WORLDWIDE CLINICAL TRIALS

WHITE PAPER

ENSURING ACCESS AND APPROVAL FOR INNOVATIVE THERAPIES IN SCLERODERMA

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ENSURING ACCESS AS WELL AS APPROVAL

Clinical research and development programs for innovative therapy must accommodate the diverse data needs of multiple stakeholders. Ensuring regulatory approval and market authorization will have primacy; however, creating a clinical trial database that facilitates adoption and patient access is part of the mandate.

Design and operational approaches that enhance product value require planning and preemptive problem-solving. It begins with a systematic review of potential barriers to formulary placement and reimbursement to inform program design and concludes with practical suggestions for trial design, study placement, and patient outcomes (as opposed to study measures) that may facilitate favorable review. The strategic imperative is to create an integrated program capable of demonstrating the "value" of a new product, as well as clinical utility and therapeutic novelty.

IT IS OUTCOMES, NOT MEASURES

FDA approval of a new therapy can bring much-needed relief to patients – as long as they have access to it. In the US particularly, if payers dictating formulary access and reimbursement are unwilling to add a new drug to their formulary, or to reimburse that therapy at a level commensurate with its clinical utility, the efficacy of the new treatment measured through traditional measures of symptomatology or disease progression within randomized controlled trials is only partially successful. The spectrum of objectives addressed for commercial research and development activities must result in a product which is "approvable" as well as "accessible."

This general constraint is present across diverse indications, particularly those characterized by significant morbidity such as systemic sclerosis (SSc).

For these indications, the cost of therapy should convincingly map against reductions in healthcare utilization that have been demonstrated empirically as part of the clinical development program.

In the absence of these data, methods of controlling patient access within commercial plans of the US may be imposed, including preauthorization, high coinsurance or prohibitive co-pays; insistence on step-edit therapy which in aggregate result in restricted adoption and access unless data are available at the time of launch to inform these decisions.

The type of clinical data required to influence decisions impacting adoption and access may vary considerably by payer; e.g., Centers for Medicare and Medicaid services versus commercial plans versus self-insured employers. Calibrating the development program against the anticipated needs of different stakeholders becomes part of the remit.

COST DRIVERS IN SYSTEMIC SCLEROSIS

A 2017 review of the literature found that, in the US, the total direct annual health care costs of SSc were reported to be $17,365 to $18,396 per patient. Direct costs reported included hospitalizations, outpatient visits, and medication.[1] Ambulatory costs accounted for the largest portion of overall health care costs among patients with SSc (38.7% of total costs). Monitoring hospitalizations, outpatient visits, and the extent and detail of medication use provide useful parameters for incorporation into prospective clinical trials.

The second-largest driver of overall medical costs was inpatient costs (31.0% of total costs), followed by pharmacy costs (22.2% of total costs). The review

estimated the total cost of SSc to account for $1.9 billion per year across North America. In most of the included studies, indirect costs represented the largest component of the total costs, with the relative proportion of indirect cost to total costs varying among the included studies from 35% to 73%. **Early retirement associated with disease progression was a key driver of indirect costs.**

Costs associated with the diffuse form of SSc were higher than those of the limited form of disease, as might be anticipated. Disease severity, health status, and younger age had a great impact on economic burden. The presence of SSc-related complications was associated with increased costs, reinforcing general observations that it is the presence of comorbidities and complications that are most impactful on healthcare expenditures.[2]

Another review found annual direct and indirect costs of SSc in the US were $1.5 billion. Morbidity represented the major cost burden, with costs of $819 million (56%) of total costs. The value of lifetime earnings lost was $179 million (12%) or $300,000 per death. **Direct costs were $462 million (32%) or $4,731 per person annually, indicating that costs are spread over the long duration of the disease.[3]**

A 2019 review examined the economic burden among commercially insured patients with SSc in the US using administrative claims data from 2005-2015. This administrative "claims-based analysis" may be particularly relevant as large percentage of patients are likely to be covered by commercial plans. The adjusted difference in annual direct and indirect costs was $12,820 and $3,103 between patients with SSc and matched controls, respectively. Increased costs were mostly driven by medical costs (difference of $9,756). In addition, patients with SSc had about 14 more days of work loss due to disability or medically related absenteeism in the first year after diagnosis.[4]

The rather recent year of this publication places an emphasis on the importance currently placed on evaluation of healthcare utilization within systemic sclerosis by payers in the US.

A 2010 review of cost-of-illness of patients with SSc in a tertiary care center found that the costs of patients with diffuse cutaneous scleroderma (dcSSc) were higher than those with intermediate cutaneous scleroderma (lcSSc) and the difference in direct costs was significant. Consistent with expectations, the greatest difference was detected in transportation costs because a higher proportion of dcSSc patients were using ambulance services with a higher frequency, but hospitalization and informal care-related costs also exceeded the limited cutaneous scleroderma (lcSSc) group's amounts. Disease activity had significant impact on both direct and indirect costs, while disease severity, disability (measured by disease severity scale (DSS), S-HAQ and - health assessment questionnaire - disability index HAQ-DI) and patients' perception of health status based upon a visual analog scale (VAS) correlated significantly only with direct costs. Severity of peripheral vascular symptoms had a significant correlation with indirect costs as well.[5] The location of studies in a tertiary care center provides additional data points in that hospitalization, emergency room visits are accessible. **"Site topology" thus becomes a variable in the selection of research centers for a prospective interventional trial.**

In aggregate, available data clearly demonstrate that the indirect and direct cost of illness of SSc is high, reasonably well defined, and could be monitored as part of a coherent research and development strategy. Common key drivers of direct costs consistently are demonstrated across studies and include hospitalizations, outpatient costs, and medications (see Figure 1 on the following page).

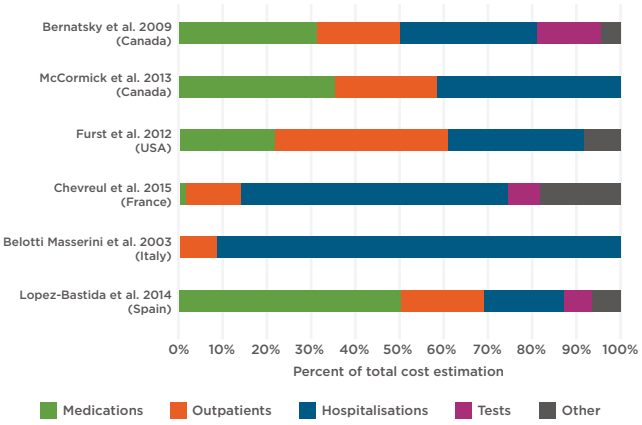
Common key drivers of indirect costs also are notable, particularly productivity losses and early retirement, and interest in both absenteeism and

presenteeism may be a variable in the decision process for self-insured employers. Costs associated with the diffuse form of SSc consistently were higher than those of the limited form of disease, with disease severity, disease activity level, health status, and younger age impacting economic burden providing additional potential covariates in analyses. Similarly, the presence of SSc-related complications was associated with increased costs.

What about the impact of geography?

Differences in expenditures by class and by country also are notable. Although healthcare utilization data may not translate well regionally due to differences in clinical care practices, the significant heterogeneity noted in the figure below suggested some countries might provide an ideal setting to measure reductions in high cost expenditures from a novel therapy (e.g., Italy versus Spain provide different country substrate for addressing this hypothesis).

Figure 1: Reported Direct Cost Drivers of SSc from Studies Conducted in Various Countries [6]



ON THE IMPORTANCE OF COMORBIDITIES

A 2018 retrospective cohort analysis examined healthcare claims databases from 2003 to 2014 to evaluate all-cause healthcare costs and mortality in patients with SSc with lung involvement. The authors found that scleroderma patients with newly diagnosed pulmonary arterial hypertension (PAH) had significantly higher healthcare costs than those without PAH, as did scleroderma patients with interstitial lung disease (ILD). Healthcare costs were highest in PAH patients – an average of $254,425 over five years. Costs for ILD patients averaged $191,107 and $101,839 for scleroderma patients with no lung disease. Costs tended to be the highest in the fifth year.[7] The majority of costs involved medicine, outpatient services, and hospital admissions. The biggest difference among the three groups was in costs for medicine. The drug costs of those with PAH were nearly four times higher than those of scleroderma patients without a lung disease and twice that of the ILD group.[8]

These data reinforce a generally acknowledged axiom that healthcare expenditures are greatly accentuated in a percentage of any given study population, reinforcing a commonly cited axiom that "10% of the patients drive 90% of the expenditures." Therefore, maximizing the inclusion of patients with more severe manifestations of SSc to provide insights on the impact of new therapy on clinical care has appreciable value.

A study sample including patients with pronounced comorbidities and concomitant medications will make the investigation more complex from an operational and analysis perspective when the primary objective is to demonstrate evidence of a clinically relevant biological effect (specialized investigative sites with highly selected patient populations). However, introducing these concepts into a later phase investigation results in a protocol that is more attractive when effectiveness rather than efficacy is important (representative sites,

more heterogeneous patients, more generalizable to clinical care).

RESTRICTIONS TO ACCESS IN THE US

Current treatments for SSc include immunosuppressives, cellular therapies, vasoactive treatments, antifibrotics, specific organ treatments and non-pharmacologic approaches.[9] For immunosuppressives, cyclophosphamide (CYC) remains the first choice for treatment of SSc-ILD in a recent review.[10] Studies have shown that CYC is able to stabilize forced vital capacity (FVC) and respiratory functions but has side effects and requires long-term treatment.[11 12] Other chemical immunosuppressants, such as tacrolimus, may represent an option for the treatment of SSc-ILD but clinical data is limited.

Rituximab, a B-cell depleting treatment, has been investigated in patients refractory to CYC with promising results.[13] Tocilizumab, a monoclonal antibody targeted against IL-6, has been investigated in the treatment of dcSSc. Results derived from clinical trials show that treatment was associated with a substantial stabilization of skin and lung involvement.[14] **Data available with diverse agents, some of which are available for other approved indications, emphasize the importance of exploring payer reimbursement policy for off-label use in order to determine variables for inclusion in trial designs.**

Autologous hematopoietic stem cell transplantation may represent a good therapeutic choice for patients with signs of rapidly progressive SSc and has shown improved prognosis with treatment,[15] yet requires further study. By far, this particular procedure garners considerable payer scrutiny because of the cost of the procedure and its uncertain therapeutic benefit.

Vasoactive treatments of PAH as a comorbidity include monotherapy with endothelin receptors antagonists, phosphodyestherase-5 inhibitors, prostacyclin analogues and riociguat, while combination therapies have demonstrated superior efficacy.[16] Among vasodilating agents, one of the most important treatments is intravenous Iloprost for the treatment of severe Raynaud's phenomenon when oral treatment is insufficient.[17] Recently, encouraging clinical data have been published on antifibrotic treatment with nintedanib, and other antifibrotic agents are in preclinical development.[18 19 20]

Targeted organ treatment has been prescribed when complications develop – for example, pyridostigmine for constipation,[21] antibiotic therapy for small intestinal bacterial overgrowth,[22] dietary intervention for gastrointestinal disturbances,[23] and laparoscopic gastric bypass for patients refractory to medical interventions.[24] ACE inhibitors are used for scleroderma renal crisis[25] and kidney transplant for end-stage renal disease.[26] Low-level light therapy and non-invasive oxygen-ozone therapy have been studied for the treatment of local SSc digital ulcers.[27 28] Finally, non-pharmacologic approaches such as exercise therapy and even pet therapy have been explored.[29 30] **This last observation reinforces an important element that might influence formulary placement and reimbursement: specifically, the utility of low-cost expenditures, lifestyle modifications, and nonpharmacologic therapy may be examined as critically as those of formal pharmacotherapy.**

Thus, a systematic survey of therapeutic modalities currently available for the treatment of indicates that a new therapeutic entity will enter a complex mosaic of novel chemical and biological entities, combination therapies, and off-label use following commercialization.

POTENTIAL PAYER SENTIMENTS IN THE US

Because there can be significant differences in policy regarding coverage and reimbursement mechanisms, Worldwide routinely recommends a survey of payer policies using a target product profile before the design of controlled studies or observational longer-term extension studies are complete. A survey including a spectrum of different plans will inform the importance of those elements of healthcare utilization that might influence policy decisions. Patient eligibility, the location of the study, and the range of potential outcomes that might be evaluated within planned interventional trials are influenced by this process.

In the US, scleroderma treatment typically is covered by commercial health insurance when Medicaid or Medicare coverage is not available. Individual drugs or treatments might not be covered by some plans, especially if the treatment is considered experimental.[31] Insurance policies for coverage of SSc can be restrictive in these cases, especially if complex procedures are required, such as stem cell transplantation. These policies use prior authorization and restrictive eligibility criteria to control access.

For example, Blue Cross Blue Shield will cover autologous hematopoietic cell transplantation as medically necessary as a treatment of SSc only if all of the following conditions are met:

- Adult patients < 69 years of age; **and**
- Maximum duration of scleroderma of five years; **and**
- Modified Rodnan Scale Scores > 15; **and**
- Internal organ involvement as noted in the Policy Guidelines; **and**
- History of < 6 months treatment with cyclophosphamide; **and**
- No active gastric antral vascular ectasia; **and**
- No exclusion criteria as noted in the Policy Guidelines.

Additionally, Blue Cross will cover this treatment only if the condition is rapidly progressing and the prognosis for survival is poor, without severe internal organ involvement.[32] Blue Cross Blue Shield also requires prior authorization and step therapy programs to approve Ofev (nintedanib) for the treatment of declining pulmonary function in patients with SSc-associated interstitial lung disease.[33] Aetna considers autologous hematopoietic cell transplantation medically necessary for the treatment of adults (18 to 69 years of age) with rapidly progressive SSc at risk of organ failure only when active interstitial lung disease is present against the background of previous scleroderma-related renal disease, and there are various exclusion criteria.

Aetna also considers adipose-tissue-derived stem cell injection for the treatment of SSc experimental and investigational because it believes its effectiveness has not been established.[34] [35] United HealthCare states that autologous adipose-derived regenerative cell therapy for scleroderma of the hands is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.[36] Likewise, Cigna considers hematopoietic stem cell transplantation for the treatment of SSc experimental, investigational, and unproven.[37]

Thus, the more expensive the overall burden of care, the more scrutiny that is likely be applied to product introduction and the more diverse and complex the matrix likely encountered for coverage. Capturing outcomes relevant for diverse objectives would be a part of a proposed program, particularly applicable to longer-term trials that might occur as part of treatment extension.

CAPTURING RELEVANT OUTCOMES

Collecting healthcare utilization data may occur either through "piggybacking" onto an established registration program or through observational research studies, occurring as a companion to an interventional research initiative. These data in aggregate may be subjected to budget impact analyses (particularly within the US) or cost-effectiveness analysis (particularly within EU focus).

For the assessment of healthcare utilization, prototypical registration studies are considered constrained in that the visit structure, assessments, caregiver access, and therefore associated expenditures are dictated by the design of the study, not the natural evolution and complication of the disease.

Therefore trial-based approaches that attempt to "piggyback" utilization data on top of requirements for a registration study are laudable but are difficult to complete before drug approval and, moreover, have limitations because of the protocol structure, eligibility criteria, inability to capture outcomes based on trial duration (frequently the studies are too short), and customarily have limitations in the methods of analysis.

An open labeled investigation, particularly with more relaxed eligibility criteria and fewer restrictions regarding the type of concomitant and supportive therapy that a patient could receive, is an informative addition to a clinical development program.

Design and operational techniques, requiring minimal modifications to a clinical development plan, include:

- Using micro-environments (integrated delivery networks (IDN)) in the US as "centers of excellence" during the registration process for a potentially pivotal study, in which every patient's transaction can be systematically captured through the use of electronic medical records existing within these environments;
- Nesting studies within strategic countries within the EU to gather utilization data in those countries that have proven to be influential for product market authorization and pricing (e.g., UK, Germany, Italy, France and Spain); and
- Creating an optional within-study claims analysis for enrolled patients within the registration study based upon administrative claims data, then applying "pre-versus-post" analyses to determine inflection points in healthcare utilization.

Program considerations, which would involve a modest increase in operational footprints, include:

- Creation of a concurrent, longitudinal cohort study for screen failure patients – every screen failure patient enters a separate observational study in which healthcare utilization on the aforementioned parameters are captured over the same time course in which the interventional study occurs for other patients; this program option also facilitates examination of temporal trends in healthcare occurring over a longer duration trial.
- Use of a Research Contact Center (direct-to-patient call center) that specifically focuses on the types of utilization that a patient with SSc would likely encounter through the use of a separate case report form (CRF) and separate sets of analyses. A representative CRF that would be adaptable to SSc might include the following elements capture using paper-based or electronic self-assessments over relatively brief durations. A customary "look back" period would be 6 months.
    - Example domains include:
        - Type of insurance coverage;
        - Number of visits to any healthcare professionals;
        - Types of healthcare professionals visited;
        - Time and money (out of pocket) spent on visits;
        - Diagnostic tests performed;
        - Time spent by caregivers assisting patient with visits to healthcare professionals;
        - Prescriptions issued, filled, and cost associated;
        - Medical equipment used and cost associated;
        - Community services used and cost associated; and
        - Difficulty working or conducting household chores or leisure activities.
- Most importantly, a set of publications can be created to establish a background for the use of an investigational product, which should be available at the time of product registration. If a new compound in SSc also achieves breakthrough designation, the importance of the publication record is key, as policies regarding formulary placement and reimbursement might be based upon more limited trial data. The publication portfolio would provide an overview of the pathophysiology of the disease affected by a novel intervention, the heterogeneity of its expression, and, importantly, the known cost drivers that have been reduced through the use of a novel therapy.

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