized Benefit-Risk Assessment (BRA): Closing the Knowledge Gap

Pinto CA, **Tervonen T, Marsh K, Lambrelli D, Schultze A**, Tershakovec A, Hyacinthe J, Prawitz T, Hammad T

Use of Real-World Evidence in Personalized Benefit-Risk Assessment: Detecting Treatment Patterns Using Gaussian Mixture Models

Tervonen T, Pinto CA, **Marsh K, Lambrelli D, Schultze A, Prawitz T**, Tershakovec A, Hammad T

POSTERS

Awareness Strategies, Referral Sources, and Impact on Enrollment in Pregnancy and Lactation Studies

Covington D, Hurst N, Moore T

Cardiovascular Outcomes and Mortality in Type 2 Diabetes with Associated Cardio-Renal-Metabolic Comorbidities in the UK

MacLachlan S, Hunt P, Chen H, Repetto E, Vora J

How Is Outcome Misclassification Addressed in Pharmacoepidemiology Database Studies?

Gini R, Lanes S, Mehta V, Zhou X, Ferreira G, **Reynolds MW**, Hall GC

Electronic Health Data in Pharmacoepidemiology: Guidance for Assessing Appropriateness and Feasibility

Rivera DR, Gokhale MN, **Reynolds MW**, Andrews EB, Chun D, Haynes K, Jonsson-Funk ML, Lynch KE, Lund JL, Strongman H, Raman SR

Overall Survival and Treatment Patterns among Real-World Patients with Metastatic Non-Small Cell Lung Cancer Not Previously Treated with Systemic Therapy for Advanced Cancer

Simeone JC, Nordstrom BL, Patel K, Klein AB

Overall Survival and Treatment Patterns among Real-World Patients with Metastatic Urothelial Carcinoma Treated with First-line Therapy

Simeone JC, Nordstrom BL, Patel K, Klein AB, Horne L

Treatment Guidelines: Adherence and Use among Type 2 Diabetes Mellitus Providers and Their Patients

Olsson K, Chitnis M, Huelin R

Trends in FDA Post-Marketing Commitment Requirements for Pregnancy Registries

Covington D, Bronwen M, **Buus R**

International Congress on Neuromuscular Diseases

July 6-10, 2018; Vienna, Austria

POSTER

Patient Perspectives on the Side Effect Burden of Treatments for Myasthenia Gravis (MG) and their Impact on Daily Life

Bacci ED, Coyne KS, Harris L, Poon JL, Boscoe AN

American Headache Society 60th Annual Scientific Meeting

June 28-July 1, 2018; San Francisco, CA, USA

POSTER

Psychometric Validation of the MSQ v2.1 ePRO for Use in Patients with Episodic and Chronic Migraine

Speck RM, Shalhoub H, Ayer DW, Ford J, Wyrwich KW, Bush EN

American Diabetes Association 78th Scientific Sessions

June 22-26, 2018; Orlando, FL, USA

POSTERS

Cost-Effectiveness Analysis of Empagliflozin Compared to Canagliflozin or Standard of Care (SoC) in Patients with T2DM and Established Cardiovascular (CV) Disease

Kansal A, Reifsnider O, Lee J, Fahrbach K, Gandhi P, Pfarr E, Ustyugova A

Evaluating Preferences for Profiles of Glucagon-like Peptide-1 Receptor Agonists Among Type 2 Diabetes Patients in the United States

Bacci E, Rentz AM, Brooks A, Polonsky W, Gray G, Yu-Isenberg K

2018 SMA Researcher Meeting

June 14-17, 2018; Dallas, TX, USA

POSTER

Development of the SMA Independence Scale (SMAIS), a Novel Assessment of the Amount of Assistance Required to Perform Daily Activities in Non-Ambulatory Individuals with Types 2 and 3 SMA

Trundell D, **Skalicky A, Cooper O**, Jethwa S, Seabrook T, **Hareendran A**

WOCN 50th Annual Conference 2018

June 3-6, 2018; Philadelphia, PA, USA

POSTER

Cost Effectiveness of a Ceramide Infused Skin Barrier among Medicare Patients in the United States Who Have Recently Undergone Ostomy Surgery

Berger A, Inglese G, Skountrianos G, Karlsmark T, **Oguz M**

ASCO 2018 Annual Meeting

June 1-5, 2018; Chicago, IL, USA

POSTER

Check X-Ray (CXR) Screening Improves Outcomes in Lung Cancer: Reanalysis of the Lung Cancer Component of the Prostate-Lung-Colorectal-Ovary (PLCO) Randomized Controlled Trial

Flores JP, Moreno-Koehler A, Finkelman M, **Caro JJ**, Strauss GM

HTAi 2018 Vancouver

June 1-5, 2018; Vancouver, Canada

ISSUE PANEL

The Use of Multi-Criteria Decision Analysis by HTA Agencies - From Concept to Action

Marsh K

ASCP 2018 Annual Meeting

May 29-June 1, 2018; Miami, FL, USA

POSTER

Elements of Desire Questionnaire Assessment of Bremelanotide Safety and Efficacy for Hypoactive Sexual Desire Disorder in the RECONNECT Study

Revicki D, Althof S, Derogatis L, Kingsberg S, Wilson H, Jordan R, Lucas J

The American Thoracic Society International Conference

May 18-23, 2018; San Diego, CA, USA

POSTERS

Concordance Between Health Care Utilization and Symptom-Defined Exacerbations in Patients with COPD: Results from the Acute Exacerbation and Respiratory InfectionS (AERIS) Study

Sung R, Collier S, Devaster J, **Leidy NK**, Ostridge K, Staples J, Locantore N. Wilkinson T, Tal-Singer R, Miller BE, AERIS Study Group

Incidence of Chronic Obstructive Pulmonary Disease Symptom-Defined Exacerbations: Exploratory Analysis from a Long-Term Open-Label Active-Controlled Safety Trial of Nebulized Glycopyrrolate/eFlow® CS

Kerwin EM, Ganapathy V, **Murray L**, Rajagopalan K

Respiratory Symptoms and Health Status in Patients with Chronic Obstructive Pulmonary Disease (COPD): Results from the Acute Exacerbation and Respiratory InfectionS (AERIS Study)

Sung R, Collier SD, Devaster J, **Leidy NK**, Ostridge K, Staples KJ, Locantore N, Wilkinson T, Tal-Singer R, Miller B, AERIS Study Group

What Symptomatic Patients with Asthma and Chronic Obstructive Pulmonary Disease (COPD) Find Important in Their Maintenance Inhaler Therapy: A Focus Group Study

Hanania N, **Hawken N**, Gilbert IA, Martinez FJ, Fox KM, **Ross MM, Duenas A, Kawata AK, Cooper O, Tervonen T**

Recent Publications

Antonini A, Stoessl AJ, ***Kleinman LS, Skalicky AM***, Marshall TS, Sail KR, Onuk K, Odin PLA. Developing Consensus among Movement Disorder Specialists on Clinical Indicators for Identification and Management of Advanced Parkinson's Disease: A Multi-Country Delphi-Panel Approach. *Curr Med Res Opin.* 2018 Jul 17:1-38. [Epub ahead of print]

Balk EM, Adam GP, Langberg VN, ***Earley A***, Clark P, Ebeling PR, Mithal A, Rizzoli R, Zerbini CAF, Pierroz DD, Dawson-Hughes B; International Osteoporosis Foundation Calcium Steering Committee. Global Dietary Calcium Intake among Adults: A Systematic Review. *Osteoporos Int.* 2017 Dec;28(12):3315-3324. doi: 10.1007/s00198-017-4230-x.

Basile J, Egan B, Punzi H, Ali S, ***Li Q***, Patel M, Neutel J. Risk of Hospitalization for Cardiovascular Events with β-Blockers in Hypertensive Patients: A Retrospective Cohort Study. *Cardiol Ther.* 2018 Sep 6. doi: 10.1007/s40119-018-0117-y. [Epub ahead of print]

Bell JA, Galaznik A, ***Huelin R, Stokes M, Guo Y***, Fram RJ, Faller DV. Effectiveness and Safety of Therapeutic Regimens for Elderly Patients with Acute Myeloid Leukemia: A Systematic Literature Review. *Clin Lymphoma Myeloma Leuk.* 2018 Jul;18(7): e303-e314. doi: 10.1016/j.clml.2018.05.003.

Bell JA, Galaznik A, ***Huelin R, Stokes M, Guo Y***, Fram RJ, Faller DV. Systematic Literature Review of Treatment Options and Clinical Outcomes for Patients with Higher-Risk Myelodysplastic Syndromes and Chronic Myelomonocytic Leukemia. *Clin Lymphoma Myeloma Leuk.* 2018 Apr;18(4): e157-e166. doi: 10.1016/j.clml.2018.02.001.

Bruyniks N, De Gregorio F, Gibbs T, Carroll R, ***Fraeman KH, Nordstrom BL***. Safety of Ospemifene during Real-Live Use. *J Gynecol Women's Health.* 2018 April; 9(3). doi: 10.19080/JGWH.2018.09.555762.

Chin KM, Gomberg-Maitland M, Channick RN, Cuttica MJ, Fischer A, Frantz RP, Hunsche E, ***Kleinman L***, McConnell JW, McLaughlin VV, Miller CE, Zamanian RT, Zastrow MS, Badesch DB. Psychometric Validation of the Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPACT®) Questionnaire: Results of the SYMPHONY Trial. *Chest.* 2018 Apr 26. pii: S0012-3692(18)30649-4. doi: 10.1016/j.chest.2018.04.027. [Epub ahead of print]

Cohen AT, Hill NR, Luo X, Masseria C, Abariga SA, Ashaye AO. A Systematic Review of Network Meta-Analyses among Patients with Nonvalvular Atrial Fibrillation: A Comparison of Efficacy and Safety Following Treatment with Direct Oral Anticoagulants. *Int J Cardiol.* 2018 Oct 15; 269:174-181.

Cox AP, Merinopoulou E. Data Sources for PASS: Social Media. In: Ali A, Hartzema A, eds. Post-Authorization Safety Studies of Medicinal Products. Cambridge, MA: Academic Press, 2018:92-103.

DeMeo DL, Ramagopalan S, Kavati A, Vegesna A, Han MK, Yadao A, ***Wilcox TK***, Make BJ, and the COPD Gene Investigators. Women Manifest More Severe COPD Symptoms Across the Life Course. *Int J Chron Obstruct Pulmon Dis.* [In Press]

Deniz B. Predicting Market Outlook: Enhancing Market Forecasting via Application of Pharmacoeconomic Modeling Techniques. *Value & Outcomes Spotlight.* 2018 Jul/Aug; 4(4):32-35.

Deniz B, Altincatal A, Ambavane A, Rao S, Doan J, Malcolm B, Michaelson MD, Yang S. Application of Dynamic Modeling for Survival Estimation in Advanced Renal Cell Carcinoma. *PLoS One.* 2018 Aug 30;13(8): e0203406. doi: 10.1371/journal.pone.0203406. eCollection 2018.

Desai U, Kirson NY, Kim J, Khunti K, King S, Trieschman E, Hellstern M, ***Hunt PR***, Mukherjee J. Time to Treatment Intensification After Monotherapy Failure and Its Association with Subsequent Glycemic Control among 93,515 Patients with Type 2 Diabetes. *Diabetes Care.* 2018 Oct;41(10):2096-2104. doi: 10.2337/dc17-0662.

Dewitt B, Feeny D, Fischhoff B, Cella D, Hays RD, Hess R, Pilkonis PA, ***Revicki DA***, Roberts MS, Tsevat J, Yu L, Hanmer J. Estimation of a Preference-Based Summary Score for the Patient-Reported Outcomes Measurement Information System: The PROMIS®-Preference (PROPr) Scoring System. *Med Decis Making.* 2018 Aug;38(6):683-698. doi: 10.1177/0272989X18776637.

Disanto G, Zecca C, ***MacLachlan S***, Sacco R, Handunnetthi L, Meier UC, ***Simpson A***, McDonald L, Rossi A, Benkert P, Kuhle J, Ramagopalan SV, Gobbi C. Prodromal Symptoms of Multiple Sclerosis in Primary Care. *Ann Neurol.* 2018 Jun;83(6):1162-1173. doi: 10.1002/ana.25247.

Dorman E, Perry B, Polis CB, Campo-Engelstein L, Shattuck D, Hamlin A, Aiken A, Trussell J, Sokal D. Modeling the Impact of Novel Male Contraceptive Methods on Reductions in Unintended Pregnancies in Nigeria, South Africa, and the United States. *Contraception.* 2018 Jan;97(1):62-69. doi: 10.1016/j.contraception.2017.08.015.

Faulkner E, Werner MJ, Slocomb T, Han D. Ensuring Patient Access to Regenerative and Advanced Therapies in Managed Care: How Do We Get There? Glen Allen, VA: ARM Monograph (*Journal of Managed Care Medicine*), 2018.

Feyerabend S, Saad F, Li T, Ito T, Diels J, Van Sanden S, De Porre P, ***Roiz J, Abogunrin S, Koufopoulou M***, Fizazi K. Survival Benefit, Disease Progression and QoL Outcomes of Abiraterone Acetate Plus Prednisone vs Docetaxel in Metastatic Hormone-Sensitive Prostate Cancer: A Network Meta-Analysis. *Eur J Cancer.* 2018 Sep 12; 103:78-87. doi: 10.1016/j.ejca.2018.08.010.

Finkelstein FO, van Nooten F, Wiklund I, Trundell D, Cella D. Measurement Properties of the Short Form-36 and the Functional Assessment of Cancer Therapy - Anemia (FACT-An) in Patients w/ Anemia Associated w/ Chronic Kidney Disease. *Health Qual Life Outcomes.* 2018 May 31;16(1):111. doi: 10.1186/s12955-018-0933-8.

Galaznik A, ***Huelin R, Stokes M, Guo Y, Hoog M***, Bhagnani T, Bell J, Shou Y. Systematic Review of Therapy Used in Relapsed or Refractory Diffuse Large B-Cell Lymphoma and Follicular Lymphoma. *Future Sci OA.* 2018 Jul 19;4(7): FSO322. doi: 10.4155/fsoa-2018-0049. eCollection 2018 Jul.

Gelhorn HL, Anand SB, Parvizi J, Morrison T, Yu H, ***Pokrzywinski R***, Al-Jassar G, Chen AF. Qualitative Interviews to Identify Burden of Illness, Impacts and Costs Associated with Surgical Site Infections. *J Comp Eff Res.* 2018 Apr;7(4):357-367. doi: 10.2217/cer-2017-0075.

Gelhorn HL, Eremenco S, ***Skalicky AM, Balantac Z***, Cimms T, Halling K, Sexton C. Content Validity and ePRO Usability of the BPI-sf and "Worst Pain" Item with Pleural and Peritoneal Mesothelioma. *J Patient Rep Outcomes.* 2018;2(1):16. doi: 10.1186/s41687-018-0039-4.

Gelhorn HL, Skalicky AM, Balantac Z, Eremenco S, Cimms T, Halling K, Hollen PJ, Gralla RJ, Mahoney MC, Sexton C. Content Validity and Electronic PRO (ePRO) Usability of the Lung Cancer Symptom Scale-Mesothelioma (LCSS-Meso) in Mesothelioma Patients. *Support Care Cancer.* 2018 Jul;26(7):2229-2238. doi: 10.1007/s00520-018-4061-0.

Ghabri S, Stevenson M, ***Möller J, Caro JJ***. Trusting the Results of Model-Based Economic Analyses: Is there a Pragmatic Validation Solution? *Pharmacoeconomics.* 2018 Sep 6. doi: 10.1007/s40273-018-0711-9. [Epub ahead of print]

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PPD, Evidera join NEWDIGS Initiative at MIT as a Strategic Partner

Pharmaceutical Product Development, LLC (PPD), and its real-world research and market access business unit, Evidera, have joined the Massachusetts Institute of Technology Center for Biomedical Innovation's New Drug Development Paradigms (NEWDIGS) initiative as a strategic partner.

PPD is the first contract research organization to join NEWDIGS, expanding the group's already large and diverse list of global collaborators, which includes biopharmaceutical manufacturers, care providers, regulators, payers, health authorities, health technology assessment bodies, patient advocacy groups, and other health care stakeholders. NEWDIGS provides its members an environment, programs, and practices for open, non-competitive collaboration so they can develop solutions for systemwide impediments to biomedical innovation and patient care.

Initially, Evidera is participating in the new Learning Ecosystems Accelerator for Patient-Centered, Sustainable Innovation (LEAPS) project, to help design and pilot an ecosystem for purpose-driven evidence generation and integration focused on a critical disease area (including both real-world evidence and data from randomized controlled trials). The project aims to create sustainable, commercially viable and scalable tools – including platform trial infrastructure and its extension into community health care settings – to drive more value faster to patients in ways that work for all stakeholders in health care development and delivery.

"We are pleased to welcome PPD and Evidera to the NEWDIGS community of health care innovators," said Gigi Hirsch, M.D., executive director of NEWDIGS. "In collaboration with the diverse stakeholders already involved, their expertise and capabilities will be important in advancing the design, piloting, and scaling of components of the LEAPS innovation ecosystem."

LEAPS work areas will evolve over time, but may include:

- Enhancing evidence planning and production across the drug development life span to fuel sustainable patient-centered innovation
- Applying systems engineering methods and tools to enable seamless, continuous learning and improvement across the innovation value chain (from R&D to care delivery) for a target disease
- Exploring potential applications of transformative technologies and methods, such as blockchain and artificial intelligence/machine learning

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For more information on these efforts, please reach out to info@evidera.com.

HRA Scientific Team Joins Evidera, Further Expanding the Largest and Most Comprehensive Patient-Centered Research Team in the Industry

Evidera welcomes the Health Research Associates (HRA) scientific team as they join our Patient-Centered Research (PCR) team in a staged transition which began on July 1st and will continue through the end of 2018. HRA scientific leaders Mona Martin and Don Bushnell, along with their team of five other patient-reported outcomes (PRO) research experts with a combined 120 years of experience, join Evidera's San Francisco and Seattle offices.

The addition of the significant qualitative and quantitative methodological and regulatory expertise of the HRA team complements and extends the Evidera PCR team, which is already among the largest, most comprehensive, and most experienced groups of dedicated patient-centered researchers in the world. Working with the Critical Path Institute PRO Consortium, the HRA team led the development of the third and fourth patient-reported outcome (PRO) instruments to receive a qualification statement from the U.S. Food and Drug Administration (FDA). Evidera developed the first and second instruments to ever receive an FDA qualification statement, making the now combined team the only organization to successfully take new instruments through the FDA PRO qualification process.

"The addition of Mona, Don, and their team is extremely exciting for us," said Margaret Vernon, PhD, Vice President and General Manager of Evidera's Patient-Centered Research team. "They share our scientific values and vision, and in joining us they further extend our ability to provide high quality and high impact solutions to our client partners."

HRA was formed 23 years ago by Mona and Don to provide patient-reported outcomes, qualitative research, cross-cultural translation, and other study management and consultation services to global biopharma organizations. Over the past two decades HRA's team of scientists and researchers have published 100+ peer-reviewed articles and given 130+ research presentations on instrument development, instrument validation, cross-cultural studies, qualitative research, and mix methods studies.

"I'm very pleased to be joining Evidera and to have a role in expanding our collective capabilities," said Mona Martin, Senior Research Leader at Evidera. "The expertise and experience of the expanded Evidera team, and the access to a full suite of drug development research solutions as part of PPD will undoubtedly allow us to push the limits of patient-centered research and accelerate our efforts in PRO/COA development. We all look forward to working together to meet the research challenges of the future and to offer our clients a full range of high quality services."

Donald Bushnell, MA

Senior Research Scientist, Patient-Centered Research

Mr. Bushnell has over 20 years of experience in global clinical and health outcomes research, specializing in instrument development and validation. He has recently supported scientific work on symptom measures of depression (Symptoms of Major Depressive Disorder Scale, SMDDS) and non-small cell lung cancer (Non-Small Cell Lung Cancer-Symptoms Assessment Questionnaire, NSCLC-SAQ); both having been qualified by the FDA's Center for Drug Evaluation and Research. He has been on the development team and provided psychometric validation for well-known measures such as the Psoriasis Symptom Inventory (PSI), Incontinence-specific Quality of Life (I-QOL), the World Health Organization Quality of Life (WHOQOL), the Parkinson's Disease Questionnaire (PDQ), the Irritable Bowel Syndrome Quality of Life (IBS-QOL), the Obesity and Weight Loss QOL Measure (OWLQOL), and Migraine Treatment Satisfaction measure (MTS). Mr. Bushnell has designed and supported the data management and analysis for a variety of large international studies including the Longitudinal Investigation of Depression Outcomes (LIDO). He has also conducted extensive research in electronic data capture (EDC) and equivalence on numerous different platforms. Mr. Bushnell received his Masters of Arts degree from the University of Washington (UW). He served as the data manager and analyst for the CDC-funded Northwest Prevention Effectiveness Center at the UW from 1986 until 1995 before becoming the director of data management and analysis at Health Research Associates, Inc. He has authored and co-authored numerous quality of life publications and has both supported and presented a wide range of research findings. He is a member of the International Society for Quality of Life Research, the International Society for Pharmacoeconomic Outcomes Research as well as a peer reviewer for the journals *Quality of Life Research, Journal of Clinical Epidemiology,* and *PharmacoEconomics.*

Mona Martin, MPA

Senior Research Leader, Patient-Centered Research

Ms. Martin has more than 42 years of experience in outcomes research, instrument development, and cross-cultural applications. She has been a part of the development teams for a variety of published quality of life measures, including the Incontinence-specific Quality of Life (I-QOL), the Irritable Bowel Syndrome Quality of Life (IBS-QOL), the Obesity and Weight Loss QOL Measure (OWLQOL), and the World Health Organization Quality of Life (WHOQOL). Her work includes a variety of clinical outcome assessments (COAs) now approved as endpoints by the FDA, including the Psoriasis Symptom Inventory (PSI) and the two recently qualified instruments with the C-Path PRO Consortium, the Symptoms of Major Depressive Disorder Scale (SMDDS) and the Non-Small Cell Lung Cancer-Symptoms Assessment Questionnaire (NSCLC-SAQ) She has helped to develop measures and explore research questions across numerous therapeutic areas including several rare diseases and those with compromised communication skills. Prior to joining Evidera, Mona was one of the founding partners and Executive Director of Health Research Associates, Inc. She earned her nursing degree and her MPA from the University of Kentucky and launched her research career at the University of Washington in 1986, spending the following nine years in research methodology and instrument development for CDC-funded health promotion programs. Ms. Martin is a long-standing member of the International Society for Quality of Life Research (ISOQOL), and past co-chair of the ISOQOL Translation and Cultural Adaptation (TCA)-SIG. As a member of International Society for Pharmacoeconomics and Outcomes Research (ISPOR), she participated in the ISPOR task force on content validity which published two key consensus papers. She has more than 80 published manuscripts in the area of patient-centered research and is a reviewer for several professional journals.

Welcome to Evidera's New President

Karen Kaucic, MD

Dr. Kaucic joined Evidera on September 1, bringing an exceptionally diverse and strong knowledge of the health care industry to her role as president. In her current position, she oversees Evidera's global team, providing strategic direction for the organization in this rapidly changing health care environment. Before joining Evidera, Dr. Kaucic was senior vice president and global head of Early Development for PPD, overseeing PPD's clinical pharmacology units, early development site network, and early development-focused operations staff. Prior to that, Dr. Kaucic served as vice president and global head of PPD® Consulting, leading regulatory and product development consulting across all major therapeutic areas and provided strategic direction for consulting in key practice areas such as biosimilars, adaptive trial design, rare diseases, and pediatrics. Before joining PPD in 2009, Dr. Kaucic was senior director in oncology clinical development at MedImmune/AstraZeneca. There, she led product development teams for several biologics compounds, including monoclonal antibodies, bispecific antibodies, and antibody conjugates. Earlier in her career, she was a staff pediatric oncologist and senior investigator at Children's National Medical Center in Washington, D.C., where she established the institution's first hematopoietic stem cell transplantation laboratory, served as an attending physician in oncology, and conducted NIH-funded research in signal transduction in human neuroectodermal tumors. Dr. Kaucic received her medical degree from The Ohio State University followed by a pediatric residency at the same institution. She completed fellowships in pediatric hematology/oncology and transfusion medicine at Children's National Medical Center and The Cleveland Clinic, respectively. She holds an active license to practice medicine in the District of Columbia.

Evidera Welcomes New Senior Staff

Chakrapani Balijepalli, PhD, MPH

Research Scientist, Meta Research

Dr. Balijepalli has extensive experience in evidence synthesis, especially in conducting systematic literature reviews and meta analyses, particularly, network meta analyses. Prior to joining Evidera, Dr. Balijepalli worked at Precision Health Economics and Precision Xtract as an associate director. He has years of experience conducting and leading systematic literature reviews and network meta analyses in a wide range of therapeutic areas, including diabetes, oncology, cardiovascular disease, asthma, psychiatric illnesses, and rare diseases. His works related to evidence synthesis and clinical epidemiology have been published in *Diabetes Obesity and Metabolism, Diabetes Therapy, Schizophrenia Research, Journal of American Geriatric Society, Cardiovascular and Interventional Radiology, Clinical Epidemiology, Cardiovascular Diabetology, European Archives of Psychiatry and Clinical Neuroscience,* and *Hypertension Research.* His research activities have also contributed to successful submissions to various HTA bodies including NICE, IQWiG, and SMC. Dr. Balijepalli has also led evidence synthesis projects that were a part of successful submissions to the FDA. Dr. Balijepalli is a trained clinical epidemiologist. He worked as a clinical epidemiologist in several internationally recognized epidemiological studies, such as the German National Cohort study and the Heinz Nixdorf Recall Study. He received his PhD in epidemiology from the University of Duisburg-Essen in Germany. He also holds a master of public health, majoring in epidemiology, from Hamburg University of Applied Sciences in Germany, and a bachelor's degree in medicine from NTR University of Health Sciences in India.

Mel Formica, PhD, MBA

General Manager, Market Access Consulting

Dr. Formica is an accomplished health care executive with 20 years of experience spanning clinical research, marketing, strategic consulting and value, and evidence generation with successful global product launches. He is primarily focused at the forefront of functional developments in integrated care solutions, market access, pricing, evidence generation, and policy. Most recently, Dr. Formica was vice president and head of global market access at Takeda, responsible for directing and creating a global market access, health economics, payer solutions, and evidence demonstration and pricing function responsible for developing, coordinating, and driving all market access and payer value generation strategies for the organization. He championed new business and customer engagement models and value-added collaborative partnerships. Prior to joining Takeda, Dr. Formica held varying market access and corporate affairs related roles of increasing responsibility at Amgen in both the U.S. and Europe. Additionally, Dr. Formica worked as a management consultant as well as holding diverse industry roles in marketing and commercial development and held academic and research appointments at the College of Physicians and Surgeons of Columbia University, New York, and St. Luke's-Roosevelt Hospital Centre and Helen Hayes Hospital, New York. Dr. Formica completed his PhD in medicine at the University of Melbourne, Australia, and his post-doctoral training in the department of medicine at Columbia University, New York. Dr. Formica also holds an Executive MBA from the Lubin School of Business, New York. His research interests include osteoporosis and metabolic bone diseases, health economics and technology assessments, and health policy analysis.

Brenda Garrison

Senior Director, Project Management, Peri- and Post-Approval Research Operations

Brenda Garrison is a Senior Director of Global Project Management and the Global Head of Hematology/Oncology for phase IIIb and phase IV interventional studies on Evidera's Peri- and Post-Approval Studies team. Ms. Garrison leads, mentors, and coaches project teams, focusing on proactive and strategic risk management to ensure that studies are delivered on time, with quality, and within budget. Her leadership style encourages teams to be empowered, creative, and challenge the status quo. Ms. Garrison partners with business development to establish new, creative business models that will set Evidera apart from the competition, and has a proven track record of developing and expanding client relationships, as well as identifying new opportunities and securing business that broadens the client base and increases revenue targets. Prior to rejoining PPD in its Evidera business unit in 2018, Ms. Garrison spent three years at ICON overseeing multiple late phase portfolios for key partnerships and over two and half years at ICON representing research services (study start-up, monitoring, and clinical operations) at bid defenses for phase II-IV interventional/non-interventional, consumer health, epidemiology, and medical device/diagnostics opportunities across all therapeutic areas. She also partnered with executive leadership on acquisition integrations and modeling and implementation of business development, operations, and financial business plans for research services. Ms. Garrison brings over 25 years of experience across multiple business units and has extensive therapeutic knowledge in oncology, hematology, rare diseases, infectious diseases, and vaccines, in both adult and pediatric populations. She has a wide range of project management experience including managing complex research hematology/oncology programs for more than 16 years at PPD, and has extensive alliance partner, key account, and business development experience spanning both biotech and pharma companies. Her strategic experience and demonstrated ability to engage, communicate, collaborate, and mitigate risks ensures a strong partner relationship with internal and external stakeholders. Ms. Garrison has a bachelor's degree in business administration from the University of Mount Olive and a professional certificate in international business from UCD Michael Smurfit Graduate Business School in Dublin, Ireland. Ms. Garrison is based in Wilmington, North Carolina.

Phil Leventhal, PhD

Principal Medical Writer, Medical Writing and Healthcare Communications

Dr. Leventhal has a total of 15 years of experience in medical writing and 5 years of experience in pharmaceutical research. He is responsible for managing, writing, and providing input, oversight, and senior review of medical writing projects. Additionally, he provides training and mentorship for other writers and participates in developing and improving department processes and standards. Prior to joining Evidera, Dr. Leventhal was employed by 4Clinics as a scientific writer where he was a lead writer for publications and a variety of other medical communications and clinical documents. His clinical areas included vaccines, immunotherapies, oncology, dermatology, rheumatology, epidemiology, circulation, cardiology, and infectious diseases. He also provided expert advice to clients on publication project management, application of publication guidelines (e.g., GPP, ICMJE, CONSORT), journal selection, responses to reviewer comments, and communication with editorial offices; assisted in business development and contract preparation; and, helped recruit and mentor new writers. Dr. Leventhal is the Editor-in-Chief of *Medical Writing*, the journal of the European Medical Writers Association and is a member of the association's Executive Committee. He also is an experienced trainer and teacher in the areas of publications and technical writing. Dr. Leventhal's educational background includes a BS in chemistry and a PhD in biomolecular chemistry from the University of Wisconsin-Madison. He also performed postdoctoral studies in the department of neurology at the University of Michigan and in the anatomy and cell biology department of the State University of New York Health Science Center in Syracuse.

Shefali Shah, MBA

Principal, Market Access Consulting

Ms. Shah brings over 15 years of pharmaceutical / biotech and consulting experience to Evidera and is responsible for guiding projects and developing strategic recommendations for clients. She fully understands the "evidence of value" challenges that clients face and the best way to effectively use the wide array of expertise within Evidera to provide needed solutions. Ms. Shah has helped clients grow businesses by building innovative approaches, focused insights, and trusted relationships. She has delivered strategies for early market assets, as well as pre-launch and launch products across specialty and chronic diseases in neurosciences and a range of genetic disorders, and she has developed successful pricing, access, reimbursement, contracting, and launch strategies / programs for her clients.

Most recently, Ms. Shah was director, market access effectiveness at Novo Nordisk where she built a team focused on connecting structured and unstructured data to develop differentiated insights and drive action. She has been an integral part of developing brand positioning and market potential of early assets based on their clinical strength and market's willingness to pay. For assets in pre-launch phase, Ms. Shah led the research and analysis to inform evidence generation plans, pricing and access strategies, value strategy, and patient support strategies. For products in market, she ensured value was captured for the brands through superior execution. Ms. Shah led teams and projects that connected the medical, market access, brand, and sales teams at Novo Nordisk to develop differentiated value strategy, communication, and execution. During her career, she has also held senior positions at inVentive Health and Wyeth Consumer Healthcare. Ms. Shah received her MBA at the NYU Stern School of Business and her BS in electrical engineering from Columbia University.

Jonathan Tosh, PhD
Research Scientist, Modeling and Simulation

Dr. Tosh is a principal investigator for health economics projects and brings over 10 years of experience to Evidera, spanning health economics, health technology assessment, cost-effectiveness modeling, simulation, clinical trials, research design, and health-related quality of life. He previously worked for a global HEOR consultancy where he developed health economic models to support global market access. Before this, he spent eight years working as an academic health economist at the University of Sheffield, with a role spanning methodological research, teaching, and supporting NICE as a member of the Sheffield Evidence Review Group and NICE Decision Support Unit. Dr. Tosh has co-authored over 20 peer-reviewed publications and is an active member of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) including as a short course instructor, and a past member of the Constrained Optimization Task Force. His experience covers a wide range of therapeutic areas including immunology, oncology, hepatology, neurology, mental health, cardiovascular disease, and ultra-orphan conditions. He is an editorial board member for *PharmacoEconomics - Open*. Dr. Tosh was awarded his PhD in health economics from the University of Sheffield in 2015, which was funded by the National Institute for Health Research. He also has an MSc in health economics from the London School of Economics and a BA(Hons) in economics from the University of Leicester.

Evidera Acknowledges Excellence with Senior Staff Promotions

David January, PhD, Associate Scientific Director, Market Access Communications

Marissa Betts, MS, Research Scientist, Meta Research

Henri Folse, PhD, Research Scientist, Modeling and Simulation

Elizabeth Froom, PharmD, Director, Medical Writing and Healthcare Communications

Heather Gelhorn, PhD, Senior Research Leader, Patient-Centered Research

Rachel Huelin, BA, Executive Director and General Manager, Meta Research

Amber Martin, BS, Research Scientist, Meta Research

Katri Niemi, PhD, Associate Director, Market Access Communications

Helen Scrutton, MA, Managing Consultant, Market Access Consulting

Purvi Suthar, PharmD, Director, Medical Writing and Healthcare Communications

Karen Yeomans, BSc, Research Scientist and Senior Director, Real-World Evidence

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The Evidence Forum is an official publication of Evidera, addressing the scientific and strategic challenges of today's health care environment and providing a forum for the exchange of thoughts and ideas focused on evidence and value.

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