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Avoid Last Minute Rush—Planning Ahead for Successful Global Market Access

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In today's healthcare environment, there is increasing pressure to demonstrate evidence of product value, whether in terms of cost, effectiveness, or both. Both public and private healthcare payers increasingly require evidence of effectiveness to cover or reimburse for the use of drugs and medical devices. Even drugs and devices that have regulatory approval and coverage in certain indications face restrictions for indications in which evidence is not deemed sufficiently robust. To meet this increasing demand, it is crucial to begin planning an evidence strategy early to maximize the chance of success for global market access. This article will focus on three things: 1) why it is important to plan early, 2) what should be considered in this planning, and 3) how to approach the planning process.

Each organization certainly has its own definition of market access planning, but for the sake of this article, it is considered a component of the overall commercial plan for a product, including regulatory strategy, clinical development planning, and communication strategy addressed from a global perspective and not focused on local or national level activities.

SETTING THE STAGE—A CASE STUDY EXAMPLE

Challenge

Evidera was approached by a client with a compound in late Phase 2 clinical development; there was, however, no clear picture of where the product would fit in the market or what type of support was needed for market access.

Approach

The client provided Evidera with a number of materials including clinical results from Phase 2, the target product profile, and key opinion leader research. We conducted supplemental targeted

research, including looking at current and future competitors, reviewing health technology assessments for insights on evidence requirements and reviewing the clinical guidelines to look at positioning of existing products.

Results

An assessment was made of the product's potential contribution in satisfying some of the unmet need in the disease area. A document was developed outlining additional activities needed (e.g., literature review, payer research) and associated timelines. Using this document, the company could then create project priorities with transparent rationale for their internal colleagues and commission the needed work confident in the knowledge that these pieces of work fit together sensibly and coherently in a broader strategy for market access for the product.

Lessons learned

1. Thinking and planning ahead led to understanding the context of the product in the marketplace and the evidence gaps where additional activities were needed.
2. There is value in looking at all the evidence needs at one time in order to prioritize next steps wisely and avoid moving forward with near-term activities without considering the full breadth of activities needed to build the strongest evidence value story.
3. Bringing together a diverse group of colleagues with varying roles and views across the company strengthens the team's understanding that access activities are integral to the clinical development and overall commercial strategies.

WHY PLAN EARLY?

Everyone is always told to plan ahead, but what if that does not happen? Can we get away from doing only part of the planning? And how early does that really have to begin? Often in early phases of product development, budgets and people resources are limited; allocating time and energy too early is questioned when budget allocation for projects has a low probability for approval. Or the early phase product planning is under the responsibility of another department, so engagement around market access issues is delayed until the product responsibility is transferred.

We would challenge, however, that expectations of all facets of decision makers should be taken into consideration early in the product development cycle. However, internal stakeholders may have conflicting goals. Ideally, companies want to get a product label that is as broad as possible, so clinical trials and dossiers for regulatory bodies are designed to that end. Payer and reimbursement authorities, however, are asking more pointed questions.

- Who is the target audience for this product?
- Where does this product fit in the marketplace along with generics, biosimilars, etc.?
- Are there sub-populations where the product is the optimal treatment option?

Payers may prefer offering favourable reimbursement for a product that brings innovation to a small subset of patients rather than to a product that provides no additional innovation in the total disease population. There is a growing desire to provide products to niche patient groups or settings in which they are most effective. For example, a major aspiration of the U.S. comparative effectiveness research (CER) effort is to determine "what works for whom under which circumstances?" Manufacturers must consider identifying a target population (ideally, one with high unmet need) in their evidence generation planning to support the value story, without overly restricting their product. Each stakeholder has their preference in this area. For example, the U.S.

EXPECTATIONS OF ALL FACETS OF DECISION MAKERS SHOULD BE TAKEN INTO CONSIDERATION EARLY IN THE PRODUCT DEVELOPMENT CYCLE. HOWEVER, INTERNAL STAKEHOLDERS MAY HAVE CONFLICTING GOALS.

Food and Drug Administration (FDA) wants robust results without post hoc analyses, such as covariate adjustment, sub-setting, or reduced data sets, while payers may be more amenable to either post hoc or evidence development from observational studies to understand the target population. Payers have the ability to restrict usage, so they may decide on the treatment line in which the product can be used. Lastly, there is increasing importance on providing long-term or real-world data to confirm what was observed in clinical trials. The inclusion and timing of these study types must be assessed internally based on decision maker requirements and specific characteristics of the product (e.g., if the features of the product support better adherence, this is something that will need to be studied in a real-world setting).

Consequences exist when some of these issues are not considered early in the development process. Payers may reject or restrict products if the evidence requirements are not fulfilled and submissions do not contain the appropriate data, such as weak comparative clinical data, inappropriate comparators in clinical trials or health

economic modeling, or lack of agreement of economic modeling methodology or model results. As a result, products may be restricted to a specific subgroup of patients instead of the broader use the company would like. Additionally, risk-sharing schemes or value-based pricing may be required to gain access for high-cost products, where manufacturers pay for patients who fail to respond to treatment and payers only pay for those who positively respond to treatment. As an illustration of these consequences, the National Institute for Health and Care Excellence (NICE) performed 207 appraisals over a 10-year period with 409 recommendations for action.[1] Of these, NICE rejected 46 products due to lack of data—three of which are highlighted below.

- An adjuvant treatment of gastrointestinal stromal tumours—The evidence base was too undeveloped to draw conclusions about key aspects of clinical effectiveness. Two years later, newer data were available and NICE indicated they were willing to re-evaluate the evidence, but there was a two year gap because the evidence was not available for the initial submission and review.
- A treatment for metastatic colorectal cancer—The economic evidence was considered weak because disutility due to adverse events was not included; unit cost estimates for the comparator were unclear; and costs of patient access scheme were underestimated. Additional information was provided two years later that resulted in the treatment now being used as second-line treatment, but again, there was a two year delay because of insufficient evidence in the original submission.
- A treatment for locally advanced or metastatic breast cancer as a follow-on product after an aromatase inhibitor—The evidence presented was not aligned with the scope of the submission—the benefit of the drug was only for patients whose last therapy was an anti-oestrogen and not for patients whose last therapy was an aromatase inhibitor. The therapy was not recommended as an alternative to aromatase inhibitors and is still listed as a non-preferred product on NICE's website.

WHAT SHOULD BE CONSIDERED?

In planning your evidence strategy, there are several things to consider. First, what can be used for regulatory approval and what is needed for reimbursement authorities? When presenting to a regulatory authority, the main consideration is a benefit/risk assessment, i.e., is the product safe and is it effective in a controlled environment? Conversely, when communicating with a reimbursement audience, the focus should be on the relative efficacy or the relative effectiveness, i.e., compared to the treatment options that are available in the marketplace, what is the additional benefit of this new medicine?

Next to consider is internal and external validation of the evidence.

- Internal validity is the focus of a regulatory submission, so a well-controlled clinical trial where you can control all the meaningful factors and utilize randomization as a component.
- External validity focuses on real-world effectiveness and the impact on the healthcare system.

The type of data follows from this, moving from the clinical trial to observational data and modeling. Preferred endpoints for a regulatory submission focus on surrogates and hard endpoints, whereas a reimbursement authority is looking not only at the target endpoint, but also for quality of life and patient-reported outcomes.

Lastly, evidence requirements vary greatly from country to country, where some countries only require clinical data (either efficacy or effectiveness data) and others request both clinical and cost-effectiveness data. Additionally, there are implicit and explicit costs-per-quality-adjusted life year (QALY) thresholds for individual countries, and, in some circumstances, those vary depending on the class of medicine. This last point shows that once regulatory approval is received, it is important to think about the priority countries and what the evidence requirements are for those given countries.

NOW WHAT? HOW TO APPROACH THE PLANNING PROCESS

In planning a study strategy, it is important to think of this as a series of investment questions and decisions.

1. *If investment is made earlier in the process, will it change the uptake and the revenue that is generated for the molecule?*

Investment begins in research and then continues at varying levels along every stage of the process, including development, registration and commercialization. Early on, the investment is relatively low, but that investment expands at the point of registration. At this point, there are many considerations, including thought leader endorsement, formulary positioning, clinical guidelines, treatment pathways, etc., but the major three considerations are filing the first registration, targeting the first launch, and developing the dossiers for pricing and reimbursement authorities.

Typically the thinking is that the Phase 3 clinical trial program has a three to five year timeframe until the data are reported out and available. In some instances, the additional evidence, beyond the clinical trial results, such as an economic model, is not commissioned

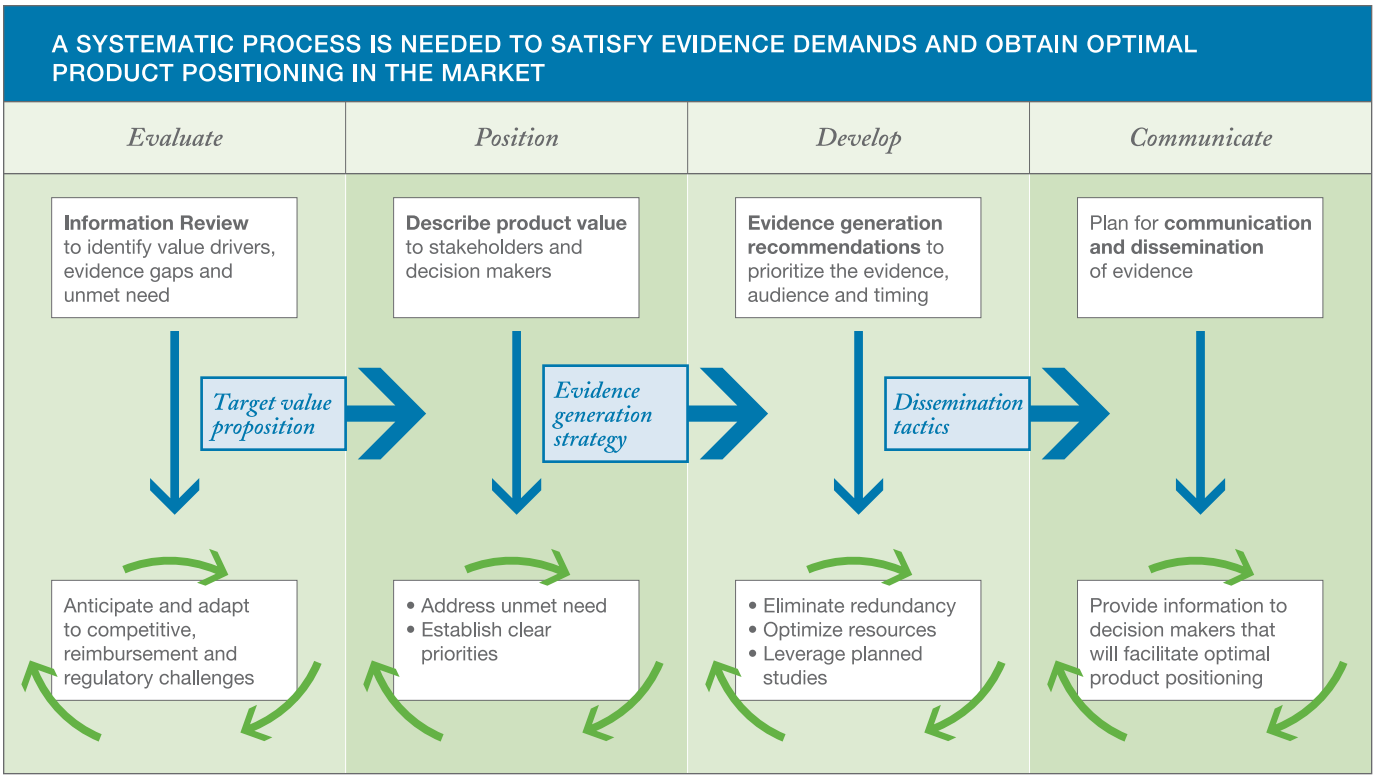

figure 1

until Phase 3 is nearly complete. But in reality, the economic modeling should begin concurrent to Phase 3, utilizing the Phase 2 results to inform product pricing through estimation of the product cost-effectiveness ratio. This allows the organization to consider possible strategies to optimize market access. This might be through evidence generation to better document the economic impact or to re-evaluate the target population.

The end goal for any product planning is to grow revenue, so by planning and investing earlier in the process, revenue and uptake should come sooner and the market share would be larger than would be expected if that parallel planning did not occur. Referring to one of the previous NICE examples, there was a two-year window that may have been significantly shortened had there been earlier thought for those particular products.

2. *Who needs to be involved in strategy discussions? What are the key activities that need to be planned and how are they aligned with the current decision-making process?*

Internal decisions can occur early, typically around Proof of Concept (PoC) and further in development, at entry into the Phase 3 program; at each of these time points the strategy is updated as commitment to launch the new product is reviewed. This is the time that market access and reimbursement strategy should also be considered. For example, at the same time that external clinical experts are being included in the process, advice should be sought from payers and payer representatives on the gaps that exist in the evidence and how to plan activities to meet their needs. Aligning your value development strategy with internal stakeholders, such as commercial, medical affairs, market access, etc., at key decision points and activities is essential to ensure appropriate planning and strategy across all areas of the company.

Beyond the global strategy, the process also needs to be considered at the study level. One might consider the following:

- When designing Phase 3 trials, are the right comparators available and being used?
- Are endpoints being considered which are needed to populate an economic model or begin to link to the real-world or clinical practice data?
- If there is a particular lab value being looked at in the study as a surrogate efficacy endpoint, what is known about that lab value in clinical practice, and can changes in that parameter be linked to the economic impact for the patient?

3. How is the plan executed within the organization?

A systematic process is needed to satisfy evidence demands and obtain optimal product positioning in the market. As previously mentioned, each company approaches this differently, so the first step is assessing a company's current process to see where adjustments may need to be made for optimal evidence generation and planning.

In developing a full evidence development plan, or value demonstration strategy the first step is to do a complete information review to identify where evidence gaps exist and where there are opportunities for the product to address unmet need. This helps to establish the value proposition for the product. Once this is known, an evidence generation strategy can be developed that specifies what evidence is crucial to support the product and what approaches or studies are needed to develop the value story for all stakeholders in a coherent and cost-efficient manner. Lastly, the right communication plan must be established to disseminate the evidence in the right way to each stakeholder *(see Figure 1)*.

Evidera has collaborated with clients where the timing of the preparation of value demonstration strategy (VDS) was not ideal. In a number of circumstances, this resulted in siloed activities, duplicity in effort, and inefficient use of company resources. The following case describes an effective, early approach to creating a VDS.

SUCCESSFUL CASE STUDY

Challenge

A large global pharmaceutical company had a new compound in Phase 2 with a novel mode of action and expected to be first in a new class of drugs. The treatment would offer significant benefits to patients and providers, but would face considerable challenges from payers and health technology assessment (HTA) agencies. The client needed a health economics and outcomes research (HEOR) strategy to meet payer and HTA agency evidence needs once Phase 2 data was available.

Approach

The process described above was used to outline the needs. A targeted literature review was conducted to specifically look at health technology assessments (HTAs) that had been done in the disease area and identify evidence gaps. Those gaps were then prioritized in light of the compound's target product profile based on Phase 2a results.

Results

A priority list of projects was identified, along with costs and proposed timelines, to generate and communicate the evidence required for payers and HTA agencies in Europe. Simultaneously, the company sought advice from an HTA agency and was then able to compare our recommendations against those of the HTA agency, which were found to be in alignment. This gave the company confidence in the health economics and outcomes research (HEOR) strategy proposed and they were able to move forward with the planning with the knowledge that the strategy was aligned with the overall commercial strategy and would also address likely questions and challenges that payers and HTA agencies would pose at the time of launch. Local affiliate companies were also able to align with the company's R&D division's approach, capturing efficiencies across Europe in the preparation for launch.

With continually growing requirements from different decision makers, the need for credible evidence and strong value stories geared towards the right audiences at the right time also grows. Add that to the challenge of constrained company budgets and it becomes clear that the strategy needs to be developed as early as possible to ensure the right evidence is generated in the most cost-effective manner. While companies are still hesitant at times to make large investments in new treatments early in the development stage, there is increasing awareness that early investment can be more cost-effective in the long run. Yes, things have changed over the years, and if this evolution toward more rigorous evidence requirements is ignored, there can be consequences—consequences which impact the trajectory of product uptake and the size of the peak revenue.

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Avoiding the Fast Track Disconnect

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SHORTENING TIME TO MARKET FOR IMPORTANT NEW THERAPIES

Few people will disagree that striving to make effective new drugs in high unmet need indications reach the patient as soon as possible is a worthy aim. Many countries allow "early access" to drugs before approval, but administrative burden and additional costs that go with the strict follow-up of named patients constitute a serious hurdle for broad access. Therefore there was broad support when the U.S. Food and Drug Administration (FDA) introduced procedures such as "fast track," "accelerated approval," "breakthrough therapy," and "priority review." The European Medicines Agency (EMA), on the other side of the ocean, initiated "accelerated assessment" and "conditional approval" *(see Table 1).* Some of these procedures skim only a few months from the assessment time, however, all stakeholders are more interested by the gains that can be made when products are approved substantially faster. Adopting an accelerated approval approach in oncology, for example, in which drugs were evaluated based on surrogate endpoints, resulted in launches about four years sooner to the market than they would have been with regular approval.[1]

BENEFITS OF FASTER APPROVAL

Of course, the first thoughts go to the patient in need who may have access to valuable treatment options before it is too late. However, the corollary is that yet unknown safety aspects or failure to confirm efficacy in later studies may expose the patient to a harmful risk/benefit ratio. An illustrative example includes a leukemia drug that achieved fast approval by both the FDA and EMA, but within a year it was taken off the U.S. market and faced strong restrictions by the EMA. Moreover, there is more and more criticism about companies not fulfilling the obligations for further research in a timely fashion as this may be interpreted as a significant risk to public health.[2]

The benefit to the patient increases with time gained, but for many patients waiting a few months longer for a new therapy may not be that important. For the innovator company however, a few months may be important with regard to competitors and may prolong patent protected life. Additional months added to the end of the patent life may mean substantial additional sales. A company may also benefit from an authority-endorsed recognition of product value, which should support obtaining faster market access, possibly better prices with payers, and faster adoption by physicians.

However, companies also face substantial risks:

- The investment of upscaling of production and the marketing effort to create awareness for the new drug, the two most expensive activities after development cost, may not be recouped if issues are discovered and the treatment does not receive full approval.
- The upscaling of production can be more expensive as a company may need to ask third-party producers to fill the gap, e.g., many oncology companies had to involve a now closed third-party laboratory for their early sourcing of new products; a biopharmaceutical company had a significant challenge in sourcing the first fusion inhibitor for HIV.[3]
- The inability of the innovator to source the new product adequately may lead to treatment issues with patients and damage the company's image well beyond the launch period.
- The obligations that the innovator company will have to fulfil, e.g., Risk Evaluation and Mitigation Strategy (REMS) requirements and post-marketing surveillance (PMS), drive faster awareness and create real-world data, however, they also create substantial cost.
- Serious side effects that show during the sales of any drug, equal for fast tracked or standard drugs, always increase risks for legal consequences.

WHAT DOES FAST TRACK MEANS FOR MARKET ACCESS?

Products that achieve fast track in one way or another should all deliver therapeutic value in high unmet need indications. Hence, one would expect that the fast track designation will only exert some time pressure on the market access, pricing, and HEOR functions. Market access may already have produced a target value dossier and target value proposition at the end

CONCEPTS TO MAKE IMPORTANT DRUGS AVAILABLE AS SOON AS POSSIBLE TO THE PATIENT		
Concept	*Most important characteristic*	*Eligible products*
EMA		
Accelerated assessment	Review time is reduced from standard 210 days to 150 days	Expected to be of major public health interest from the point of view of therapeutic innovation
Conditional approval	Marketing authorization (MA) can be granted even while comprehensive clinical data have not been provided; to be renewed annually and with obligations (additional studies)	Products for seriously debilitating or life-threatening diseases or emergency threats; orphan drugs
Approval under exceptional circumstances	MA granted even while applicant will be unable to provide comprehensive clinical data; to be renewed every 5 years	Same as for conditional approval; lack of data acceptable because of: • Rarity of the disease • Present state of scientific knowledge • Ethical constraints
FDA		
Fast track	Rolling Review: company can submit completed sections of its Biological License Application (BLA) or New Drug Application (NDA) for review by FDA one by one	Drugs treating serious conditions and filling an unmet medical need
Breakthrough therapy	Fast track plus intensive guidance and organizational commitment	Drugs for treating a serious condition; preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s)
Accelerated approval	Allows FDA to approve drugs based upon surrogate endpoints, without the need to wait for proof of full clinical benefit. Implies confirmatory trials after launch.	Drugs for serious conditions that fill an unmet medical need and have a positive effect on a surrogate or an intermediate clinical endpoint reasonably likely to predict clinical benefit
Priority review	Drug review time 6 months instead of the standard 10 months	Drugs showing significant improvements in safety or effectiveness, diagnosis, or prevention of serious conditions

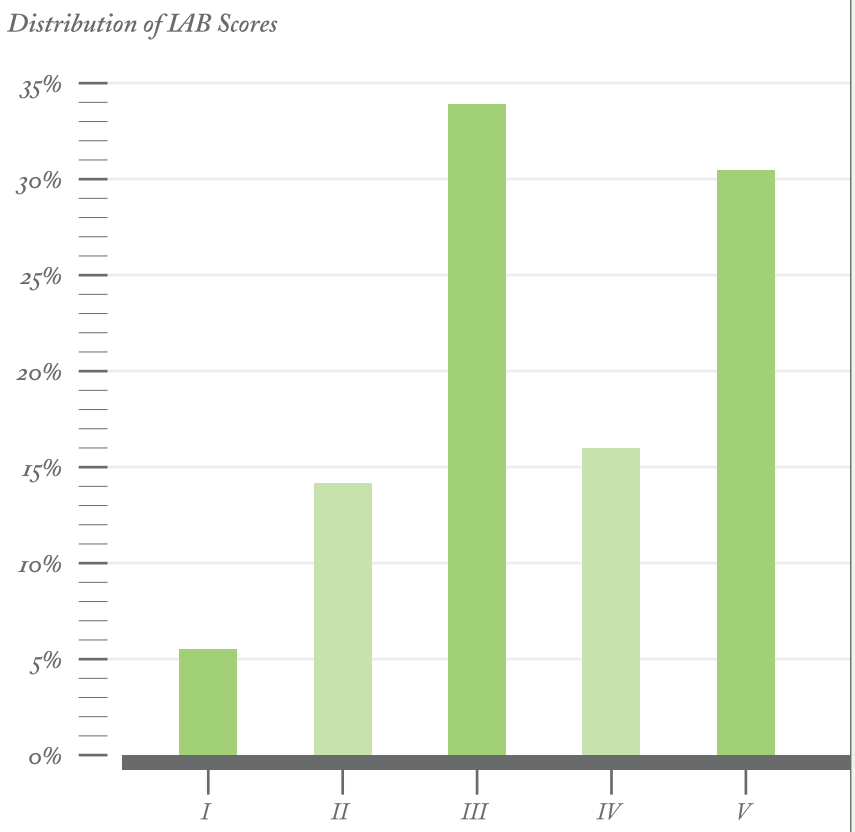
table 1

of Phase IIb, but global value dossier content, comparative effectiveness data, cost-effectiveness (CE) models, budget impact models, and the launch value proposition would normally be carefully developed and underpinned with the necessary data during the later phases of development. Hence, the faster approval will in essence create a void in this data package at the time the company will be discussing launch price and reimbursement. Would this not be compensated by the clear sign of product value given by the fast track designation?

To better understand how HTA bodies were assessing these fast tracked products at launch, we selected and studied the assessment process of 35 products that had accelerated approval, conditional approval, or any other sign of expedited approval process with the EMA. Typically these products were approved on Phase II data, or only one Phase III study, or while Phase III studies were still ongoing. Some of these products were simply lacking full clinical benefit data.

The French Transparency Commission (TC) has the most flexible attitude versus these "fast tracked" products *(see Figure 1)*. About half of the assessed products had an Improvement of Actual Benefit (IAB, ASMR) score of I-III, acknowledgement of their perceived therapeutic value. [Note the scale used for IAB scores for improvement of actual benefit: I (major); II (important); III (moderate); IV (minor); V (no improvement).] However, 11 products were deemed offering no therapeutic value versus existing standard of care. Lack of comparative data and perceived small effect size are mentioned frequently as main

DISTRIBUTION OF 36 TC SCORES FOR "FAST TRACK" PRODUCTS AT FIRST PASS



Note: The scale used for IAB scores for improvement of actual benefit: I (major); II (important); III (moderate); IV (minor); V (no improvement)

figure 1

reasons for the negative decisions, clearly showing the TC did not always follow EMA thinking.

The Scottish Medicines Consortium (SMC) is able to make evaluation decisions in the shortest timeframe. However, this advantage also means that companies have less time to prepare their dossier, which can result in sub-optimal submissions. Nine products were not recommended because the company did not submit a dossier to SMC. At first appraisal SMC accepted only seven products of the selection for use by NHS Scotland, and four of these were allowed for a smaller patient segment than specified in the label ("restricted"). Half of the products were not recommended for use, although four of these achieved this shortly thereafter by agreeing with a patient access scheme. The most important reason for not recommending a new product was related to cost effectiveness of the product (e.g., "the economic case was not demonstrated").

NICE assessed less than half of the products in the selection and did not recommend half of these. Four other products were recommended only after the companies agreed to lower cost through a patient access scheme.

Because many products were launched before AMNOG (Act on the Reform of the Market for Medical Products), the German HTA body IQWiG (Institute for Quality and Efficiency in Healthcare) reviewed only 12 of the products from the selection. Five assessments resulted in the negative outcome "benefit not quantifiable/benefit not established." Four products received "significant benefit"; and three received the appraisal "small incremental benefit."

In conclusion, payers seem very critical of the products that have had an expedited approval process by EMA. They seem leery of offering positive recommendations when in their view there is insufficient proof of the value of the product. Payers fail to follow suit for many products where regulatory authorities feel it is important for these to reach the patients quickly.

SOME EXAMPLES OF THE HTA—EMA DISCONNECT

A quick review of just six examples illustrates a clear disconnect between HTA and EMA evaluations. An orphan drug for the treatment of chronic lymphocytic leukemia received conditional approval from the EMA on January 6th, 2010. In June 2010, NICE was "unable to recommend cancer drug in draft guidance owing to lack of robust data." The TC concluded in October 2010 an IAB score of V (no improvement) explaining "the effect size is difficult to assess because of the methodology used, an interim analysis of a subgroup of patients in a non-comparative study and historical comparison with the results of a retrospective study." SMC did not recommend use in August 2010 because the manufacturer did not present a sufficiently robust economic analysis.

After Marketing Authorization (MA) in July 2011 for a multiple sclerosis (MS) treatment, the TC decided in April 2012 for IAB V because "the gain was minimal and was only observed in a sub-group of patients; the identification of these patients as "responder" after two weeks of treatment has yet to be validated. The changes observed in secondary endpoints were not clinically relevant." SMC did not recommend the product because of the lack of submission of a dossier. IQWiG concluded in July 2011 that an incremental benefit could not be established due to incomplete documentation.

A treatment for Pompe Disease received the score "important" (IAB II) in September 2006 from the TC. However, SMC decided not to recommend the product in March 2007.

At first pass, the TC assessed an antifungal agent as just offering another therapeutic option without proof of incremental benefit, whereas one year later with additional data, the conclusion was revised to moderate benefit. SMC, however, accepted to fund the product at first pass.

A few months after approval in 2007 of an orphan drug for the treatment of paroxysmal nocturnal hemoglobinuria (PNH), the TC decided to award the IAB score "important actual benefit." SMC repeatedly decided not to recommend the product as there was no proof of cost-effectiveness, whereas NICE challenged how the company could explain the high cost of the product.

HTA bodies do not always come to the same conclusions for these "fast tracked" products. As a result patients may not have access to a new "fast tracked" product if they are living in the "wrong" country. Payers might avoid this inequity of access by accepting novel concepts for reimbursement, such as reimbursement with obligations for evidence development.

WHAT CAN A COMPANY DO TO AVOID THE FAST TRACK DISCONNECT?

It is clear that with most payers a company cannot rely on a priority treatment for a fast tracked product. Hence the challenge will be to deliver the necessary substantiation of product value even while timelines are shorter and data are lacking.

If a product has a remote or clear chance for rapid approval, a company should prepare a back-up approach in case fast track would be achieved, including:

- Identifying minimum of resource use measurements and patient-reported outcomes (PRO) data in Phase II (if there is any chance of fast track on Phase II data)
- Develop target value dossier and target value proposition during Phase II
- Be ready for quick price finding
- Develop some simple CE and budget impact models
- Prepare for a fast, market access strategy development process
  - Plan the activities in case of fast track
  - Pre-define suppliers and partners, and set up a fast procurement process
- Ensure you have people and resources available for the work (may be external)

Once the fast track decision is made, good preparation will enable the company to implement an efficient market access process. Moreover, at approval there are other strategies to mitigate the evidence gap:

- Mitigation of lack of comparative data with indirect comparisons
- Utilization of REMS and PMS opportunities for real-world data

When companies request pricing and reimbursement for their fast tracked product, they should be aware of the dilemma payers are facing, including the uncertainty of product value and certainty of budget shortage, when making their determinations. Payers would like to approve these products as soon as they feel they will deliver value for money. Hence, offering options up front that handle uncertainty—such as patient access schemes, conditional reimbursement, conditional pricing—may help overcome the disconnect.

Finally, in a time where most companies are struggling to show any positive differentiation for their new products, they should be happy if the product is fast tracked. It definitely beats having a me-too.

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Indirect Treatment Comparison Without Network Meta-Analysis: Overview of Novel Techniques

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BACKGROUND

There is generally a paucity of evidence about the relative effectiveness of a new treatment and its competitors. And yet, this is a critical consideration in reimbursement decisions as well as in the planning of future research. In the absence of head-to-head studies, comparative evidence is derived through indirect comparisons, relying on common comparators to link data from trials of the various treatments of interest. That is, treatments A and B, which were compared to treatment C in their respective trials, can be indirectly compared to each other by contrasting effects of A vs. C to that of B vs. C. Network meta-analysis or mixed/indirect treatment comparison (MTC) is the standard technique used for this purpose. This approach is broadly used and accepted by the research community as well as health technology assessment agencies, in part because it can incorporate data from all competing treatments in a therapeutic area, thus reflecting the totality of evidence that is available.

In some cases, however, MTCs may not be able to produce the comparisons of interest (i.e., when common comparators were not available), or may be subject to limitations (e.g., heterogeneity between trials) affecting the reliability of the results. Two alternative approaches—simulated treatment comparisons (STCs)[1] and Matching Adjusted Indirect Comparisons (MAICs)[2] can overcome these issues by making *targeted* comparisons of outcomes observed for the new treatment and those observed in the treatment arms of the comparators of interest. Thus, the units of analysis in these targeted comparisons are outcome measures like event rates rather than effect estimates like hazard ratios as in MTCs. This poses an important challenge, however; outcomes observed in treatment arms from different studies are not necessarily comparable. These not only reflect the effects of the treatments received but are also impacted by the profiles of the populations and possibly design

EXAMPLE OF AN EVIDENCE NETWORK based on four studies providing indirect data about the relative effectiveness of treatments A and B

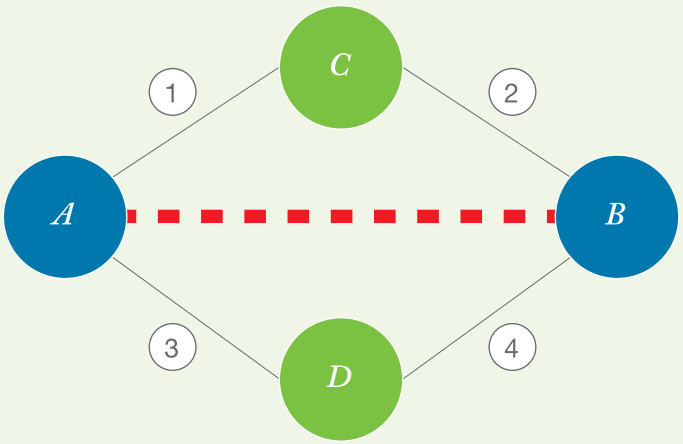


figure 1

STCs AND MAICs CAN BE APPLIED, OR AT LEAST CONSIDERED AND ASSESSED FOR FEASIBILITY, IN SITUATIONS WHERE STANDARD TECHNIQUES HAVE SIGNIFICANT LIMITATIONS OR CANNOT BE APPLIED AT ALL.

features of the studies. STCs and MAICs are designed to deal with these issues and produce reliable comparisons by making analytical adjustments to balance the populations being compared. Unlike MTCs which rely only on published data, these novel methods require patient-level data on at least one of the treatments to be able to adjust for differences in populations.

WHEN SHOULD STCs OR MAICs BE CONSIDERED?

STCs and MAICs can be applied, or at least considered and assessed for feasibility, in situations where standard techniques have significant limitations or cannot be applied at all. Three specific scenarios are described below.

HETEROGENEITY

Figure 1 illustrates a simple evidence network (i.e., representation of the studies and treatments involved in the MTC) to evaluate a comparison of treatments A and B. The network includes four studies, identified by lines connecting the treatments compared in each of these. For instance, trial ① compared treatment A to C, and trial ④ compared treatment B to D. Thus, the indirect comparison of A and B (represented by the dashed red line) is informed by the relative effects of these treatments to their effects compared with common comparators C and D. Suppose, however, trials ② and ③ have similar populations and design, and differ significantly from the other two studies.

Such variation causes *heterogeneity* in the results being pooled and compared, which is dealt with in MTCs by adding parameters that account for *excess* variability in results. It is assumed, however, that differences between trials only cause random fluctuation, so that the indirect comparison derived from the MTC effectively averages over differences in populations, design features, measurement techniques, etc., across studies. This can be problematic, however, when there is significant

EXAMPLE OF AN INCOMPLETE OR DISCONNECTED EVIDENCE NETWORK in which treatments A and B cannot be linked through common comparators

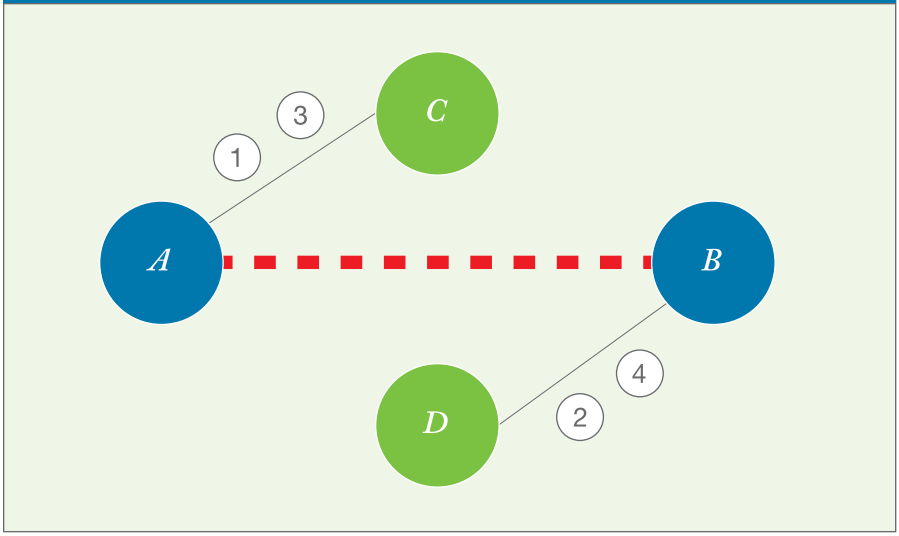


figure 2

heterogeneity, and specific differences that may distort results are noted. Published data are often too limited to allow a closer examination and adjustment for such factors in MTCs.

STCs and MAICs can deal with this type of heterogeneity by focusing the comparison of the studies that are deemed more closely comparable—② and ③ in this example. Outcomes observed for treatment B in study ② are compared with outcomes for C in study ③. It is possible that the profiles of the populations of these studies may differ, even if only due to chance and requires adjustment to obtain an unbiased comparison. The way this is handled in each approach is further described below.

INCOMPLETE EVIDENCE NETWORK

STCs and MAICs would also be useful in situations where the evidence network is incomplete or disconnected. That is, the treatments to be compared cannot be linked through common comparators. This is illustrated in *Figure 2,* where two trials comparing A to C and two trials comparing B to D make up the evidence network. Since the comparators in the trials of A and B are different, it is impossible to obtain an indirect comparison of these treatments with an MTC. Approaches like STC or MAIC may be the only way to achieve an indirect comparison in these situations, since this would be obtained from a targeted comparison of the specific arms of interest in the trials of A and B. This may be done by selecting two specific trials that are most compatible, as in the example of the previous section, or by using data from all four of the trials, and pooling data as appropriate to serve as the basis of analyses.

MULTI-STEP COMPARISON

STCs and MAICs may also be useful in situations where the treatments of interest can only be linked through multiple intermediate comparisons. This is illustrated in *Figure 3.* In this evidence network, trials of A and B do not have a common comparator,

STCs AND MAICs WOULD ALSO BE USEFUL IN SITUATIONS WHERE THE EVIDENCE NETWORK IS INCOMPLETE OR DISCONNECTED. THAT IS, THE TREATMENTS TO BE COMPARED CANNOT BE LINKED THROUGH COMMON COMPARATORS.

and must rely on trials that compared their respective comparators to make the link. That is, A is linked to B through a comparison of C to E and F and D (i.e., A vs. C, C vs. E, E vs. B, and A vs. F, F vs. D and D vs. B). The reliability of MTCs in this situation may be compromised as heterogeneity may impact comparisons at intermediate steps and distort the main comparison of interest. The problem is amplified as the number of steps involved to link treatments increases (e.g., to link A to D in *Figure 3*). The targeted comparisons involved in STCs and MAICs bypass the issue by targeting the analyses on specific arms of interest, as long as the trials of treatment A and B can be considered sufficiently compatible for a targeted comparison.

WHEN ARE STC AND MAIC FEASIBLE?

The first consideration in the assessment of the feasibility of these novel methods lies in the availability of patient-level data on at least one of the treatments being compared. This should generally be possible when these analyses are initiated by a manufacturer. One or more trials of the manufacturer's product (the index trial(s)) would then serve as the basis of the STC and MAIC and would be used to adjust for differences in populations of comparators' trials. In most situations data on the comparator treatments will only be available from publications. This is not a limiting factor, as long as information on the profile of the population and outcomes of interest are reported with adequate detail.

In addition to the availability of patient-level data, the feasibility of these novel techniques depends on the availability of one or more compatible studies for comparators of interest. Compatibility is determined based on the similarity of the populations and the designs of the trials. It is not necessary for the populations to be identical, since the methods are designed to balance differences. This can only be done, however, when there is sufficient overlap in the profiles of the two samples. For example, a difference of 20% in the proportion of male patients in the two trials is not problematic, but the comparison may be unreliable if one study was based on male patients and the other on female patients. Similarly, the duration of the trials and timing of measurements should be similar but not necessarily identical, and likewise for other design features such as admissibility criteria, concomitant medications, treatment protocols, etc.

Finally, reliable application of STCs and MAICs requires that all determinants of the outcomes of interest that may confound the comparison are available in both the index trial data and reported in the publication(s) for the comparator(s) (which will be in summary form, such as means and percentages). The results are subject to residual confounding in cases where determinants are available in one but not both sources.

EXAMPLE OF AN EVIDENCE NETWORK involving multiple intermediate comparisons to link treatments A and B

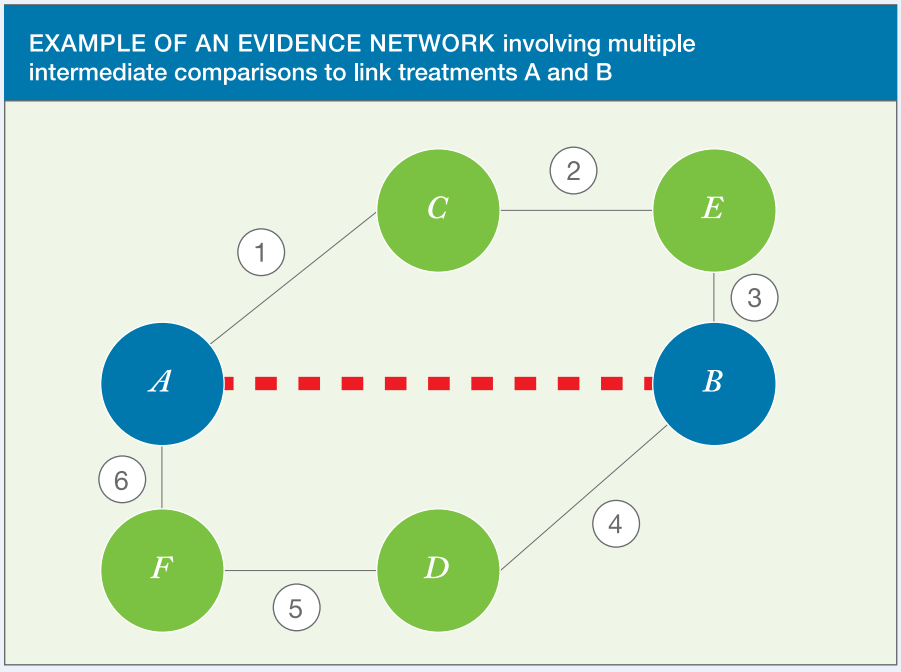
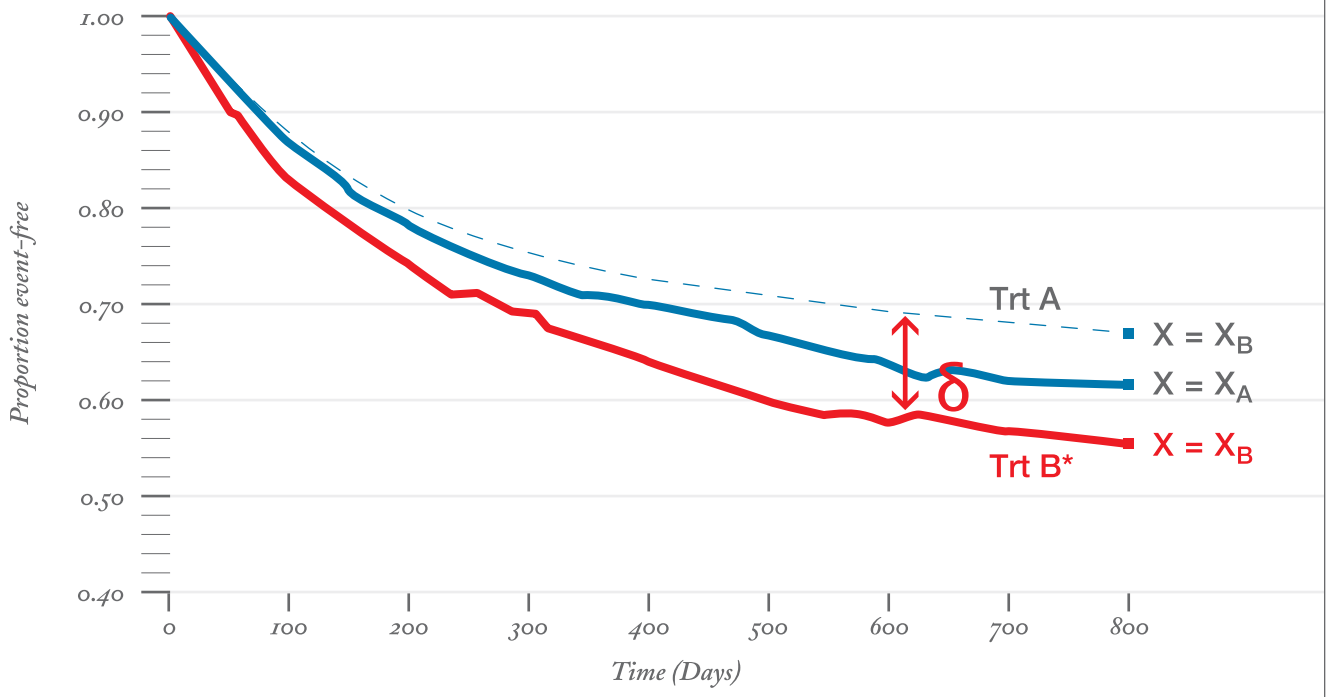


figure 3

CONCEPTUAL REPRESENTATION of how comparisons are derived with adjustment for differences in population profiles with STC and MAIC



* KM Curve for endpoint for Trt B from comparator study publication

figure 4

HOW DO STCs AND MAICs WORK?

STCs and MAICs are very similar conceptually. *Figure 4* shows a representation of how balanced comparisons are derived in STCs and MAICs. In this illustration, the outcome of interest is a time-to-event endpoint. The solid blue line represents the time-to-event distribution from the index trial of treatment A, while the red solid line represents the distribution for the comparator B obtained from a published report or manuscript. A comparison of these lines is biased by the fact that the profile of the population represented in the blue line (denoted by X_A) may differ, even if only by chance to the profile in the red line (X_B). Thus, to adjust for potential imbalances, these methods aim to generate an adjusted time-to-event curve that reflects what outcomes may have been with treatment A in a population that matches the profile for treatment B. This is represented by the dashed blue line, which can now be compared directly with the observed outcomes for treatment B (i.e., red line) to measure the relative effectiveness of A and B (denoted by δ).

STCs and MAICs differ in the way they generate the adjusted outcomes for treatment A (dashed blue line). STC accomplishes this by creating a predictive equation for each outcome being compared. The equations are then used to predict outcomes that would have been observed for treatment A in patients with characteristics matching those in X_B. That is, the adjusted line is produced by setting predictors to their corresponding values in X_B.

MAICs deal with the adjustment by reweighting patients in the index trial so that the weighted average values of determinants of outcomes in the index trial (i.e., X_A) match X_B. These weights are derived from a propensity-score-type analysis using the index trial data, predicting membership into the index vs. comparator's trial. An individual weight is then predicted for each patient in the index trial, and applied in Kaplan-Meier analyses (for example) to generate the adjusted curve.

The methods can be applied following the same process with all types of outcomes (e.g., continuous or dichotomous measures). Furthermore, both approaches produce an estimate

of the relative effectiveness along with measures of uncertainty, like standard errors or confidence intervals.

WHEN TO CHOOSE STCs VS. MAICs?

STCs and MAICs are conceptually very similar and use the same data to accomplish the goal of adjustment for potential confounding. It is, therefore, reasonable to expect that the two methods would yield very similar results. (This is, indeed, what we have observed in actual analyses.) Differences between STCs and MAICs lie in potential efficiencies associated with each approach.

STCs involve generating predictive equations for each of the outcomes of interest. The identification of predictors is added insight and the equations themselves may have utility in other applications. For instance, the equations can be integrated into a simple disease model to serve as the basis of a trial simulation tool allowing the evaluation of designs for future studies (e.g., to test different population profiles). STCs can be more efficient than MAICs in situations where comparisons with multiple comparators are to be made for a given set of outcomes. Equations for the outcomes would be derived once from the index trial and applied with data from each comparator treatment's study. With MAIC, a separate set of weights would be required for each comparator treatment's study population. By the same token, MAICs would offer efficiencies in situations where there is a single comparator but many outcomes to be compared. A single set of weights would be required to balance the two populations, and could be applied in analyses for each outcome.

SUMMARY

STCs and MAICs are robust and reliable methods to derive indirect comparisons between treatments. These novel methods can produce comparative evidence in situations where standard techniques are inadequate, but can also be complementary to NMA or MTC, providing a more targeted assessment of the relative effectiveness of the treatments. Whereas the MTC may provide an averaged effect estimate, by using the index trial as the basis of the analysis, the STC or MAIC reflects the relative effectiveness that might have been observed if the comparator had been included as an additional arm in the index trial.

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Innovations in Technology in the Development and Collection of Patient-Reported Outcomes

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Advances in technology have had a significant impact on data collection in all phases of the drug development process, including the process of developing and implementing a patient-reported outcome (PRO) measure. Although the most frequently noted technological advance in the data collection of PROs is the adoption of electronic PRO (ePRO) devices, which allows for real-time collection of patient outcomes, there are also technological approaches in other phases of the PRO instrument development process. The purpose of this article is to briefly review and consider the innovative approaches to data collection for both qualitative and quantitative data used in the development and validation of PROs.

HYPOTHESIS GENERATION OF THE CONCEPTUAL FRAMEWORK: NATURAL LANGUAGE PROCESSING OF WEB CONTENT

The PRO instrument development process typically begins with a literature review in the therapeutic area of interest to inform the hypothesized conceptual framework for the relevant concept of interest. Often interviews with therapeutic area experts provide content expertise to refine the hypothesized conceptual framework. Analysis of Web content (e.g., patient blogs) through natural language processing or other qualitative software analysis approaches may offer an additional complementary tool to inform the hypothesized conceptual framework in this early concept elicitation phase of PRO development.

At the most basic level, an analysis of Web content using natural language processing provides a summary of the frequency of various text fields within a selected sample of text. Examples of sample text include generic blog and microblog sites, such as Wordpress[1] and Twitter[2], patient support forums or Facebook pages that are organized by relevant patient interest groups,[3,4] patient-centric platforms designed specifically for patients to connect,[5,6] or more broadly all Web content available through a keyword search (i.e., "fibromyalgia") on a search engine. More complex models provide interpretative structure to the text data, and the more sophisticated software applications include data visualization approaches to summarizing the frequency and structure of the text data. Several commercial and open source software applications are available to perform text analysis through natural language processing of Web content (see link for text mining software examples: http://en.wikipedia.org/wiki/List_of_text_mining_software).

Figure 1 presents a foam tree diagram generated through a Web content analysis using Carrot[2],[7] an open-source Web content analysis tool using the search term "fibromyalgia." In this case, the sample is the 86 most relevant of 2,380,000 website hits through the Carrot[2] search engine, and as evident by the diagram, the most common content addresses "treatment of fibromyalgia." From the perspective of early concept elicitation for a fibromyalgia symptom questionnaire, further examination of the diagram highlights the potential importance of muscle pain, sleep disturbance, soft tissues, and the possible relationship with chronic fatigue and arthritis. This example is provided to demonstrate the type of exploratory analysis that might be conducted. A natural language processing-based content analysis of a more select sample of text—for example, fibromyalgia patient forums or blogs written by fibromyalgia patients—may provide insights more directly relevant to a symptom measure.

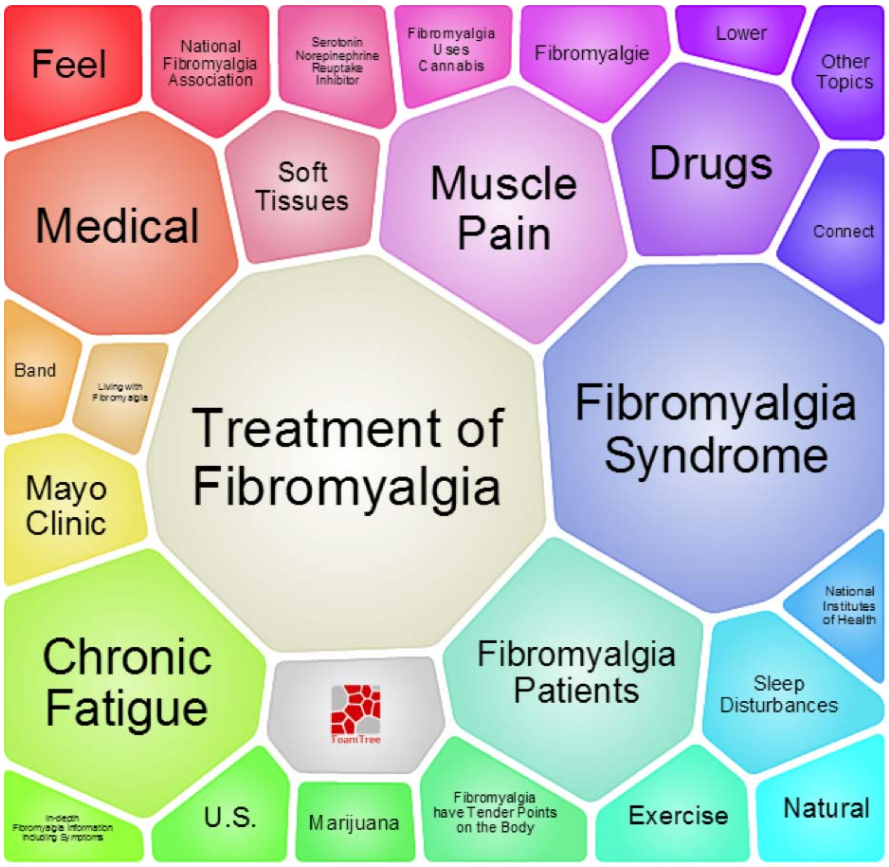


figure 1—*Extracted on April 15, 2014 (Source: Weiss D, Osinski S. 2014)*[13]

What advantage does analyzing diverse Web content provide to early stages of concept elicitation beyond what a structured literature review and therapeutic and patient experts might provide?

- One key advantage is that due to the emergent nature of the data, there is no unintended influence of the interaction between the researcher and participant responses. Patients may be more authentic in speaking about sensitive issues and may discuss issues that they would not discuss with their clinicians.
- Given the potential for analysis of large amounts of data, concepts or domains that are relevant to only a subset of participants that may be missed in a more focused qualitative analysis of only a few patients may be uncovered.
- The approach may be particularly useful in an indication where there is limited existing evidence characterizing the disease, or in cases where the disease is rare and access to patients is limited.
- Published manuscripts and the opinions of therapeutic area experts introduce their own bias, and by combining these approaches with a patient-centric, conversational data element, a richer picture of the conceptual framework may be realized.

While there are a variety of advantages, the following limitations should also be considered with this approach:

- As of 2012, over half of American adults aged 65 years and older are online and growing, but despite increasing socio-demographic reach of Internet use, the online population is still biased in favor of young, educated, and white participants[8].
- Sample bias may also be introduced by the selection of materials to be analyzed (e.g., differences among Twitter users relative to those in a specific disease forum).
- The importance of certain concepts may be over-estimated by one or two users or websites that focus on a specific concept.
- The analysis is a combination of computationally driven analysis of the text and user guidance, so it is subject to interpretation bias and error that is introduced as part of the models used in the natural language processing software.

- As an emerging field, there is no standard analytic approach or guidance related to ethical considerations surrounding the privacy and confidentiality of analyzing this type of data.

Despite these challenges, the approach offers an efficient way to gather information related to a concept of interest, and may offer a unique perspective that is not readily available through the traditional literature reviews, patient surveys, and qualitative interview approaches used at this stage in PRO development.

NOVEL APPROACHES TO ENGAGING PATIENTS FOR CONCEPT ELICITATION AND COGNITIVE INTERVIEWING

In-person interviews are the "gold standard" in qualitative research, however this approach is arguably the most expensive and time-consuming, and often recruitment is limited to narrow geographic locations. Telephone, video-conferencing, and Web-based interview mediums are alternatives that offer potential cost and time savings and broader geographical reach.

Telephone interviews may be conducted at a considerable cost-savings, and may also allow access to geographically disparate subjects;[9] however, despite these advantages, they are less frequently utilized than face-to-face interviews in qualitative research.[10] The primary limitation noted for this modality is the lack of visual cues, which is perceived to lead to the loss of important nonverbal and contextual data, although the empirical evidence for this frequently cited rationale is lacking with limited comparison of telephone and in-person qualitative interview modalities.[10]

Video teleconferencing provides the added benefit of observation of facial visual cues for both the participant and interviewer. However, most often the image only covers the head, so other body language is not observable. Either audio, or both audio and video, may be recorded dependent on the software that is used. Participants may travel to a video-conferencing center, which may be available and rented on an hourly basis, or alternately they may utilize at home, high-speed Internet, Web browser, and HIPAA-compliant video-conferencing software.[11] The availability and accessibility of HIPAA-compliant video conferencing software does impact the socio-demographic reach of this medium relative to teleconferencing. However, in cases where face-to-face interviews might offer an advantage in rapport development and observation of facial cues, it is an important medium to consider.

Online forums created for the purpose of the research study, where participants can discuss specific topics through posting a series of messages and a researcher moderates the discussion is another, although little used, Web-based option for conducting qualitative research.[11] The posts made by participants are the unit of analysis and are analyzed in a similar fashion to transcripts. Participants may be recruited from other relevant Internet communities, or through community settings, or alternately a patient-centric research platform designed specifically for patients to connect with researchers, such as Patients LikeMe.[5] In contrast to other mediums, these types of interactions are asynchronous—such that participants log on at different times and dialogue is not conversational at a set point in time. This offers an advantage to collection and participation across geographical time zones, but it also does not allow for prompt and immediate response, which may be considered a disadvantage in some contexts.[10] Given the sensitivity of the health information that is being discussed, security measures should be considered, although no clear guidelines exist around this issue. The inability to confirm diagnosis is a further limitation to the documentation of content validity in the target population of interest. However, it is possible for patients to consent to the release of their medical records for diagnosis confirmation.

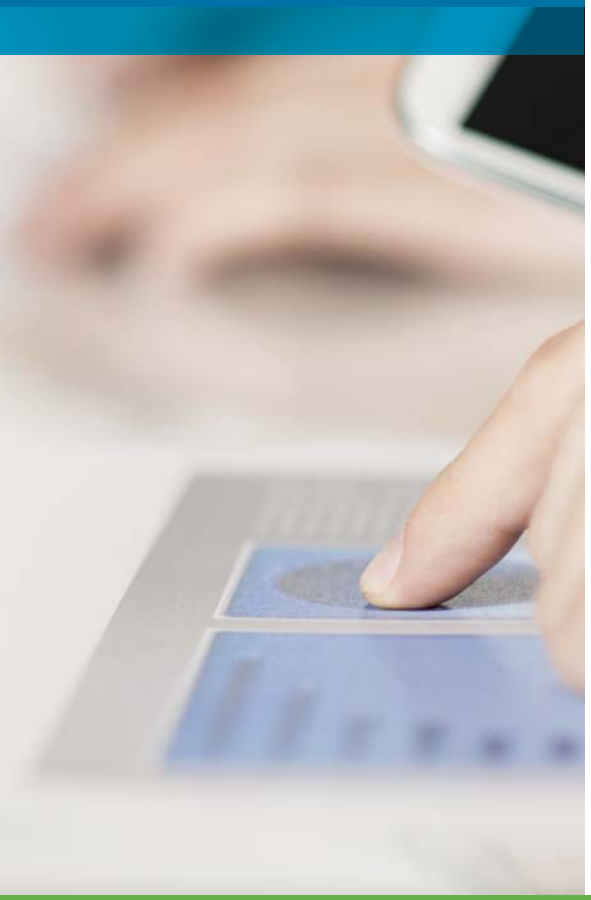
WEB-BASED DATA COLLECTION

Historically, ePRO technologies have included personal digital assistants (PDA), interactive voice response (IVR), Web-based systems, smartphones, tablets, purpose-built devices such as peak flow meters with integrated diary capabilities, and digital pens. As technology permeates every aspect of daily life, further innovation in ePRO is taking place in Web-based data collection and in "device agnostic" data collection, also termed "Bring Your Own Device" (BYOD).

Web-based data collection has been associated with large screen devices like desktop or laptop computers. Thus, Web-based questionnaires were designed with these browsers and screen sizes in mind, and assumed peripherals including a keyboard and mouse were available for response entry. However, mobile devices are now capable of accessing the Web through specific mobile Web browsers, which have a very different look and feel compared to large screen devices and require touchscreens or navigation buttons for response entry. Therefore, the Web-based approach has been more broadly defined to include the use of a wide range of devices with access to the Internet, including mobile browsers.

Smaller, mobile Web-browsing devices have the portability of a smartphone or PDA device, and may provide larger screen sizes which allow for longer questions, longer responses, and can accommodate translations more easily than smaller handheld devices.

THE OTHER MAJOR INNOVATION IS THE MOVE TOWARD A DEVICE-AGNOSTIC APPROACH TO DATA COLLECTION, IN WHICH STUDY SUBJECTS ARE ABLE TO USE THEIR OWN DEVICES FOR DATA COMPLETION.



Web-based data collection requires that the user interface be optimized to work with and be validated on a combination of the operating system (i.e., Windows, iOS, Android) and the browser (i.e., Internet Explorer, Firefox, Chrome, Safari, etc.), but device-specific validation is not required.[12] In most cases, a choice has to be made to optimize the interface for a larger screen browser or a mobile browser. Another concern is the need for uninterrupted access to the Internet during questionnaire completion. In some cases, the questionnaire can be saved and resumed later, but unexpected interruptions can lead to loss of data already entered and would require the study subject to start over from the beginning.

BRING YOUR OWN DEVICE (BYOD) APPROACH

The other major innovation is the move toward a device-agnostic approach to data collection, in which study subjects are able to use their own devices for data completion. The BYOD approach appeals to study sponsors because it reduces the cost of providing devices to all study subjects, the logistics of deploying devices internationally, training issues, maintenance and help desk issues during a study,[12] and the need to maintain the devices after study completion. Study subjects who have their own devices may prefer to use a device with which they are familiar rather than carrying a second device around with them. Two approaches to BYOD are currently in use: "Apps" and Mobile Web.

"APPS"

An "App" version of the PRO questionnaire can be downloaded to the study subject's own device to be accessed for data collection during a trial. The App is programmed to work on a specific operating system, most prominently Apple's iOS or Android. Advantages include consistency in display across devices within a given operating system, the ability to answer the questionnaire offline and then transmit the data when completed, and using the device's own alarm feature to remind the subject to complete the questionnaire, critical for daily diaries with limited completion windows.

The main disadvantage to the App approach is the need for a compatible smartphone that can accept the App and the need to download it to the device. The subject's device must be assessed to ensure it has the right operating system version and screen size, which puts the burden on sites to determine if a study subject's device is acceptable. Provisioning backup devices to subjects who do not have a phone or compatible device must be considered. Security and privacy are also major concerns. The App must be 21CFR Part 11 compliant and requires validation on every type of mobile phone, tablet and computer used in the trial.[12] Data entered on the device may not be as secure as on a standalone device because the patient's own device is used for many other purposes. There are also concerns regarding data loss if the device is lost or fails.[12] Finally, there are cost considerations because subjects must pay for the data transmission using their own mobile service plans, while in traditional ePRO these costs are covered by the sponsor.

MOBILE WEB

Advantages of the Mobile Web approach to BYOD are that accessing the questionnaire is much simpler as only a link to the website is needed, there is "zero footprint on the patient device and no need for local installation,"[12] and no data reside on the device as it is merely an interface to access the Web-based browser. Device-specific compatibility may be less of an issue although the questionnaire still needs to be optimized to work with Mobile Web

browsers in general. A broader range of devices may be used with Mobile Web than with the App-based approach.

The need for constant Internet connectivity is a major disadvantage because it is required to access the questionnaire initially, and mobile access can drop suddenly during questionnaire completion.[12] Variability across devices and screen sizes is also a concern; it is impossible to test all possible variations of browsers and devices to ensure that the instrument displays consistently. Although some question the need for device specific validation,[12] different screen sizes may lead to incorrect responses if text is not visible on the screen without scrolling. The subject must also have a mobile data plan and therefore has to bear the cost of accessing the Internet to participate in the study. Reminders in the Mobile Web approach may be sent via email or text messaging/short messaging service with a link to access the system, but the audible approach of an alarm on the device is not as feasible. Therefore, the reminder could be easily missed if the subject is not near the device, resulting in lower compliance due to inadequate reminders.

CONCLUSION

This year (2014) marks the 25th anniversary of the World Wide Web.[8] With the advent of Web 2.0 in the last decade—a medium which allows users to interact and collaborate with each other, versus passively consume Web content—people are now able to engage in ongoing, interactive dialogue through various social media networking sites, blogs, and communities. The changing landscape of Internet access and engagement is shaping health care and the research process. Technological innovations in data collection have the potential to improve and streamline the PRO development process, from hypothesis generation to data collection in clinical trials, and to facilitate patient engagement on many levels. However, when considering newer technology options, it is important to consider some general limitations noted above. Perhaps even more importantly, clear guidelines and approaches to managing the privacy and security of these Web-based approaches are needed. When considering novel approaches to data collection, it is also important to balance the costs, sampling bias, logistical challenges and the patient's desire for convenience against privacy and security concerns.

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Growing Interest in Using Utilities to Assess Treatment Process Preferences

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Methodology used to obtain utilities for use in cost-utility models is strongly influenced by guidelines from health technology assessment agencies. The guide published by the National Institute for Health and Care Excellence (NICE) is possibly the most influential of these guidelines, with the most prescriptive approach to utility assessment. The 2013 NICE Guide indicates a preference for utilities derived from the EQ-5D in order to maximize "consistency across appraisals," while allowing for alternative approaches when the EQ-5D is not "available" or "appropriate."[1]

A wide range of alternate methods are used when the EQ-5D is inappropriate or unavailable, including direct utility assessment, mapping, and other generic measures. Direct valuation of health state descriptions, often called vignettes, is one commonly used alternate approach. In this type of study, health state descriptions are drafted based on a combination of literature review, clinician interviews, patient interviews, and/or clinical trial data. Then, these vignettes are valued in time trade-off or standard gamble tasks by either general population respondents or patients with knowledge of a specific condition.

This vignette-based assessment approach is well-suited for isolating preferences associated with specific health-related characteristics, such as rare diseases and adverse events, that may not be captured by generic preference based instruments such as the HUI[2] or EQ-5D.[3] This practical approach allows researchers to obtain utilities associated with specific attributes, while requiring only a single assessment and a manageable sample size.

Another type of characteristic that may be captured in vignette-based utility studies is the treatment process, and there is a growing body of research focused on these "process utilities." Studies have found that utilities vary depending on a range of treatment modalities including surgical vs. nonsurgical management;[4]

inhaled vs. injected treatment;[5] oral vs. injectable treatment;[6,7] dose frequency;[6,7] inpatient vs. outpatient treatment;[8] two types of prenatal genetic testing;[9] injection vs. infusion;[10] early-stage cervical cancer treatment options;[11] and specific medication options.[12] Across these studies, more convenient treatments were consistently associated with greater utility values. Although treatment process is likely to have a smaller effect on utility than symptom severity or treatment outcome, small differences in utility associated with treatment process can have a substantial impact on cost-utility results, particularly when modeling large numbers of patients.

The vignette-based approach to estimating the impact of treatment process does have some limitations that should be considered when designing and interpreting these studies. For example, while the vignette-based approach is useful for assessing utility impact of specific treatment attributes, it lacks the standardization and comparability of a generic preference-based measure such as the EQ-5D. Second, vignette-based utilities represent preferences among hypothetical health states, rather than the quality of life of a person living in one of the health states. It is not known how closely utilities derived from vignette assessments would correspond to utilities of patients living in these health states. Third, utilities derived from vignette assessments are based only on the characteristics described in the health state, rather than a broad assessment of patients' quality of life or experiences with treatment. Consequently, the utilities gathered with vignettes should only be interpreted as a representation of the perceived shift associated with specific attributes.

For cost-utility models comparing medications with similar efficacy and tolerability, treatment process variables could be an important way to differentiate among comparators. In recent years, we have been asked with growing frequency to conduct vignette-based studies to identify process utilities. For example, one of our recent studies found that route of administration and treatment convenience had an impact on utility in the context of health states representing cancer with bone metastases.[10] At the ISPOR 19th Annual International Meeting to be held May 31 to June 4, 2014, in Montreal, we will be giving a podium presentation on utilities associated with various treatment regimens for hepatitis C.[13]

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Estimating Quality-Adjusted Life Years from Patient-Reported Visual Functioning

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There is increasing recognition of the desirability of cost-utility analysis to inform decision making for new drugs and technologies. Cost-utility analyses used to assess the value of new interventions need to incorporate health outcomes through the measurement of utilities, which can be measured through various methods including the Time Trade-off (TTO), the Standard Gamble (SG), or through multi-attribute questionnaires such as the EQ-5D. In the UK, the NICE reference case recommends the use of the EQ-5D within clinical studies for collection of clinical data. However, in clinical trials, health-related quality of life (HRQoL) data is often not collected using generic preference-based measures, but instead is collected using a disease-specific measure that is not designed to generate utilities. The most recent NICE guidelines specify that when EQ-5D data is not available, mapping from a disease specific measure to the EQ-5D is an acceptable way to obtain utility data.[1]

Mapping is an approach that involves estimating the relationship between a non-preference-based measure and a generic preference-based measure using a statistical association. This method requires the two measures to have been administered to the same population, and a statistical model can then be used to estimate health state utilities, which can in turn be used to calculate quality-adjusted life years (QALYs) for cost-per-QALY analysis within economic evaluations.

Vision is a disease area where EQ-5D data are often not readily available. However, the impact of glaucoma on vision has been shown to have implications for patients' health related quality of life.[2,3] The primary aim of this study was to estimate a mapping algorithm to predict EQ-5D and SF-6D utility values based on the 25-item Visual Functioning Questionnaire (VFQ-25), as well as clinical measures of visual function, including integrated visual field (IVF), visual acuity (VA), and contrast sensitivity (CS). Mapping relationships were estimated using a range of techniques and statistical specifications. The mapping functions are compared across the EQ-5D and SF-6D.

Data was collected over 12 months on 132 patients with primary open-angle glaucoma. Fourteen mapping functions were estimated to predict the EQ-5D and SF-6D from a combination of the VFQ-25 overall score, the VFQ-25 dimensions, tests of visual function, and demographics. Mapping requires regression techniques to be used on the estimation data to estimate a statistical relationship between measures. In order to minimize modeling uncertainty within this study, three different models for prediction were used, including ordinary least squares (OLS), Tobit models, and censored least absolute deviations (CLAD). The model performance was then assessed by looking at the root mean square error (RMSE), the R-squared, and the mean absolute error (MAE).

MAPPING IS AN APPROACH THAT INVOLVES ESTIMATING THE RELATIONSHIP BETWEEN A NON-PREFERENCE-BASED MEASURE AND A GENERIC PREFERENCE-BASED MEASURE USING A STATISTICAL ASSOCIATION.

When estimating the EQ-5D, the lowest errors were found in the mapping function containing the VFQ-25 dimension, visual function, and demographics. However, when estimating the SF-6D, the best performing mapping function only used the overall VFQ-25 score. In both models, the OLS regression was found to be the best performing model of the three, as this produced the lowest errors and the best R-squared, showing how well the observed outcomes were replicated by the model.

There has been limited research into the field of HRQoL and glaucoma, and there is an ongoing debate as to how to best measure utilities in glaucoma patients. The EQ-5D does not have a vision dimension and has been found to be insensitive to HRQoL in this population. Studies using this measure found mean scores that did not differ substantially from their respective population norms,[4,5] meaning that important HRQoL impacts would be undervalued in an economic evaluation. In fact, this study found almost 27% of the patients recorded the maximum EQ-5D score of 1 in the original data, indicating a significant ceiling effect within this measure. It is, therefore, important to have accurate models of measurement of the relationship between disease and HRQoL as this allows clinicians to potentially benchmark their interventions against the potential loss or improvement of HRQoL to the patient. The study has provided models for the initial algorithm to convert the VFQ-25 to the EQ-5D and SF-6D when they would not have originally been used. However, further analysis is needed to validate the models and algorithms.

This study aimed to provide an estimation of mapping algorithms, which could be used in future studies using the VFQ-25 when no HRQoL measure is used. The patients in this study had relatively mild glaucoma, and therefore, there were minimal effects on their HRQoL. Further work needs to be done with a larger sample of patients with a much broader spectrum of the disease to establish the exact pattern of the relationship between decline in HRQoL as the disease progresses. Accurate models of measurement of the relationship between disease and HRQoL will allow clinicians to potentially benchmark their medical or surgical intervention against the potential loss or improvement of HRQoL to the patient.

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Survival Modelling in UK Oncology Technology Appraisals Since the Publication of Good Practice Guidelines

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INTRODUCTION AND GOALS

Progression-free survival (PFS) and overall survival (OS) are the most important clinical outcomes used in the assessment of clinical effectiveness and cost-effectiveness of oncology products for reimbursement decisions. The National Institute for Health and Care Excellence (NICE) in the UK, one of the most influential health technology assessment (HTA) agencies in Europe, requires that the time horizon of the cost-effectiveness analyses is long enough to capture all relevant differences between health interventions.[1] This is supported by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the Society for Medical Decision Making (SMDM) guidelines.[2] Thus oncology products need to be evaluated over a lifetime horizon. However, these outcomes, particularly OS, are often incomplete—during the follow-up period of the trial not all patients experience an event. Thus, to comply with guidelines, long-term projection of data is required. Long-term extrapolation of trial data is rarely straightforward. As demonstrated by several HTAs and specific papers, different methods of extrapolation may lead to different conclusions about the mean-life expectancy of the patients, and consequently about the cost-effectiveness of interventions.[3,4,5]

In recognition of the significant impact of the choice of method and lack of sufficient documentation of the techniques applied, the NICE Decision Support Unit (DSU) issued a technical guideline on survival analysis for economic evaluations alongside

clinical trials in June 2011.[6] The DSU publication focuses on the case where individual patient level data is available for the analysts. Additional papers have since been published on aspects of the current extrapolation practices and approaches.[3,4,5,7,8]

The basic steps for extrapolation with parametric models are similar in the various recommendations *(see Figure 1)*. The objective of this current study is to assess the effect of the DSU guidance and these recommendations in the extrapolation of OS and PFS in oncology technology appraisals conducted by NICE.

METHODS

NICE technology appraisals

A review of all NICE technology appraisals completed between June 2011 and August 2013 for oncology drugs was conducted, and manufacturer submissions were reviewed and extracted. NICE ERG (Evidence Review Group) reports were also reviewed to identify any criticisms of the approach chosen by the manufacturer and alternative methods recommended. The next step was to assess if the criticism and recommendations were applied in the ERG's models developed for Multiple Technology Assessments (MTAs) or within the manufacturer's model in Single Technology Appraisals (STAs).

Data extraction

The following data were extracted and reviewed for both the data submitted by the manufacturer and the final data accepted by the Review Committee:

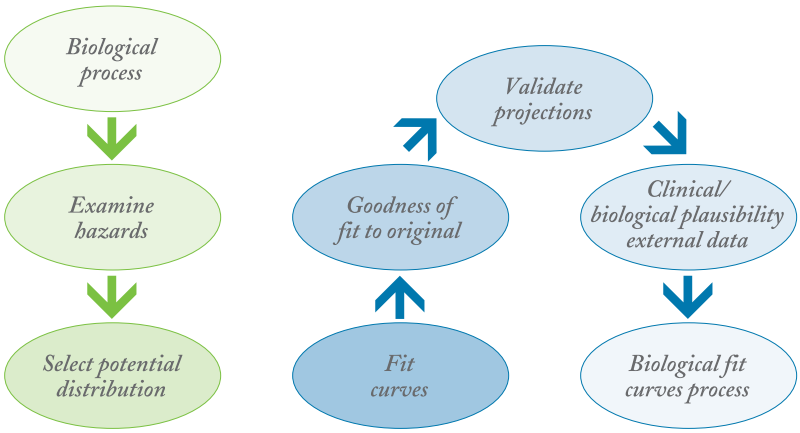
- Details of the technology appraisal
  - Disease area and line of therapy
  - ERG
  - Issue time of the guidance
  - Modelling approach
  - Model time horizon and mean/median age of patients
- Details of the extrapolation of PFS and OS
  - If data was extrapolated
  - If yes, what was the final methodology applied
  - How was the extrapolation method chosen
  - How the choices are validated
- Criticism and conclusions of the ERG
- Final decision of the committee regarding the drug appraised

RESULTS

Appraisals

In total 21 technology appraisals (TAs) were identified. Of these 21 TAs, one for bone metastasis was excluded, and 20 were extracted. There were 15 STAs and 5 MTAs—including 33 separate models altogether—7 by ERGs and 26 submitted by manufacturers. Four models, which were part of an MTA, were excluded

MAIN STEPS FOR EXTRAPOLATION WITH PARAMETRIC SURVIVAL CURVES



Source: *Remak, et al. ISPOR workshop 2012, Berlin, Germany*

figure 1

as publicly available descriptions were insufficient to assess the extrapolation techniques applied. Indication for the TAs included breast cancer (5 TAs); haematological cancers (5 TAs); ovarian cancer, lung cancer, prostate cancer and melanoma (2 TAs each); and, colorectal and transitional cell urothelial tract carcinoma (1 TA each). Ten of the solid tumour TAs included advanced and/or metastatic disease.

Characteristics of the models

In the TAs for solid and haematological tumours, model structures were different. Models for solid tumours included the following three main health states *(see Table 1):*

- Stable or pre-progression health state defined mostly by the PFS curve (with or without adverse events)
- Post progression or progressed health state
- Death defined by OS

Although labelled differently in the submissions (e.g., state-transition model, survival partition model or Markov or semi-Markov model), the underlying structures were similar, with PFS and OS describing disease progression modelled independently of each other.

The models presented for some haematological cancers included health states for various phases of the disease, as well as response status and, therefore, had considerably more complex structures.

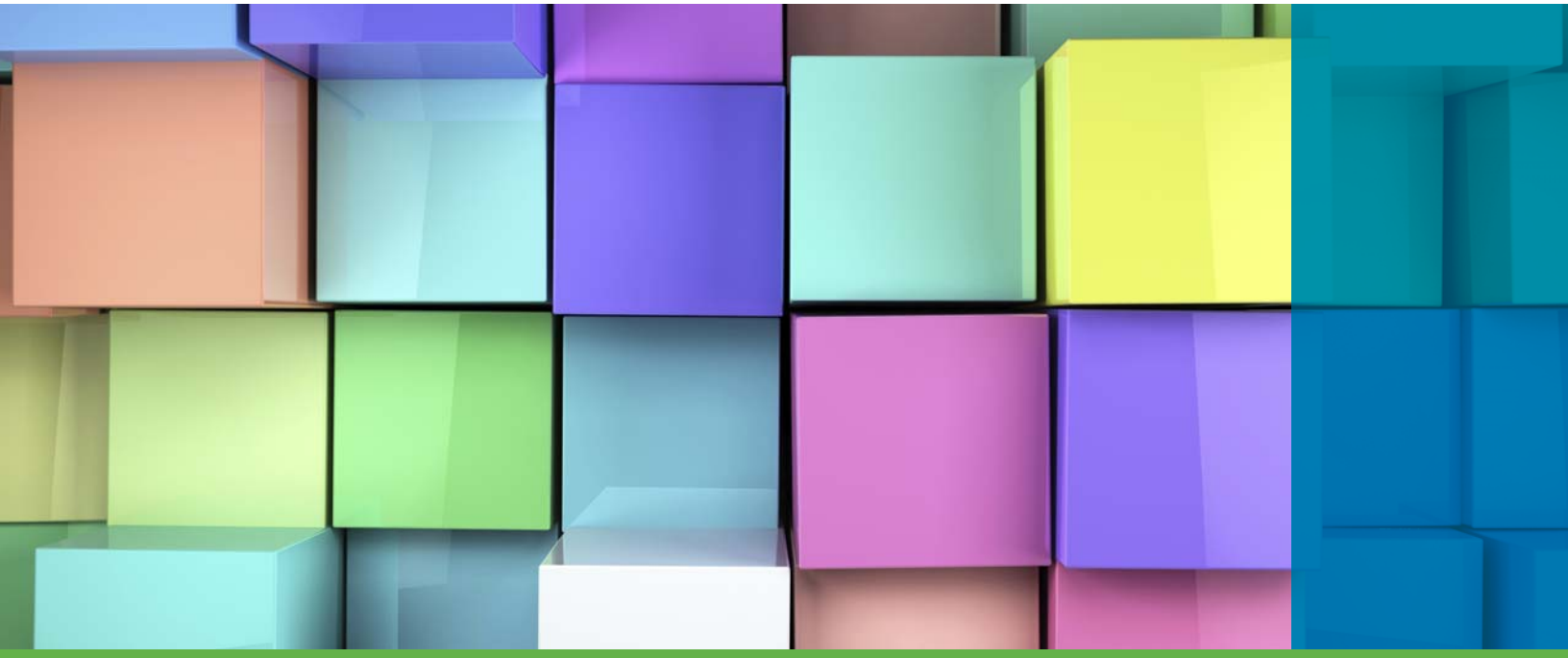
Survival modelling approaches

For the intervention of interest, PFS and OS were modelled at least partially based on patient-level trial data in 75% of the models. The remaining quarter of models were prepared by ERG groups without access to patient level data and relied on published literature, including plots of Kaplan-Meier curves submitted by manufacturers. In oncology the comparators included in the trial may not be the relevant comparator in the UK due to regional variation in treatments and rapid change in treatment patterns. As a result, literature and data from meta-analyses also played an important role in modelling PFS and OS of comparators.

The extent of extrapolation (i.e., the difference between model time horizon and time span of trial data) was on average 15.5 years (ranging from 2.6 to 29.2 years). Data from Kaplan-Meier curves were applied directly in 24% of the models. However, apart from one submission where data was fully mature, some form of parametric extrapolation was applied for the part of the time horizon not covered by the trial data.

Parametric extrapolation was applied in 75.9% of the models, with the most commonly used distributions being Weibull and exponential *(see Table 2).* Usually the same type of distributions were chosen across treatment arms, however, in a small proportion of cases, the distributions differed. When different distributions provided the best fit for the treatment arms, best-fitting distributions were in some cases rejected in favour of using the same distribution based on clinical expert opinion. The treatment arms were mainly modelled separately, with joint models fitted in only 25% of cases for both PFS and OS.

Approaches to statistical modelling of PFS seemed better documented than that of OS. The final choice was mostly supported by results



CHARACTERISTICS OF THE 29 MODELS EXTRACTED	
Characteristics	
Model duration (mean, range)	25.2 (2.9-50)
Data duration in years (mean, range)	2.90 (0.8-8.0)
Survival partition model with 3 health states, n (%)	17 (60.7%)
Extrapolation used?	
Yes (%)	28 (96.6%)
No (%)	1 (3.4%)
Data sources for PFS/ OS, n (%) / n (%)	
Clinical trial data	21 (72%) / 16 (55%)
Literature	5 (17%) / 5 (17%)
Other (not reported; mix of trial data plus literature)	3 (10.4%) / 8 (27.6%)

table 1

DESCRIPTION OF FINAL PARAMETRIC EXTRAPOLATION		
	PFS	*OS*
Non-parametric techniques only	1 (3.4%)	1 (3.4%)
Parametric techniques	22 (75.9%)	22 (75.9%)
Mix of non-parametric and parametric approach	6 (20.7%)	6 (20.7%)
Distributions tested in number (%) of submissions		
Exponential	15 (51.7%)	14 (48.3%)
Weibull	16 (55.2%)	13 (44.8%)
Gompertz	8 (27.6%)	5 (17.2%)
Lognormal	8 (27.6%)	7 (24.1%)
Loglogistic	8 (27.6%)	7 (24.1%)
Gamma	4 (13.8%)	4 (13.8%)
Fitting of treatment arms?*		
Joint	11 (37.9%)	8 (27.6%)
Separate	15 (51.7%)	16 (58.6%)

**Note: Does not sum to 100%, included mixed approach in both counts, remaining items include "not reported"*

table 2

of statistical tests such as the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC) and visual inspection. Diagnostic plots were rarely mentioned and even more rarely presented. This may partly be due to lack of space or not publishing appendices submitted by the manufacturer.

Validation approaches that were reported or presented are shown in *Table 3.* External validity of extrapolations, plausibility with clinical practice and biological/ clinical explanation were rarely explored. No clinical rationale was provided for the modelling approaches in most cases.

Structural uncertainty was explored by assessing the effect of applying various extrapolation methods on the cost-effectiveness results with corresponding ICERs reported in 31% of models.

VALIDATION OF FINAL CHOICE OF DISTRIBUTION	
	PFS / OS
Proportionality test mentioned?	6 (20.7%)
Monotonicity tested specifically?	2 (6.9%)
Fits observational data well graphically?	7 (24.1%)
Statistical tests presented or mentioned (e.g. AIC, BIC, -2LL)?	10 (34.5%)
Diagnostic plots presented or mentioned?	14 (48.3%)
Plausibility with what is seen in clinical practice discussed?	3 (10.3%)
Biological/clinical explanation discussed?	2 (6.9%)

table 3

Comments on survival analysis by the ERG

Modelling of OS and PFS and their extrapolation was an important topic in all ERG reports due to its critical impact on results. Alternative scenarios for survival modelling were explored and implemented in the submitted models by the ERG in several STAs. The most important comments and criticisms were that:

1. choice of survival function was not justified;
2. the parametric distribution could not capture changes in hazard expected during the course of the disease, therefore, a piecewise model would have been preferred;
3. no clinical rationale was provided for the modelling approach;
4. the long-term extrapolation of OS was highly uncertain; and,
5. use of extrapolation methods applied in prior TAs as guidance without exploring the data.

Criticisms were consistent for ERG groups and the ERGs often had strong views about the appropriate extrapolation methods. However, there were often differences between the views of the different ERGs.

DISCUSSION

Based on the examined evidence, methods of selecting the extrapolation approach in oncology TAs by manufacturers and ERGs were heterogeneous despite the available guidance.

Several assessments incorporated some form of parametric modelling for the extrapolation of survival data, either in the form of a single curve or as piecewise models. Kaplan-Meier curves were also often relied on for the duration of the pivotal trial in the assessment, with the distributions incorporated only from the end of the follow-up period. For the final choice of the approach, the majority of submissions depended mainly on the statistical goodness-of-fit criteria and visual assessment.

Beyond statistical goodness of fit and visual assessment, clinicians' opinions about the shape of the OS curves and pragmatic modelling aspects were also taken into account. A pragmatic aspect is important in the case when indirect treatment comparison is only available via incorporation of a hazard ratio estimates. That most often led to selection of the Weibull model despite its worse fit in terms of statistical measures.

Biological/clinical explanation was discussed in very limited number of cases—making it the biggest gap in extrapolation practices. However, validation by key opinion leaders was more often sought in TAs published in 2013, particularly for the selection of the base case distribution for OS as the extent of the extrapolation, and therefore the uncertainty about the tail of the curve is much greater than for PFS.

Although the recently published methodological guidelines recommend various steps to reduce this uncertainty, the implementation of these is still rare. However as a welcome new trend, for some more recent models, actual cost-effectiveness outcomes are presented not only for the base case extrapolation but for alternatives, addressing a key structural uncertainty in modelling.

Muszbek and colleagues[3] along with Grieve, et al.,[4] suggest that large registries may be a good source of data for testing plausibility. However, such a validation comes with its own issues, such as how to handle differences between the registry data and the trial population, and how to account for changing treatment patterns over time in registries.

Ishak, et al.,[7] review the most commonly used statistical distributions, and describe an objective process of identifying the most suitable parametric distribution in a given dataset that can be applied with both individual-patient data and with survival probabilities derived from published Kaplan-Meier curves. Grieve[4] and colleagues highlight some weak points of the DSU guidelines and encourage further debate. Bagust and Beale,[8] from the Liverpool Evidence Review Group for NICE, aim to provide a "practical guide" to the broad health technology assessment (HTA) community about extrapolation. They also criticize some points of the DSU guidance, including the use of log cumulative hazard-log time plot for diagnostics, and recommend the cumulative hazard-time plot instead; and recommend a piecewise approach, whereby the parametric function is only fitted to later parts of the Kaplan-Meier curve. The disagreement between researchers at the Liverpool ERG and the authors of the DSU guidance is tangible in the HTA reports assessed by this specific group.[5,7]

Evaluations issued by the Liverpool group criticized manufacturers for following the approach outlined by the DSU. This can be disorienting for manufacturers preparing a submission.

In light of the above discussions within and outside NICE, it would be helpful if further specific guidance would be developed on:

- How to carry out external validation/plausibility testing, including guidance on external validation
  - for clinical/biological plausibility
  - with the help of additional datasets, including registry data
- The relative importance of the various elements of testing (statistical criteria; clinician opinion, external data)

The present analysis has important limitations. It relies on information reported in the published TA documents. Potentially not all validation work was reported; e.g., diagnostic tests for survival analyses may have been conducted and not reported, or presented only in appendices to the main body of the manufacturer submission and therefore not publicly available. As a consequence, practices may be closer to the guidelines than reported here. Second, several changes were made to the extrapolation approach during the appraisal process, and these changes were not incorporated in the data extraction.

CONCLUSION

Since the publication of various publications on survival extrapolation, and the publication of NICE technology assessment reports, the practice and description of extrapolations have improved within the oncology technology appraisals in the UK, contributing to more transparent decision-making. However, there are still several areas where further discussion and more specific guidance would be welcome.

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Evidera Presents at ISPOR's 19th Annual International Meeting

May 31–June 4, 2014 Montreal, Canada

SHORT COURSES

MORNING SESSION: Sun, June 1
8:00am–12:00pm

Discrete Event Simulation for Economic Analyses—Concepts

INSTRUCTORS: **J. Jaime Caro, MDCM, FRCPC, FACP,** Chief Scientist, Evidera; **Jorgen Moller, MSc Mech Eng,** VP, Modeling Technologies, Evidera; **Denis Getsios,** VP, Modeling and Simulation, Evidera

AFTERNOON SESSION: Sun, June 1
1:00–5:00pm

Discrete Event Simulation for Economic Analyses—Applications

INSTRUCTORS: **J. Jaime Caro, MDCM, FRCPC, FACP,** Chief Scientist, Evidera; **Jorgen Moller, MSc Mech Eng,** VP, Modeling Technologies, Evidera; **Denis Getsios,** VP, Modeling and Simulation, Evidera

WORKSHOPS

SESSION III: Tues, June 3
5:00–6:00pm

W17: Understanding and Modeling Business Decisions in Market Access and Reimbursement Using Multi-Criteria Decision Analysis Techniques

DISCUSSION LEADERS: Ansgar Hebborn, PhD, Head, Global Market Access Policy, F. Hoffmann-La Roche; Maarten J. IJzerman, PhD, Prof. and Chair, Univ. of Twente; **Kevin Marsh, PhD,** Sr. Research Scientist and European Dir., Modeling and Simulation, Evidera; **Tereza Lanitis, MSc,** Sr. Research Associate, Modeling and Simulation, Evidera

SESSION IV: Wed, June 4
1:45–2:45pm

W24: The Role of Patient-Reported Outcomes Data in Health Care Decision Making in Rare Diseases

DISCUSSION LEADERS: **Margaret K. Vernon, PhD,** Sr. Research Scientist and European Dir., Outcomes Research, Evidera; Philip Ruff, PhD, Dir. Global Market Access, Shire; Isabel Kalofonos, MBA, Dir. Global Market Access, Shire; **Asha Hareendran, PhD,** Sr. Research Leader, Outcomes Research, Evidera

W26: Big Data and Little Diseases: Meeting the Challenges for Rare Disease Outcomes Research

DISCUSSION LEADERS: Alaa Hamed, MD, MPH, MBA, Sr. Dir. Evidence and Value Development, Genzyme; **Alex Ward, PhD, MRPharmS,** Sr. Research Scientist, Modeling and Simulation, Evidera; Sumeet Panjabi, PhD, Dir. Global Health Economics, Onyx Pharmaceuticals; **Kathleen W. Wyrwich, PhD,** Sr. Research Leader, Outcomes Research, Evidera

ISPOR FORUM

SESSION II: Tues, June 3
6:15–7:15pm

PRO and OBSRO Measurement in Rare Disease Clinical Trials—Emerging Good Practices

MODERATOR: Laurie B. Burke, RPh, MPH, Founder, LORA Group, LLC;
SPEAKERS: Katy Benjamin, PhD, Dir. Patient Reported Outcomes, ICON; **Margaret Vernon, PhD,** Sr. Research Scientist, Outcomes Research, Evidera

PODIUM PRESENTATIONS

SESSION I: Mon, June 2
2:15–3:15pm

PP1: Preferences for Prostate Cancer Outcomes: A Comparison of Patient and General Population Perspectives

Gries K, Regier D, Ramsey S, Patrick D

SESSION II: Mon, June 2
3:45–4:45pm

UT2: Health State Utilities Associated with Attributes of Treatments for Hepatitis C

Matza LS, Sapra S, Kalsekar A, Dillon JF, **Davies E, Devine MK, Jordan J, Landrian A,** Feeny DH

POSTER PRESENTATIONS

SESSION I: Mon, June 2
8:30am–2:15pm

PND11: Budget Impact Analysis of Using Amyloid Positron Emission Tomography (PET) in the Diagnosis of Alzheimer's Disease (AD) in the United States (US)

Hernandez L, Guo S, Sandor S

PHP143: Multi Criteria Decision Analysis Methods in Health Care: Current Status, Good Practice and Future Recommendations

Thokala P, **Marsh K,** Devlin N, van Til J, Reddy B, Baltussen R, IJzerman MJ

PND45: Screening for PBA Symptoms Using a Single Question vs. a 7 Question Measure and Assessment of the Association of PBA Symptoms with HRQOL Burden

Fonda JR, McGlinchey RE, Rudolph JL, Milberg WP, **Hunt PR,** Yonan C, **Reynolds MW**

PHP98: Shortcutting Drug Development: Economic Benefits of Using Genome-Wide Association Studies (GWAS) to Reposition Existing Drugs to Other Therapeutic Areas

Caro JJ, Richards B

SESSION II: Mon, June 2
3:45–7:45pm

PCN88: A Novel Colorectal Cancer Model with Sessile Serrated Adenoma Pathway to Evaluate the Cost-Effectiveness of Various Screening Strategies

Zheng P, Dinh T

PCV81: An Economic Analysis of a Hypothetical Value-Based Insurance Design Program Using the Archimedes Model

Rael MB

PCV49: Long Term Health Care Costs for Patients with Stable Coronary Artery Disease (CAD) After Myocardial Infarction in US

Mellstrom C, **Hunt PR,** Kem DM, Westergaard M, Wu B, Tunceli O, Hammar N, DeVore S

PCV75: Pharmacoeconomic Analysis of Dabigatran in Patients with Atrial Fibrillation: Comparison with Rivaroxaban or Apixaban

Gay-Molina JG, Herran S, **Sorensen S,** Gonschior A

PCV29: Rates of Acute Coronary Events and All Cause Mortality in Patients with Stable Coronary Artery Disease (CAD) After Myocardial Infarction and Additional Cardiovascular Risk Factors

DeVore S, Mellstrom C, **Hunt PR,** Kern DM, Tunceli O, Wu B Westergaard M, Hammar N

PCV114: Statin Dosing Patterns and Lipid Levels Among Patients with High-Risk Vascular Disease

Nordstrom B, Collins J, Donaldson R, Engelman W, Zhu Y, Zhao Z

PCN22: The Effect of Groundbreaking Medical Therapy on the Incidence of Disease: A Case Study of Rituximab and Non-Hodgkin's Lymphoma

Rotella P, Telsch D, Swain R, Ishak J, Reynolds M, Robinson Jr. D

PCV115: Treatment Patterns with Lipid-Altering Drugs in High-Risk Vascular Disease in the United Kingdom

Zhao Z, Zhu Y, Collins J, **Donaldson R, Engelman W, Nordstrom B**

PCV67: Validation of the Apixaban Cost-Effectiveness Model in Patients with Non-Valvular Atrial Fibrillation

Kachroo S, Phatak H, Dorian P, **Kongnakorn T, Lanitis T,** Kuznik A, Mardekian J, Liu X, Lawrence J, Lip GY

SESSION III: Tues, June 3
8:30am–2:15pm

PRS58: Evaluation of the Psychometric Properties of the Early Morning Symptoms of COPD Instrument (EMSCI)

Mocarski M, **Hareendran A,** Jen MH, **Zaiser E,** Make B

PRS57: Pediatric Asthma Symptoms: Assessments by Subjects and Caregivers

Nelson L, **Currie B,** Norquist J, Peter S, **Vernon MK**

PIH54: Time Trade-off Utility Assessment with a 10-year Time Horizon: When Should Alternative Approaches be Considered?

Boye KS, **Matza LS,** Feeny DH, Johnston JA, Bowman L, **Jordan J**

PHS74: Treatment Patterns and Healthcare Resource Utilization of Patients with Neuroendocrine Tumors in the United States

Chuang CC, Dinet J, Bhurke S, Chen SY, Brulais S, Gabriel S

Stop by Booth 70!

- Speak with our presenters, scientists and consultants
- Learn more about Evidera's acquisition of Archimedes
- See how Evidera can support your evidence needs
- Meet with our experts to discuss specific product needs and challenges
- Identify opportunities to join Evidera's team

PHS47: Utilization, Costs and Reimbursement of Inpatient and Ambulatory Treatment of Acute Bacterial Skin and Skin Structure Infections among the Medicare Fee-For-Service Population

LaPensee K, Fan W, Sulham K, **Ciarametaro M,** Hahn B

PHS75: Utilization, Costs and Reimbursement of Inpatient Treatment of Acute Bacterial Skin and Skin Structure Infections among the Medicare Fee-For-Service Population

LaPensee K, Fan W, **Ciarametaro M,** Hahn B

SESSION IV: Tues, June 3 3:45–7:45pm

PRM49: A Software Platform to Synthesize Evidence from Heterogeneous Data Sources

Shum K, Zheng P, Dinh T, Azimi M, Inumpudi A

PSY28: A Systematic Literature Review of Economic Evaluations Related to Patients with Relapsed or Relapsed and Refractory Multiple Myeloma

Rizzo M, Xu Y, Panjabi S, **Iheanacho I**

PMH67: Content Validity of the SR-MAD RX Opioids Instrument for use in Patients with Acute or Chronic Pain

Setnick B, Roland CL, Barsdof AL, **Brooks A, Coyne KS**

PRM88: Evaluation of Dimensionality in Physical Functioning Construct When Combining the Health Assessment Questionnaire with the SF-36 Health Survey Physical Functioning Scale

Lin CY, Al Sawah S, Zhu B, **Wyrwich K, Kawata A,** Zhang X, Naegeli AN

PRM129: Hybrid Time and Motion, Patient Survey and Chart Review Study Methodology: A Case Study of Subcutaneous Allergen Immunotherapy in the US and Canada

Yeomans K, Payne KA, **Blume SW,** Tao S, Hubbard SM, Allen-Ramey F

PMH63: Mediation Analysis of Effect of Lurasidone on Patient Functioning in Bipolar Depression: Direct Effects and Indirect Effects Mediated Through Improvement in Depression Symptoms

Hassan M, **Dansie E,** Rajagopalan K, **Wyrwich K,** Loebel A, Pikalov A

PRM141: Modeling All-Cause Mortality in Health Economic Models

Hernandez L, Altincatal A, Pelligra C

PSY43: Psychometric Properties of the ADHD Rating Scale-IV (ADHD RS-IV) and Adult ADHD Self-Report Scale (ASRS) in a Phase 3B Clinical Trial of Patients with Phenylketonuria

Wyrwich KW, Auguste P, Yu R, Zhang C, Yu S, DeWees B, Winslow B, Merilainen M, Prasad S

PMH67: Content Validity of the SR-MAD RX Opioids Instrument for use in Patients with Acute or Chronic Pain

Setnick B, Roland CL, Barsdof AL, **Brooks A, Coyne KS**

PMH9: The Effect of Lurasidone on Functional Remission among Patients with Bipolar Depression

Hassan M, **Dansie E,** Rajagopalan K, **Wyrwich K,** Loebel A, Pikalov A

PSY11: The Epidemiology of Gaucher Disease: A Comprehensive Review of the Literature

Nalysnyk L, Stewart A, Gilchrist A, **Rotella P, Simeone J**

SESSION V: Wed, June 4 8:45am–2:45pm

PDB101: A Discrete Choice Experiment Conducted Among Patients with Type 2 Diabetes Mellitus from the United States

Gelhorn H, Stringer S, Lee E, Palencia R

PDB41: Healthcare Resource Utilization and Costs Associated with Various Stages of Chronic Kidney Disease among Type 2 Diabetes Mellitus Patients

Chuang CC, Lee E, **Yang E, Tawah A,** Ghosh S, Chen SY

PIN101: Methodological Issues Associated with the Use of Social Media in Outcomes Research: Case Study of Adult Vaccination

Yang HK, **Abogunrin S, Cox A, Khankhel Z, Martin A, Merinopoulou E**

PDB58: Modeling the Long-term Costs and Outcomes of Antidiabetics in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events

Zheng Y, Sorensen S, Palencia R, Ruffolo A, Hass B, **Kansal A**

Upcoming Presentations

COOPERATIVE MEETING OF THE CMSC AND ACTRIMS

May 28–31, 2014
Dallas, TX, USA

POSTER

Understanding Drivers of Employment Change in a Multiple Sclerosis (MS) Population

Coyne K, Currie B, Landrian A, Boscoe A, Wandstrat T

EFNS/ENS JOINT CONGRESS OF EUROPEAN NEUROLOGY

May 31–June 3, 2014
Istanbul, Turkey

POSTERS

Factors Influencing Clinically-Meaningful Physical Deterioration in Patients with Relapsing-Remitting Multiple Sclerosis: Results from the ADVANCE Study

Kinter E, **Guo S, Altincatal A, Proskorovsky I,** Phillips G, Sperling B

Peginterferon beta-1a Reduces the Psychological Impact of Multiple Sclerosis Relapses: Results from the ADVANCE Study

Kinter E, **Guo S, Altincatal A, Proskorovsky I,** Phillips G, Sperling B

ERA-EDTA 51ST CONGRESS

May 31–June 3, 2014
Amsterdam, Netherlands

POSTER

A Systematic Literature Review of the Humanistic Burden of Anaemia Associated with Chronic Kidney Disease

Rizzo M, Iheanacho I, van Nooten FE, Goldsmith D

HEALTH DATAPALOOZA

June 1–3, 2014
Washington, DC, USA

WORKSHOP

Forecasting the Effects of Prevention and Population Health Management Initiatives—A Workshop Using the Archimedes Healthcare Simulator (ARCHeS)

PRESENTERS: Kenny Shum, PhD, Scientist, Modeling and Simulation, Evidera; **Richard Thi,** Business Development Associate, Evidera

QCOR (QUALITY OF CARE AND OUTCOMES RESEARCH) AMERICAN HEART ASSOCIATION

June 2–4, 2014
Baltimore, MD, USA

POSTER

Applying Clinical Trial Data to Real-World: Apixaban, Dabigatran, and Rivaroxaban

Amin A, **Stokes M, Wu N,** Gatt E, Makenbaeva D, Wiederkehr D, Lawrence JH

SMDM ANNUAL MEETING OF THE SOCIETY FOR MEDICAL DECISION MAKING

June 8–10, 2014
Antwerp, Belgium

WORKSHOP

Selecting an Appropriate Multi-Criteria Decision Analysis Weighting Method in Health Care

Kevin Marsh, PhD, Sr. Research Scientist, Modeling and Simulation, Evidera; Kimberley Hockley, Imperial College London; Praveen Thokala, Univ. of Sheffield, London; **Tereza Lanitis, MSc,** Sr. Research Associate, Modeling and Simulation, Evidera

POSTER

Uncertainty in Uncertainty: a Review of Probabilistic Sensitivity Analysis Conducted in Health Technology Appraisals

Lanitis T, Muszbek N, Tichy E

MDS 18TH INTERNATIONAL CONGRESS OF PARKINSON'S DISEASE AND MOVEMENT DISORDERS

June 8–12, 2014
Stockholm, Sweden

POSTER

AbobotulinumtoxinA in the Management of Cervical Dystonia (CD) in the United Kingdom (UK): A Budget Impact Analysis (BIA)

Dinet J, **Desai K, Brand S, Abogunrin S,** Gabriel S, Harrower T

EULAR 2014

June 11–14, 2014
Paris, France

POSTER

Evaluation of Dimensionality and Sensitivity in Physical Functioning Construct When Combining the Health Assessment Questionnaire with the SF-36 Health Survey Physical Functioning Scale

Lin CY, al Sawah S, Zhu B, **Wyrwich K, Kawata A,** Zhang X, Naegeli A

ADA 74TH SCIENTIFIC SESSIONS

June 13–17, 2014
San Francisco, CA, USA

POSTERS

The Pooled Cohort Equations for Non-Hispanic Whites Overestimates the Risk in Hispanics with Diabetes

Shum K, Zheng P, Dinh T

An Archimedes Model of Mild Hypoglycemia

Samuel S, Boye KS, **Rengarajan B,** Curtis B, Curtis S

DIA 2014 50TH ANNUAL MEETING

June 15–19, 2014
San Diego, CA, USA

ORAL PRESENTATIONS

Bolstering Development Programs in Rare Diseases: Simulating Clinical Trials with a Virtual Patient Population

Badri Rengarajan, MD, VP Medical Affairs and Sr. Principal Consultant, Evidera

Using Virtual Population Simulation to Forecast Likely Study Outcomes as a Trial is Enrolling

Badri Rengarajan, MD, VP Medical Affairs and Sr. Principal Consultant, Evidera

Using Virtual Population Simulation to Generate Insights on Drug Performance in Special Populations

Badri Rengarajan, MD, VP Medical Affairs and Sr. Principal Consultant, Evidera

ICE/ENDO 2014

June 21–24, 2014
Chicago, IL, USA

POSTERS

Reasons for Non-Treatment of Osteoporosis among Postmenopausal Patients in the United States—Patient Perspective

Krishna A, **Olsson K, Sadasivan R,** Weaver J, Sen S

Reasons for Non-Treatment of Osteoporosis among Postmenopausal Patients in the United States—Physician Perspective

Krishna A, **Sadasivan R, Olsson K,** Weaver J, Sen S

EU WONCA

July 2–5, 2014
Lisbon, Portugal

POSTER

The Patient Impact of Opioid-Induced Constipation (OIC) on Pain Management and GI Symptoms

Datto C, LoCasale R, Wilson H, **Coyne K,** Tack J

AAIC ALZHEIMER'S ASSOCIATION INTERNATIONAL CONFERENCE

July 13–17, 2014
Copenhagen, Denmark

POSTERS

A Prospective, Systematic Literature Review and Meta-Analyses to Evaluate Brain Amyloid by Positron Emission Tomography (PET) Imaging as Biomarkers of Alzheimer's Disease (AD) Progression

Ashaye AO, Travers KU, Strand L, Di Tanna GL, Wyman BT, Booth K, Styren S, Brashear HR, Margolin R, Schmidt M, Liu E

A Prospective, Systematic Literature Review and Meta-Analyses to Evaluate Cerebrospinal Fluid (CSF) Phosphorylated Tau (p-tau) and Total Tau (t-tau) as Biomarkers of Alzheimer's Disease (AD) Progression

Ashaye AO, Travers KU, Strand L, Olsson K, Di Tanna GL, Booth K, Styren S, Brashear HR, Streffer J, Liu E

A Prospective, Systematic Literature Review and Meta-Analyses to Evaluate Global and Regional Brain Volumes by Structural MRI as Biomarkers of Alzheimer's Disease (AD) Progression

Ashaye AO, Travers KU, Strand L, Olsson K, Di Tanna GL, Wyman BT, Booth K, Styren S, Brashear HR, Einstein S, Novak G, Liu E

JSM JOINT STATISTICAL MEETINGS

Aug 2–7, 2014
Boston, MA, USA

SESSION SPEAKER

Big Data Tool for Estimating Baseline Event Rates in Clinical Trials

Roshan Shah, Manager, Client Services, Evidera

ESC EUROPEAN SOCIETY OF CARDIOLOGY

Aug 30–Sep 3, 2014
Barcelona, Spain

POSTERS

Cost-effectiveness of Apixaban Compared to Edoxaban for Stroke Prevention in Non-valvular Atrial Fibrillation

Lip GYH, **Kongnakorn T, Lanitis T,** Phatak H, Liu JXC, Kuznik A, Lawrence J, Dorian P

Cost-effectiveness of Apixaban Compared to Other Anticoagulants for the Acute (6-month) Treatment of Venous Thromboembolism

Lanitis T, Leipold R, Hamilton M, Rublee D, **Quon P, Browne C,** Cohen A

ISPOR 6TH ASIA PACIFIC CONFERENCE

Sept 6–9, 2014
Beijing, China

WORKSHOPS

The German Efficiency Frontier Approach for Economic Evaluation and the Applicability in Asia

DISCUSSION LEADERS: Isao Kamae, MD, DrPH, Prof., HTA and Public Policy Project, The Univ. of Tokyo; **J. Jaime Caro, MDCM, FRCPC, FACP,** Adjunct Prof. of Medicine, Epidemiology and Biostatistics, McGill Univ. and Chief Scientist, Evidera; Andreas Gerber, PhD, MD, Head, Health Economics, IQWiG

Development of Individual Simulation Models for HTA Submission in Asia

DISCUSSION LEADERS: Ying Zheng, MS, MHSA, Research Associate, Modeling and Simulation, Evidera; Roberto Palencia, MA, Global Manager, HE&OR, Corporate Market Access, Pricing and Outcomes Research, Boehringer Ingelheim; **Thitima Kongnakorn, PhD,** Research Scientist, Modeling and Simulation, Evidera; John Cai, PhD, Director, Center for Healthcare Management and Policy, China Europe International Business School

DGRh CONGRESS—2014

Sep 17–20, 2014
Dusseldorf, Germany

POSTERS

Resource Use and Associated Costs Among Patients with Rheumatoid Arthritis in Germany

Hartz S, **Lambrelli D, Karlsdotter K,** Barrett A, Zimmermann T, Paget MA, de la Torre I, Bergner R, Schubert I, Hein R

Treatment Patterns of Patients with Rheumatoid Arthritis in Germany

Lambrelli D, Barrett A, Hartz S, ZimmermannT, Paget MA, Liu-Leage S, Bergner R, Schubert I, Hein R

ISOQOL 21ST ANNUAL CONFERENCE

Oct 15–18, 2014
Berlin, Germany

WORKSHOPS

An Introduction to Health-Related Quality of Life Assessment

Heather Gelhorn, PhD, Research Scientist, Outcomes Research, Evidera; **Kathleen W. Wyrwich, PhD,** Sr. Research Leader, Outcomes Research, Evidera

Translation Methodology for Clinical Outcomes Assessments in Global Trials

Mona Martin, RN, MPA, Exec. Dir., Health Research Associates; Valeska Kantzer, Language Dept. Manager, Health Research Associates; **Sonya Eremenco, MA,** Director, ePRO New Products, Outcomes Research, Evidera; Katrin Conway, Managing Director, Mapi Research Trust; Donald Patrick, PhD, MSPH, Seattle Quality of Life Group

AAPM&R 2014 ANNUAL ASSEMBLY

Nov 13–16, 2014
San Diego, CA, USA

ORAL PRESENTATION

Economic Modeling of the Use of Botulinum Toxin A in a Homogenous Patient Population Based on Real-life Clinical Practice: ULIS-II (The Upper Limb International Spasticity Study)

Jerome Dinet, PharmD, Evidence Generation Director, Ipsen; **Dimitra Lambrelli, PhD,** Research Scientist, Retrospective Observational Studies, Evidera; Jovita Balcaitiene, Global Medical Affairs Director, Ipsen

Recent Presentations

ATS 2014 INTERNATIONAL CONFERENCE

May 16–21, 2014
San Diego, CA, USA

POSTERS

Can We Find Undiagnosed, High-Risk Patients With COPD In Primary Care? Qualitative Results Of A Multi-Method Study To Develop A New Screening Tool

Leidy NK, Murray L, Steenrod A, Kim K, Clifford S, Houfek JF, Mannino DM, Thomashow B, Rennard SI, Make BJ, Yawn B, Han MK, Martinez FJ

Can We Find Undiagnosed, High-Risk Patients With COPD In Primary Care? Using Random Forests To Identify Best Variable Sets For COPD Case Identification

Leidy NK, Malley KG, Steenrod A, Williams A, Mannino D, Make B, Thomashow B, Rennard S, Houfek JF, Yawn B, Han MK, Martinez F

Clinical Characteristics in the Two-year Pre-diagnosis Period among Patients Newly Diagnosed with Idiopathic Pulmonary Fibrosis in US

Yu Y, **Wu N, Chuang CC, Wang R, Benjamin N,** Coultas D

Cost-effectiveness of Riociguat for the Treatment of Chronic Thromboembolic Pulmonary Hypertension (CTEPH) in the United States

Kadambi A, Chapman R, Quon PL, Brand S, Sikirica M, Joish VN

Evaluation of the Psychometric Properties of the Nighttime Symptoms of COPD Instrument (NiSCI)

Mocarski M, **Hareendran A,** Jen MH, **Zaiser E,** Make BJ

Study Design of a 1-year Prospective, Observational Registry of Treatment Patterns and Outcomes for Patients with Chronic Obstructive Pulmonary Disease (iSTEP)

Massaro S, Zhang J, Williams J, Hakanson D, Arcona S, Turner SJ, **Wilcox TK,** Desrosiers MP, Payne K

AACE 23RD ANNUAL SCIENTIFIC AND CLINICAL CONGRESS

May 14–18, 2014
Las Vegas, NV, USA

POSTER

The Economic Burden of High Body Mass Index (BMI) by Glycemic Stage in the United States

Li Q, Blume SW, Huang JC, Hammer M

BIG DATA IN PHARMA CONFERENCE

May 12–13, 2014
London, UK

WORKSHOP

Designing and Commissioning Studies Using Big Data to Support Drug Development and Marketing

Andrew Cox, PhD, Sr. Research Assoc.; **Rob Thwaites, MCom,** VP, Strategy Solutions; **Radek Wasiak, PhD,** Sr. Research Scientist, Evidera

APA ANNUAL MEETING

May 3–7, 2014
New York, NY, USA

POSTER

The Effect of Lurasidone on Functional Remission Measured by the Sheehan Disability Scale

Hassan M, **Dansie E,** Rajagopalan K, **Wyrwich K,** Loebel A, Pikalov A

PRO/COA SUMMIT

May 6–7, 2014
Philadelphia, PA, USA

SESSION SPEAKER

Psychometrics—Rasch Item Response Theory vs. Classical Test Theory

Kathleen W. Wyrwich, PhD, Sr. Research Leader, Outcomes Research, Evidera; Joseph C. Cappelleri, PhD, Sr. Director, Biostatistics, Pfizer

DDW DIGESTIVE DISEASE WEEK

May 3–6, 2014
Chicago, IL, USA

POSTERS

Symptom Burden and Treatment of Patients with Opioid-Induced Constipation for Non-Cancer Pain

LoCasale R, Datto C, **Sexton C, Coyne K,** Yeomans K, Chavoshi S, King F, Tack J

Comparing Gastroparesis Symptoms Severity between Patients with Idiopathic and Diabetic Gastroparesis: The GCSI-DD Reliably Assesses Symptoms from both Diabetic and Idiopathic Gastroparesis

Revicki DA, Camilleri M, Parkman HP

EVIDERA ESTABLISHES CENTERS OF EXCELLENCE FOCUSED ON KEY SCIENTIFIC DISCIPLINES

Evidera is pleased to announce the creation of Centers of Excellence (CoEs) in:

- Epidemiology
- Health Economics
- Statistics

These CoEs have been established to ensure we remain on the forefront of science in each of these fields. CoEs in the areas of Outcomes Research and Pricing and Reimbursement are under development and will be announced in the coming months, and additional CoEs may be created as the company expands into other areas.

The goals of these CoEs are to:

- Guarantee Evidera remains the scientific leader in each discipline
- Ensure the application of best practices in these core disciplines
- Develop novel methodologies for incorporation into Evidera offerings
- Enhance our flexible and integrated response to client priorities through further scientific collaboration across the company
- Promote best-in-class capabilities, skills and training in these core disciplines

"At the core of Evidera's mission is to bring world-class science, methodological expertise, and thought leadership to bear on everything we do," says Dr. Jaime Caro, Chief Scientist at Evidera. "The creation of these Centers of Excellence supports this mission and our commitment to scientific integrity and providing the best solutions to today's healthcare challenges."

We are pleased to announce the first three Centers of Excellence and the Executive Directors who will lead them.

Agnes Benedict, MSc, MA
(Budapest, Hungary)
Senior Research Scientist

Executive Director,
Center of Excellence for Health Economics

K. Jack Ishak, PhD
(Montreal, Canada)
Senior Research Scientist

Executive Director,
Center of Excellence for Statistics

Matthew W. Reynolds, PhD
(Lexington, MA)
Vice President

Executive Director,
Center of Excellence for Epidemiology

Company News

EVIDERA WELCOMES NEW SENIOR STAFF

Stephanie Reisinger
Vice President,
Technology Solutions

Stephanie (Steph) Reisinger leads a team tasked with building and launching new technology products as well as supporting the technology development requirements of other Evidera business units. The creation of this position is an acknowledgement of the increasingly important role of technology-enabled solutions to our clients and the healthcare industry. Steph has more than 15 years' experience working in the life sciences industry and is a recognized thought leader in the development of healthcare analytic technology throughout the pharmaceutical industry. She joins Evidera from UBC, where she led the database analytics automation practice area. In that role, Steph was responsible for overseeing the development and delivery of innovative software to facilitate rapid analysis of large patient databases, with a particular focus on pharmacovigilance and safety signal detection tools.

Previously, Steph held senior positions with ProSanos (acquired by UBC in 2010), where she led the co-development of innovative data analytic software that became the market leader within three years of launch, and GeneFormatics, where she led the development of the company's database and data mining technologies for identifying potential drug targets using genomic data. During her career, she has also been an active collaborator with organizations such as the Observational Medical Outcomes Partnership (OMOP) and the Observational Health Data Sciences and Informatics (OHDSI) Program. Steph received her undergraduate degree from Widener University in Philadelphia, and is currently pursuing her MBA from Penn State University.

Susanne Michel, MD
European Practice Lead,
Payer Strategy

Dr. Susanne Michel has more than 11 years of experience in market access consulting and delivering measurable business results in new product development and repositioning products on the market. Her expertise includes HCV, oncology, psychiatric conditions and diabetes, and she has experience in projects such as clinical trial assessment, payer positioning, value strategy, and pricing strategy.

Prior to joining Evidera in April 2014, she was vice president at Kantar Health leading the EU Market Access team and was responsible for business development, engaging with payer bodies and developing new service offerings. From 2005 to 2008, Susanne was a director at THS, a specialized market access and pricing and reimbursement consulting company. She has worked with the top 10 pharmaceutical companies for a broad range of indications to deliver targeted strategic advice on how to position products in market access. Susanne also spent three years at PricewaterhouseCoopers where she was the Leader of the European Health Policy Research Institute, as well as time with the Department of Health in England where she was a strategy policy leader for two years when NICE was established. She has also worked for the Ministry of Health in Berlin.

Susanne holds a medical degree and a Masters in Strategy from the London School of Economics and Political Science.

META RESEARCH—A NEW NAME FOR AN EXPANDING EVIDERA TEAM

The Evidera team specializing in evidence review and synthesis has changed their name to Meta Research to better reflect the expanding services they provide to clients. In addition to providing traditional focused and systematic literature reviews and meta-analysis, this team also partners with clients on creative, integrated, high-quality, and trusted solutions through a combination of therapeutic expertise and new technologically and methodologically advanced offerings.

The new name encompasses the larger and fast developing area of meta research and represents the value we place on our specialized research using both traditional approaches (e.g., systematic literature reviews of peer-reviewed publications) as well as newer ways of synthesizing information (e.g., social media reviews, other growing areas of healthcare information and data). As the industry changes and sources of information become more diverse, we see the need to change our way of thinking and working to provide the best solutions to our clients.

The term 'meta research' means 'conducting research about research'. Recent years have seen an increase in the use of the term in its various forms (e.g., meta analysis) and an increased recognition of its importance (e.g., the recent establishment of the Meta Research Innovation Center at Stanford University). The new name emphasizes both the type (i.e., meta) and the nature of our work (i.e., research).

Our Meta Research team consists of approximately 30 staff who are located across our offices in the U.S. and UK and is comprised of epidemiologists, health economists and clinicians.

Company News

SENIOR LEVEL PROMOTIONS ANNOUNCED

Luke Boulanger, MBA
(Lexington, MA)

Executive Director, Retrospective Observational Studies

Luke is also a Senior Research Scientist.

Denis Getsios
(Lexington, MA)

Vice President, Modeling and Simulation

Asha Hareendran, PhD
(London)

Senior Research Leader, Outcomes Research

Becky Hyde
(Bethesda, MD)

Executive Vice President, Commercial

Dimitra Lambrelli, PhD
(London)

Research Scientist, Retrospective Observational Studies

Clark Paramore, MSPH
(Lexington, MA)

Vice President, Strategy Solutions

Edit Remak, MSc
(Budapest)

Senior Research Scientist, Modeling and Simulation

Radek Wasiak, PhD
(London)

Executive Director, Meta Research

Radek is also a Senior Research Scientist.

EVIDERA OPENS NEW EUROPEAN HEADQUARTERS

Evidera has opened a new London office, consolidating two previous sites in the city, to house approximately 100 of our 350 market access and evidence experts. This new European head office will accommodate our rapidly growing team, better facilitate client collaboration, and strengthen our global footprint. Evidera also has offices in Bethesda, Maryland (U.S. headquarters); Budapest; Lexington, Massachusetts; Montreal; San Francisco, California; and Seattle, Washington.

The new space, customized to facilitate collaboration between the company's teams, is located in the thriving west London office hub of Hammersmith, alongside major corporations such as L'Oreal and Coca-Cola. Well placed for international travel and convenient access within London, the office provides a modern, comfortable and effective space for staff and clients to work together collaboratively. The bright, open design will address the needs of the business as it grows and facilitate expansion into new and adjacent services.

The main phone numbers, as well as all direct dial numbers for our London staff, have changed. The main address and phone numbers for this new office are listed here.

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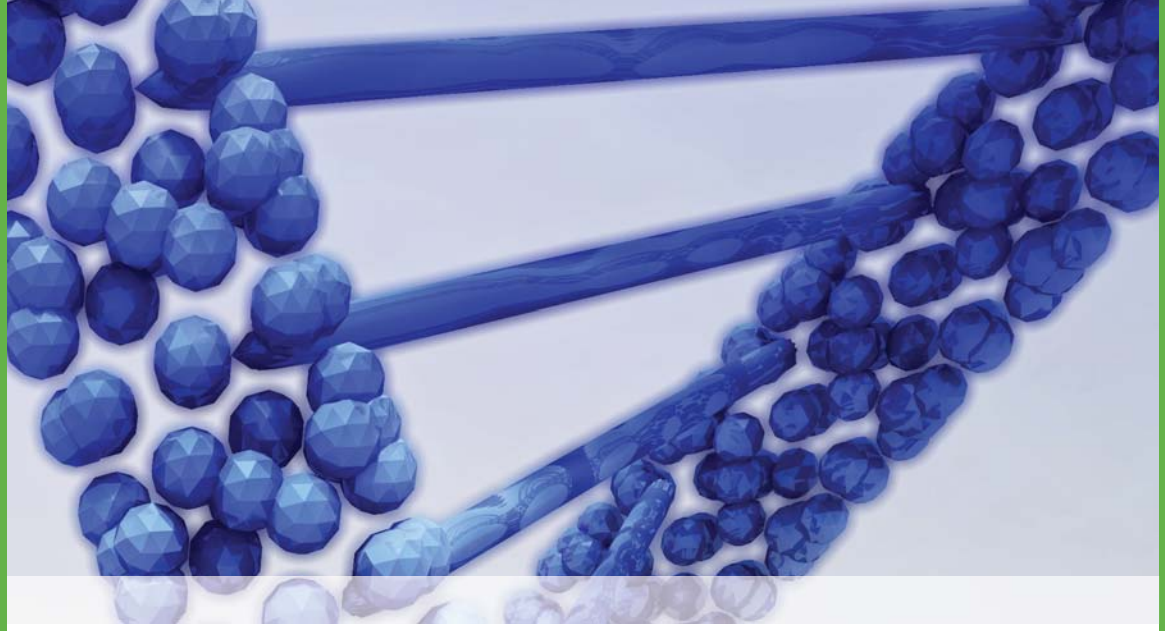
fax + 44 (0) 208 576 5195



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The Evidence Forum is an official publication of Evidera, providing evidence, value and insight through evidence-based solutions that enhance patient care and help people live longer, healthier lives.

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