Optimizing Access to Care for Patients with Idiopathic Pulmonary Fibrosis

Summary report and draft recommendations

October 2015

IHE INSTITUTE OF HEALTH ECONOMICS ALBERTA CANADA

Boehringer Ingelheim

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Abbreviations

All abbreviations that have been used in this report are listed here unless the abbreviation is well known, has been used only once, or has been used only in tables or appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

CADTH	Canadian Agency for Drugs and Technologies in Health
CARE-PF	Canadian Registry for Pulmonary Fibrosis
COPD	chronic obstructive pulmonary disease
FVC	forced vital capacity
HTA	health technology assessment
IPF	idiopathic pulmonary fibrosis
IPFnet	Idiopathic Pulmonary Fibrosis Clinical Research Network
PF	pulmonary fibrosis
SGRQ	Saint George's Respiratory Questionnaire

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EVENT SUMMARY

On October 3rd, 2015, the Institute of Health Economics (IHE), through support and partnership with Boehringer Ingelheim (Canada) Ltd./Ltée., held a consensus discussion regarding special considerations for policymaking and health care decision-making for patients with idiopathic pulmonary fibrosis (IPF). Meeting details can be found in Appendix A, and a version of the background document provided to meeting participants beforehand can be found in Appendix B.

The meeting brought together 11 representatives of key stakeholders: patients, care providers, and policy researchers from across Canada. The purpose of the meeting was to discuss the current state of evidence and information regarding IPF. This led to draft recommendations for policymakers and health care administrators who must make purchasing or reimbursement decisions regarding the care and treatment of patients with IPF.

Participants first discussed factors that require consideration when implementing service for IPF patients. The following key factors were identified:

- There are many important considerations for IPF that are not specific to IPF, and apply to other degenerative, chronic, and fatal conditions (such as amyotrophic lateral sclerosis [ALS], cystic fibrosis, and cancer) that also require a focus on palliation and providing end-of-life support as well as symptom management.
    - Participants stressed the importance of recognizing that symptoms related to dyspnea and breathlessness and their significant and debilitating impact on all aspects of quality of life are central to understanding what patients value when receiving care.
    - Participants noted that the most urgent and unmet needs in IPF are adequate symptom control, the need to improve health-related quality of life, and the need for interventions to lengthen life.
- Unlike other similarly debilitating diseases, there may be less awareness of the severity of IPF as well as less available resources, compared to these other diseases.
    - Participants noted that access to pulmonary rehabilitation programs, which are recognized as providing benefits to patients, is limited.
    - Participants noted gaps in homecare services that are specific to IPF, particularly dying at home, which is valued by patients and requires coordination and planning that is not always easy to arrange.
    - Participants noted similar gaps in service for home oxygen delivery, particularly rules in place for qualifying and re-qualifying for oxygen that may better apply to other respiratory conditions.
    - Participants noted that there is considerable inconsistency in the home oxygen supply across jurisdictions (due to the above mentioned point), creating disparities in medically necessary care.
- An important consideration is the value of integrated care approaches, especially as it is convenient for patients and can improve patient experiences through providing effective patient navigation, improving diagnostic accuracy (and reducing unnecessary utilization of

services, including new interventions), improving specialist productivity, and creating a platform for standardized approaches to care.

  - Participants noted that, beyond some direct evidence for integrated care in IPF, there is also indirect evidence of benefit from other disease areas, such as chronic obstructive pulmonary disease (COPD), cystic fibrosis, and programs that coordinate transplantation for patients.
  - Participants noted that there will be some potential overlap of benefits seen with integrated care approaches in other respiratory diseases (such as the Implementing a Novel and Supportive Program of Individualized Care for Patients and Families Living with REspiratory Disease [INSPIRED] COPD program, which reduces in-hospital visits), although the magnitude of benefit may differ.
  - Participants noted that integrated care approaches through specialty centres also have spill-over benefits for informal caregivers, providing opportunities for end-of-life care, education, and other support.
  - Participants noted that specialist centres are also important for maintaining diagnostic accuracy, providing appropriate IPF specific therapies, addressing non-pharmacological interventions required, and assisting with advance care planning and terminal care palliation.

- Given the above, any new intervention for IPF has the potential to be more effective and cost-effective in the context of a multidisciplinary team.
  - Some participants noted that, despite the great potential to improve cost-effectiveness of care using integrated care approaches, these approaches will still require up-front investment.
  - Some participants noted that, despite the potential for standardization of care approaches through integrated centres, IPF information is in constant evolution, and rules will need frequent revisiting.
- Because of considerable uncertainty regarding emerging and existing treatments, it is important to consider how to collect information on an ongoing basis, in order to best revisit past decisions and re-assess available interventions.

POTENTIAL CRITERIA FOR DECISION-MAKING

Participants considered criteria identified from current models of decision-making for treatments for rare diseases, predominantly those for new medicines where frameworks have been more fully developed. The potential criteria considered for decision-making for IPF treatments were as follows:

- Severity/morbidity of the disease, including premature death
- Evidence of clinical benefit of new treatments (with some flexibility overcome by mathematical modelling or less strict statistical standards)
- Magnitude of clinical benefit
- Consideration of costs and cost-effectiveness
- Availability of alternatives
- Availability of recommended adjunct therapies (e.g., oxygen)
- Alignment with patient values
- Wider consultation with stakeholders
- Requirements for reassessment and revisiting decisions
- Starting and stopping rules

With regards to the above criteria, the following were noted by participants as important considerations:

- Clinical benefit and its magnitude needs to consider the effect of any new intervention on (health-related) quality of life, as well as quality of death and dying, in addition to whether the treatment is able to prolong survival or change the disease course.
- It is essential to consult with disease experts due to the complex nature of the disease, and in order to avoid misapplying thinking from other diseases that appear to be (but are not) similar, such as COPD.
- Participants noted that knowledge regarding IPF and its management is in evolution, and clinical care rules and treatment decisions will need frequent revisiting and re-assessment.
- While potentially sensible in other rare disease conditions, the use of stopping rules for new treatments for IPF specifically does not align well with patient values, and are difficult to accept when there is no clear evidence that supports an arbitrary cut-off or threshold.
    - In particular, participants noted that patient foreknowledge of a stopping rule, coupled with high variability in the tests used to determine stopping, can diminish quality of life and create unnecessary fear and anxiety in patients who already have a degenerative condition.
    - Participants noted that the declaration of a stopping rule, when there is no clear evidence to support its use, does not align with the value that payers and society should place on the use of evidence to support decisions.

- Treatment of IPF, especially new treatments associated with considerable clinical and economic uncertainty, should be left to integrated centres, or at least dedicated respiratory sub-specialists, as a means to reduce unnecessary utilization of services and to maximize cost-effectiveness of care.
    - Participants suggested that much of the value of dedicated sub-specialists stems from a greater improvement of diagnostic accuracy, and is a means to avoid unnecessary use of new treatments in patients who will not derive a benefit.
    - Participants noted that the use of dedicated sub-specialists and integrated care approaches is a more sustainable model of health care, and is in line with the stated values of many health systems.

DRAFT RECOMMENDATIONS FOR POLICYMAKERS

When deciding on whether to fund new goods and services (that is, innovative products, processes, or approaches to care) for patients with IPF, the panel recommends that health care policymakers consider using the following criteria to guide decision-making:

1. Clinical benefit

- Health-related quality of life
  - How does the new treatment affect the way that patients feel and function?
  - Is the measure to determine this effect valid?
- Quality of death and dying
  - Does the new intervention improve the many dimensions of the experience of dying that go beyond simple control of physical distress?
- Effect on survival and disease progression
  - Does the treatment likely affect survival or reliable measures of disease progression?

2. Patient values

- Were patients consulted regarding their current experience with the disease and what they would value with a new treatment?

3. Severity/morbidity of the disease including premature death

- IPF is a fatal condition with no cure (other than lung transplantation) or treatments to stop disease progression. The disease course is rapid with distressing symptoms of dyspnea and 50% of patients dying within four years of diagnosis. There is considerable evidence to suggest society places an increased value on improvements in health for relatively fatal illnesses.

4. Availability of alternatives

- There are no available alternatives shown to prolong survival, other than lung transplantation. Some pharmacological therapies have been shown to alter disease course.

5. Wider consultation with stakeholders

- Due to the complexity of the disease and evolving information regarding its treatment, dedicated sub-specialists and other care providers should be consulted.

6. Starting and stopping rules

- Due to the effect on patients, alternatives to stopping rules should be considered unless there is clear and compelling evidence to support them.
- Policymakers should consider outcomes-based risk sharing arrangements as one potential alternative, which can be implemented through linking jurisdictional administrative data to an existing national registry (CARE-PF, the Canadian Registry for Pulmonary Fibrosis). This will provide an opportunity to revisit decisions.

- Other alternatives may include limiting new treatments to narrow subpopulations who will receive the greatest societal benefit, or entering financial risk sharing agreements that account for increased expenditure (and potential benefit) when a stopping rule is not applied.

7. Integrated care centres and dedicated idiopathic pulmonary fibrosis sub-specialists

- New treatments should be restricted to dedicated sub-specialists or integrated care centres as a means of reducing inappropriate utilization through improved diagnostic accuracy, and as a means to increase the effectiveness (and cost-effectiveness) of treatment.
- Opportunities to fund these centres should be considered when negotiating prices for highly expensive treatments.

The IHE welcomes comments on these draft recommendations. A discussion of their wider implications is being planned for 2016 with a broader group of stakeholders.

APPENDIX A: MEETING DETAILS

Meeting Agenda

Renaissance Edmonton Airport Hotel

236 36th Street East

Edmonton, AB T9E 0V4

Saturday, October 3, 2015

10:00 am to 4:00 pm

10:00-10:15	**Opening, Introductions, and Opening Remarks**
10:15-10:45	**PART I: Background – What is known about IPF in Canada, the clinical and cost-effectiveness of options to treat it, available guidance, and rare disease frameworks that may apply?**
10:45-12:00	**Discussion of Backgrounder** - Participants have an opportunity to identify important missing information, or perceived inaccuracies
12:00-13:00	**LUNCH**
13:00-14:00	**PART II: What factors should be considered when implementing treatment programs for IPF (e.g., rarity of disease, use of stopping rules, education, multidisciplinary care)?** - What factors are currently often not considered? - What factors are most important? - Are these factors based in evidence? CONSENSUS: What minimum set of factors should be considered?
14:00-15:30	**PART III: Is IPF a rare disease? What characteristics of rare disease frameworks should be applied to IPF?** - What are the implications for future drug and non-drug reimbursement decisions? - Are there a set of criteria that should be applied to treatment funding? **BREAK** - What are the implications for research and future policy initiatives?
15:30-16:30	**Summary of Discussion** **Closing Remarks – Next Steps**

Meeting Attendees

(in alphabetical order)

Mehmood Alibhai (Observer), Boehringer Ingelheim (Canada) Ltd./Ltée.

Darlene Gallant, Pulmonary Fibrosis Support Group, Alberta

Don Husereau (Moderator)

Philip Jacobs, Institute of Health Economics

Meena Kalluri, University of Alberta

George Kaminsky, Canadian Pulmonary Fibrosis Foundation

Martin Kolb, McMaster University

Gillian Lemermeyer, Nurse and informal caregiver

Simon Lessard, Quebec Lung Association

Chris Ryerson, University of British Columbia

Harvey and Sylvia Wagner, Patients, Edmonton

Durhane Wong-Reiger, Canadian Organization for Rare Disorders

APPENDIX B: BACKGROUND DOCUMENT

Section One: Overview of Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF) is a disease characterized by loss of health-related quality of life and premature mortality. People with this disease experience scarring and swelling in their lung tissue. This damage to lungs cannot be attributed to a single cause, and ultimately interferes with gas exchange and breathing.

IPF is progressive, with some patients experiencing rapid loss of function while others much slower functional loss. Current data suggests that 50% of patients die, usually from lung failure, between two and five years from the time of diagnosis, with younger patients typically surviving longer.[1]

There are few effective therapies for IPF so far, with nothing that has been shown to definitively slow or stop the course of disease progression, with the exception of lung transplantation. Patients are provided supportive care that includes regular exercise or rehabilitation, management of associated illnesses or symptoms such as gastro-esophageal reflux and chest infection, and referral for lung transplantation. Oxygen therapy can help endurance and reduce perceptions of dyspnea.[2]

Disease Burden

The absolute number of people who suffer from this disease (that is, the disease prevalence*)* in Canada and internationally has been difficult to estimate. Part of the challenge is that disease definitions have changed with evolving clinical experiences and new diagnostic approaches. Another issue is the different ways those attempting to measure disease burden have identified and analyzed health data. Reviews of studies have identified a range of estimates from between 0.7 per 100,000 people (in Taiwan, using a narrow definition) to 63 per 100,000 (in the United States [US], using a broad definition) (see Table 1).[3]

The number of people of people who are newly diagnosed with the disease (that is, the disease incidence*)* yearly is similarly low, with a range of estimates from 0.22 per 100,000 (in Belgium, using a narrow definition) to 17.43 per 100,000 (in the US, using a broad definition). Most studies suggest males are more frequently diagnosed than females, with the majority of new cases diagnosed after 75 years of age. Several studies have suggested that this incidence may be on the rise, although whether this is actually happening or is an effect of larger awareness by clinicians or better analysis by researchers is still in question.

While the precise number of Canadians who suffer from IPF (that is, disease prevalence) is unknown, the best estimates of the number of Canadians with established disease, based on international studies, range from 5,000 to 9,000 Canadians, or an estimated 10 to 25 per 100,000 of

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[1] Brett Ley and Harold R. Collard, "Epidemiology of Idiopathic Pulmonary Fibrosis," *Clinical Epidemiology* 5 (November 25, 2013): 483–92, doi:10.2147/CLEP.S54815; American Thoracic Society et al., "Idiopathic Pulmonary Fibrosis: Diagnosis and Treatment. International Consensus Statement," 2000, *http://dspace.iss.it/srdspace/handle/2198/930*.

[2] Sonye K. Danoff and Elizabeth H. Schonhoft, "Role of Support Measures and Palliative Care," *Current Opinion in Pulmonary Medicine* 19, no. 5 (September 2013): 480–84, doi:10.1097/MCP.0b013e328363f4cb.

[3] Ley and Collard, "Epidemiology of Idiopathic Pulmonary Fibrosis."

the existing population.[4] However there are no commercially published figures or rigorous/peer-reviewed analyses to provide more accurate estimates.

TABLE 1: PREVALENCE OF IDIOPATHIC PULMONARY FIBROSIS

Region and study period	Age (years)	IPF prevalence per 100,000 population (95% CI)	Reference
North America			
US, 1988-1990	≥18	13.2 (female) to 20.2 (male)	[5]
US, 1997-2005	≥50	27.9 (10.4-45.4), narrow to 63.0 (36.4-89.6), broad	[6]
US, 1996-2000	≥18	14.0 (narrow) to 42.7 (broad)	[7]
Europe			
Belgium, 1992-1996	All	1.25	[8]
Czech Republic, 1981-1990	All	12.1	[9]
Finland, 1997-1998	All	16-18	[10]
Greece, 2004	All	3.38	[11]
Norway, 1984-1998	≥16	23.4 (14.9-33.0)	[12]
Asia			
Taiwan, 1997-2007	≥18	0.7 to 6.4	[13]

CI: confidence interval
Adapted from: [14]

[4] IPF Fact Sheet based on data on file from InterMune Canada, Inc.
[5] D. B. Coultas et al., "The Epidemiology of Interstitial Lung Diseases.," *American Journal of Respiratory and Critical Care Medicine* 150, no. 4 (October 1, 1994): 967–72, doi:10.1164/ajrccm.150.4.7921471.
[6] Evans R. Fernández Pérez et al., "Incidence, Prevalence, and Clinical Course of Idiopathic Pulmonary Fibrosis: A Population-Based Study," *Chest* 137, no. 1 (January 2010): 129–37, doi:10.1378/chest.09-1002.
[7] Ganesh Raghu et al., "Incidence and Prevalence of Idiopathic Pulmonary Fibrosis," *American Journal of Respiratory and Critical Care Medicine* 174, no. 7 (October 1, 2006): 810–16, doi:10.1164/rccm.200602-163OC.
[8] M. Thomeer et al., "Registration of Interstitial Lung Diseases by 20 Centres of Respiratory Medicine in Flanders," *Acta Clinica Belgica* 56, no. 3 (June 2001): 163–72, doi:10.1179/acb.2001.026.
[9] V. Kolek, "Epidemiology of cryptogenic fibrosing alveolitis in Moravia and Silesia, in the period 1981–1990." Internista 3 (1995): 105-108.
[10] U. Hodgson, T. Laitinen, and P. Tukiainen, "Nationwide Prevalence of Sporadic and Familial Idiopathic Pulmonary Fibrosis: Evidence of Founder Effect among Multiplex Families in Finland," *Thorax* 57, no. 4 (April 1, 2002): 338–42, doi:10.1136/thorax.57.4.338.
[11] A. Karakatsani et al., "Epidemiology of Interstitial Lung Diseases in Greece," *Respiratory Medicine* 103, no. 8 (August 2009): 1122–29, doi:10.1016/j.rmed.2009.03.001.
[12] C. von Plessen, O. Grinde, and A. Gulsvik, "Incidence and Prevalence of Cryptogenic Fibrosing Alveolitis in a Norwegian Community," *Respiratory Medicine* 97, no. 4 (April 2003): 428–35.
[13] Chih-Cheng Lai et al., "Idiopathic Pulmonary Fibrosis in Taiwan - a Population-Based Study," *Respiratory Medicine* 106, no. 11 (November 2012): 1566–74, doi:10.1016/j.rmed.2012.07.012.
[14] Ley and Collard, "Epidemiology of Idiopathic Pulmonary Fibrosis"; Luba Nalysnyk et al., "Incidence and Prevalence of Idiopathic Pulmonary Fibrosis: Review of the Literature," *European Respiratory Review: An Official Journal of the European Respiratory Society* 21, no. 126 (December 1, 2012): 355–61, doi:10.1183/09059180.00002512.

Economic burden of illness

People with IPF have been observed to require hospital admissions and visits to emergency departments and physicians at almost double the rate of similar people without disease. Therefore, the disease is also associated with significantly increased health system costs. Utilization of health care resources has also been observed to be increasing in several studies, and this may be due to the same factors that have led to an observed increasing incidence of disease.[15] In the US, this increase in resource utilization has been associated with annual additional costs of $12,000 per person annually.[16]

Patient-centred care

Studies that have explore what is experiences and outcome are important to patients have identified several emerging themes regarding how IPF negatively impacts quality of life. This includes frustration with diagnosis and management of care, a lack of information about their disease, negative perception from decreased libido or inability to continue sexual activity, reduced independence and the need to rely on friends and family, difficulties with carrying on relationships, and financial concerns with a diminished ability to work.[17]

Patient input on new drug applications to the Canadian Agency for Drugs and Technologies in Health (CADTH), gathered by the Canadian Pulmonary Fibrosis Foundation, similarly indicates these concerns. Patients have also acknowledged the limitations of existing treatments and the need for a treatment that will meaningfully slow the progress of disease.[18] Patients have indicated that they are willing to tolerate side effects from new therapies if there is a chance of slowing disease progression. This is also consistent with other formal studies in the area, which also indicate patient enthusiasm for trying new therapies, especially those which might change disease course.[19]

Informal caregivers and health care providers have also reported negative experiences from caring for patients with IPF.[20] This includes challenges with living with a patient with IPF and feelings of "empathy" and "devastation" for caregivers, along with frustration with an inability to relieve suffering. Informal caregivers have also described the intrusiveness of the disease and difficulty with coming to terms with its end-of-life aspects (see Table 2).

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[15] V. Navaratnam et al., "The Rising Incidence of Idiopathic Pulmonary Fibrosis in the U.K," *Thorax* 66, no. 6 (June 2011): 462–67, doi:10.1136/thx.2010.148031.
[16] Harold R. Collard et al., "Burden of Illness in Idiopathic Pulmonary Fibrosis," *Journal of Medical Economics* 15, no. 5 (2012): 829–35, doi:10.3111/13696998.2012.680553.
[17] Jeffrey J. Swigris et al., "Patients' Perspectives on How Idiopathic Pulmonary Fibrosis Affects the Quality of Their Lives," *Health and Quality of Life Outcomes* 3 (2005): 61, doi:10.1186/1477-7525-3-61.
[18] CADTH. Common Drug Review CDEC Final Recommendation - Pirfenidone Resubmission. Notice of Final Recommendation, April 15, 2015.
[19] Amanda Belkin and Jeffrey J. Swigris, "Patient Expectations and Experiences in Idiopathic Pulmonary Fibrosis: Implications of Patient Surveys for Improved Care," *Expert Review of Respiratory Medicine* 8, no. 2 (April 2014): 173–78, doi:10.1586/17476348.2014.880056.
[20] Amanda Belkin, Karen Albright, and Jeffrey J. Swigris, "A Qualitative Study of Informal Caregivers' Perspectives on the Effects of Idiopathic Pulmonary Fibrosis," *BMJ Open Respiratory Research* 1, no. 1 (2014): e000007, doi:10.1136/bmjresp-2013-000007.

TABLE 2: INFORMAL CAREGIVER EXPERIENCES AND POSSIBLE INTERVENTIONS

Milestone	Informal caregiver experiences	Potentially beneficial interventions
Diagnosis	- Devastation at life-shortening illness - Fear of unknown - Wishing disease was more treatment responsive - Relief diagnosis made - Commitment to partners	- Evaluation at IPF center of expertise - IPF expert caregiver that recognizes IPF caregiver dynamic - IPF patient resources - Maintain support network (family, religious, etc.)
Life with oxygen	Before oxygen - Trepidation over how life will change - Hoping a long time will pass before oxygen needed After oxygen - Adapting to oxygen in the home - Maintaining flexibility with social schedule	- Education, such as book "Adventures of an Oxyphile" - Have patient discuss transtracheal oxygen with physician to consider whether good option
Living with patients as disease progresses	- Feeling helpless - Living with "cranky", "impatient" love ones - Learning what to expect as IPF progresses - Adapting to new "normal" - Trying to find balance between caregiving and maintaining identify and independence	- Join online or in-person support groups - Find time/activity to promote physical and emotional self-well-being - Identify and implement coping/stress management strategies - Take care of practical plans for future
End-of-life	- Worry and fear about life without partner	- Consider palliative care/hospice/mental health

Adapted from: [21]

To capture how patients with IPF feel and function during the disease course, generic patient-reported outcome measures, including instruments that capture health-related quality of life (HRQL), have been used. Conventional instruments, such as the Short-Form-36 (SF-36) survey and Saint George's Respiratory Questionnaire (SGRQ), were shown early on to be sensitive to changes in disease progression. [22]

However, it has been increasingly recognized that these instruments may not be suitable for capturing all relevant information (that is, either quality of life "domains" or information that informs these) or may capture information that is not important to patients. For example, while dyspnea is recognized as an important contributing factor to impaired health-related quality of life,[23] patients with IPF have typically measured worse quality of life than patients with chronic obstructive pulmonary disease (COPD) and a similar level of breathing impairment.[24]

[21] Ibid.
[22] J. A. Chang et al., "Assessment of Health-Related Quality of Life in Patients with Interstitial Lung Disease," *Chest* 116, no. 5 (November 1999): 1175–82.
[23] M. Baron et al., "The Relationship of Dyspnoea to Function and Quality of Life in Systemic Sclerosis," *Annals of the Rheumatic Diseases* 67, no. 5 (May 2008): 644–50, doi:10.1136/ard.2007.075721.
[24] Cristine E. Berry et al., "Relationship between Lung Function Impairment and Health-Related Quality of Life in COPD and Interstitial Lung Disease," *Chest* 142, no. 3 (September 2012): 704–11, doi:10.1378/chest.11-1332.

Given significant "knowledge gaps" associated with existing patient-reported outcome measures (such as the SGRQ),[25] there have been some attempts to develop IPF-specific measures that better capture relevant experience. While the SGRQ has been demonstrated to be "useful",[26] an SGRQ instrument modified to more directly measure experiences in IPF patients has been developed.[27] Another tool, A Tool to Assess Quality of Life in Idiopathic Pulmonary Fibrosis (ATAQ-IPF), was also developed,[28] and validation across countries has been performed.[29]

Treatment options

Effectiveness

There is currently very little clinical evidence to support the use of specific drug and non-drug treatment measures in IPF. Investigations of newer drug therapies coupled with a small number of investigator-led trials have provided evidence both for and against the use of some treatments. For example a high-quality trial conducted by the Idiopathic Pulmonary Fibrosis Clinical Research Network (IPFnet) demonstrated a lack of effect for warfarin, leading to a strong recommendation against the use of warfarin in recently published clinical practice guidelines.[30] Other changes to this guidance are given in Table 3.

[25] Jeffrey J. Swigris and Diane Fairclough, "Patient-Reported Outcomes in Idiopathic Pulmonary Fibrosis Research," *Chest* 142, no. 2 (August 2012): 291–97, doi:10.1378/chest.11-2602.
[26] Jeffrey J. Swigris et al., "The Psychometric Properties of the St George's Respiratory Questionnaire (SGRQ) in Patients with Idiopathic Pulmonary Fibrosis: A Literature Review," *Health and Quality of Life Outcomes* 12 (2014): 124, doi:10.1186/s12955-014-0124-1.
[27] Janelle Yorke, Paul W. Jones, and Jeffrey J. Swigris, "Development and Validity Testing of an IPF-Specific Version of the St George's Respiratory Questionnaire," *Thorax* 65, no. 10 (October 2010): 921–26, doi:10.1136/thx.2010.139121.
[28] Jeffrey J. Swigris et al., "Development of the ATAQ-IPF: A Tool to Assess Quality of Life in IPF," *Health and Quality of Life Outcomes* 8 (2010): 77, doi:10.1186/1477-7525-8-77.
[29] Janelle Yorke et al., "Cross-Atlantic Modification and Validation of the A Tool to Assess Quality of Life in Idiopathic Pulmonary Fibrosis (ATAQ-IPF-cA)," *BMJ Open Respiratory Research* 1, no. 1 (2014): e000024, doi:10.1136/bmjresp-2014-000024.
[30] Ganesh Raghu et al., "An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis. An Update of the 2011 Clinical Practice Guideline," *American Journal of Respiratory and Critical Care Medicine* 192, no. 2 (July 15, 2015): e3–19, doi:10.1164/rccm.201506-1063ST.

TABLE 3: UPDATED ATS/ERS/JRS/ALAT CLINICAL PRACTICE GUIDELINES

Agent	2015 Guideline	2011 Guideline
New and revised recommendations		
Anticoagulation (warfarin)	Strong recommendation against use*	Conditional recommendation against use‡
Combination prednisone + azathioprine + *N*-acetylcysteine	Strong recommendation against use†	Conditional recommendation against use†
Selective endothelin receptor antagonist (ambrisentan)	Strong recommendation against use†	Not addressed
Imatinib, a tyrosine kinase inhibitor with one target	Strong recommendation against use*	Not addressed
Nintedanib, a tyrosine kinase inhibitor with multiple targets	Conditional recommendation for use*	Not addressed
Pirfenidone	Conditional recommendation for use*	Conditional recommendation against use†
Dual endothelin receptor antagonists (macitentan, bosentan)	Conditional recommendation against use†	Strong recommendation against use*
Phosphodiesterase-5 inhibitor (Sildenafil)	Conditional recommendation against use*	Not addressed
Unchanged recommendations		
Antiacid therapy	Conditional recommendation for use‡	Conditional recommendation for use‡
N-acetylcysteine monotherapy	Conditional recommendation against use†	Conditional recommendation against use†
Antipulmonary hypertension therapy for idiopathic pulmonary fibrosis-associated pulmonary hypertension	Reassessment of the previous recommendation was deferred	Conditional recommendation against use‡
Lung transplantation: single vs. bilateral lung transplantation	Formulation of a recommendation for single vs. bilateral lung transplantation was deferred	Not addressed

Source: [30]

It is widely recognized that treatment must be tailored to individual patients, who may have specific needs related to the specific course of their disease including specific complications and symptoms that may arise. This means that some therapies may be suitable only for specific patients. Best supportive care models, which embody a holistic approach to treatment, have been proposed in IPF. This includes a "three pillar" approach to care that recognizes the need to treat IPF based on disease-centered management, symptom-centered management, and patient education and self-management (see Table 4).[31]

Notable features of this comprehensive approach are the need for interdisciplinary or multidisciplinary care,[32] as well as a proactive approach to symptomatic treatment that could include oxygen therapy, pulmonary rehabilitation, therapy for reflux disease, and opiates, as well as integrated approach that includes palliative and end-of-life care.[33] The impact of specialized multidisciplinary centres for the management of IPF has not yet been evaluated using a robust method. [34] Evidence of its potential effectiveness stem from a retrospective observational study, which observed patients younger than 60 years old having some survival benefit associated with interdisciplinary care.[35]

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[31] Joyce S. Lee, Sally McLaughlin, and Harold R. Collard, "Comprehensive Care of the Patient with Idiopathic Pulmonary Fibrosis," *Current Opinion in Pulmonary Medicine* 17, no. 5 (September 2011): 348–54, doi:10.1097/MCP.0b013e328349721b.

[32] Markus Hofer, "Advanced Chronic Lung Disease: Need for an Active Interdisciplinary Approach," *Swiss Medical Weekly* 137, no. 43–44 (November 3, 2007): 593–601, doi:2007/43/smw-11680.

[33] Danoff and Schonhoft, "Role of Support Measures and Palliative Care"; Sabrina Bajwah et al., "Specialist Palliative Care Is More than Drugs: A Retrospective Study of ILD Patients," *Lung* 190, no. 2 (April 2012): 215–20, doi:10.1007/s00408-011-9355-7.

[34] Hofer, "Advanced Chronic Lung Disease."

[35] S. S. Lok, "Interstitial Lung Disease Clinics for the Management of Idiopathic Pulmonary Fibrosis: A Potential Advantage to Patients. Greater Manchester Lung Fibrosis Consortium," *The Journal of Heart and*

Cost-effectiveness

Lung transplantation remains the single evidence-based option for prolonging survival in patients with IPF. However, there are no formal evaluations of its cost-effectiveness. There are similarly no economic evaluations of other non-drug approaches to care, including how care is delivered and organized (that is, through specialty clinics), or the use of disease management programs, education, and other supportive measures.

A review of the effectiveness and cost-effectiveness of existing treatments,[36] commissioned by the National Institute for Health Research Health Technology Assessment (NIHR HTA) Programme, identified one existing economic evaluation. This US-based evaluation examined the cost-effectiveness of performing thiopurine S-methyltransferase (TPMT) testing to reduce the number of serious adverse events associated with the introduction of azathioprine. The authors concluded this approach was cost-effective.[37]

The review authors conducted further analysis of the cost-effectiveness of various forms of drug therapy. Making some assumptions about the potential relative effectiveness of therapies based on a thorough evidence-based review, the authors established that some therapies falls within a range of what is generally considered cost-effective (that is, less than GBP 30,000 per quality-adjusted life-year) with the exception of newer pharmacological agents such as sildenafil, pirfenidone, and nintedanib (see Table 4).[38]

TABLE 4: COST-EFFECTIVENESS OF AVAILABLE PHARMACOLOGICAL AGENTS

Treatment	Total cost (GBP)	Total QALYs	ICER vs. BSC (GBP/QALY)	ICER vs. next best option (GBP/QALY)
BSC	3,084	2.98	-	-
Azathioprine & prednisolone	4,313	2.66	Dominated	Dominated
NAC triple therapy	5,021	3.03	41,811	Extended dominance
Inhaled NAC	5,029	3.37	5,037	5,037
Sildenafil	12,008	3.11	68,116	Dominated
Pirfenidone	70,118	3.34	190,146	Dominated
Nintedanib	139,613	4.01	132,658	209,246

BSC: best supportive care; GBP: British pound; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio

Adapted from: [39]

Lung Transplantation: The Official Publication of the International Society for Heart Transplantation 18, no. 9 (September 1999): 884–90.

[36] Emma Loveman et al., "The Effectiveness and Cost-Effectiveness of Treatments for Idiopathic Pulmonary Fibrosis: Systematic Review, Network Meta-Analysis and Health Economic Evaluation," *BMC Pharmacology & Toxicology* 15 (November 19, 2014), doi:10.1186/2050-6511-15-63.

[37] Jared T. Hagaman, Brent W. Kinder, and Mark H. Eckman, "Thiopurine S- Methyltransferase [corrected] Testing in Idiopathic Pulmonary Fibrosis: A Pharmacogenetic Cost-Effectiveness Analysis," *Lung* 188, no. 2 (April 2010): 125–32, doi:10.1007/s00408-009-9217-8.

[38] Loveman et al., "The Effectiveness and Cost-Effectiveness of Treatments for Idiopathic Pulmonary Fibrosis."

[39] Ibid.

A search for other economic evaluations revealed a single analysis of the use of co-trimoxazole (an antibiotic), conducted alongside a randomized trial. The authors concluded that, compared to not using co-trimoxazole 960 mg (two tablets of 480 mg each) twice daily for 12 months, the drug showed a modest benefit (0.053 years of complete health) and a modest increased cost (GBP 1,177 per patient). The authors concluded treatment may be cost-effective, but with some uncertainty (GBP 22,012 per quality-adjusted life-year gained with a 54.44% probability of being below GBP 30,000).

Most recently, the United Kingdom (UK) National Institute for Health and Care Excellence (NICE) has published its appraisal consultation document recommending that nintedanib (OFEV™) be provided as a lower priced treatment option for IPF, in patients meeting conditions of respiratory decline (a predicted forced vital capacity [FVC] of between 50 and 80%).[40]

The NICE document also describes a stopping rule based on a functional decline of 10% FVC over 12 months, and applies the same conditional stopping rule to pirfenidone (Esbriet®); the stopping rule is based on the cost-effectiveness assessment and indirect treatment comparison. This recommendation is now out for public consultation, with final guidance expected in January 2016.

What current guidelines exist for IPF?

Clinical practice guidelines specific to the management of IPF have been published in France,[41] Spain,[42] Brazil,[43] and Germany.[44] Cross-national collaborative clinical practice guidelines have also been published between the Thoracic Societies of Britain, Ireland, and New Zealand,[45] as well as the American Thoracic Society (ATS), the European Respiratory Society (ERS), the Japanese Respiratory Society (JRS), and the Latin American Thoracic Association (ALAT).[46]

There are small differences between clinical practice guideline documents relating to either the scope (number of interventions reviewed) or time of publication. There are no clinical practice guidelines specific to IPF.

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[40] NICE, "Idiopathic pulmonary fibrosis - nintedanib [ID752]: appraisal consultation," *https://www.nice.org.uk/guidance/indevelopment/GID-TAG491/consultation/idiopathic-pulmonary-fibrosis-nintedanib-id752-appraisal-consultation*.

[41] V. Cottin et al., "Diagnosis and Management of Idiopathic Pulmonary Fibrosis: French Practical Guidelines," *European Respiratory Review* 23, no. 132 (June 1, 2014): 193–214, doi:10.1183/09059180.00001814.

[42] Antoni Xaubet et al., "Guidelines for the Diagnosis and Treatment of Idiopathic Pulmonary Fibrosis. Sociedad Española de Neumología Y Cirugía Torácica (SEPAR) Research Group on Diffuse Pulmonary Diseases," *Archivos De Bronconeumología* 49, no. 8 (August 2013): 343–53, doi:10.1016/j.arbres.2013.03.011.

[43] Bruno Guedes Baldi et al., "Highlights of the Brazilian Thoracic Association Guidelines for Interstitial Lung Diseases," *Jornal Brasileiro De Pneumologia: Publicaçaõ Oficial Da Sociedade Brasileira De Pneumologia E Tisilogia* 38, no. 3 (June 2012): 282–91.

[44] J. Behr, "Idiopathische Lungenfibrose - moderne, leitliniengerechte Diagnostik und innovative Therapien," *DMW - Deutsche Medizinische Wochenschrift* 137, no. 12 (March 2012): 601–4, doi:10.1055/s-0031-1299003.

[45] B. Bradley et al., "Interstitial Lung Disease Guideline: The British Thoracic Society in Collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society," *Thorax* 63 Suppl 5 (September 2008): v1–58, doi:10.1136/thx.2008.101691.

[46] Raghu et al., "An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline."

Section Two: Idiopathic Pulmonary Fibrosis as a Rare Disease – A Policy Challenge

Given the unique nature of IPF, there have been several unique initiatives that have been proposed internationally and in Canada. These fall into several categories:

- **Registries** – Registries have proven to be an important component of research and collaboration in other rare diseases, such as cystic fibrosis. Pulmonary fibrosis registries have already begun in some jurisdictions, such as the US (PFF Registry) and Europe (eurIPFreg), and proposals of the development of a Canadian registry (CARE-PF, the Canadian Registry for Pulmonary Fibrosis) and a global registry (network of registries) have also been developed.[47]
- **Patient support programs** – Regional patient support programs for patients and caregivers have been developed, as well as product-specific programs. For example, Boehringer Ingelheim (Canada) Ltd./Ltée. has developed its HeadStart Patient Support Program along with the release of nintedanib (OFEV™), which provides patients receiving the drug with education and information regarding where to receive the drug and how it can be funded.

  A more active and individualized support program is INSPIRED (Implementing a Novel and Supportive Program of Individualized Care for Patients and Families Living with REspiratory Disease), which was originally designed for patients with COPD and is currently being adapted for IPF.
- **IPF clinical trial networks** – US-based IPFnet and European eurIPFnet were created in an effort to be able to conduct randomized trials in larger numbers of populations in a more efficient manner. The first IPFnet trial sought to better understand whether treatment with sildenafil would improve function and quality of life in patients with advanced IPF. Other trials have explored the effect of antioxidants and anticoagulants.
- **Ambassador program** – The US-based Pulmonary Fibrosis Foundation (PFF) Ambassador Program "encourages and empowers patients, caregivers, and health care professionals to become spokespeople for the PF community on behalf of the Pulmonary Fibrosis Foundation."[48]
- **Patient advocacy groups** – Groups such as the Canadian Pulmonary Fibrosis Foundation act as a hub for providing education to patients and caregivers as well as raising awareness about IPF, and representing the needs of PF patients to other key stakeholders.

Regulatory policy

Rare diseases have gathered increasing attention over the last several decades; a turning point was US legislation in 1983 (the *Orphan Drug Act*) providing incentives to drug manufacturers to develop drugs for rare diseases, called "orphan" drugs. Orphan drugs were defined in the act as those drugs "intended to treat a condition affecting fewer than 200,000 people in the United States" (that is,

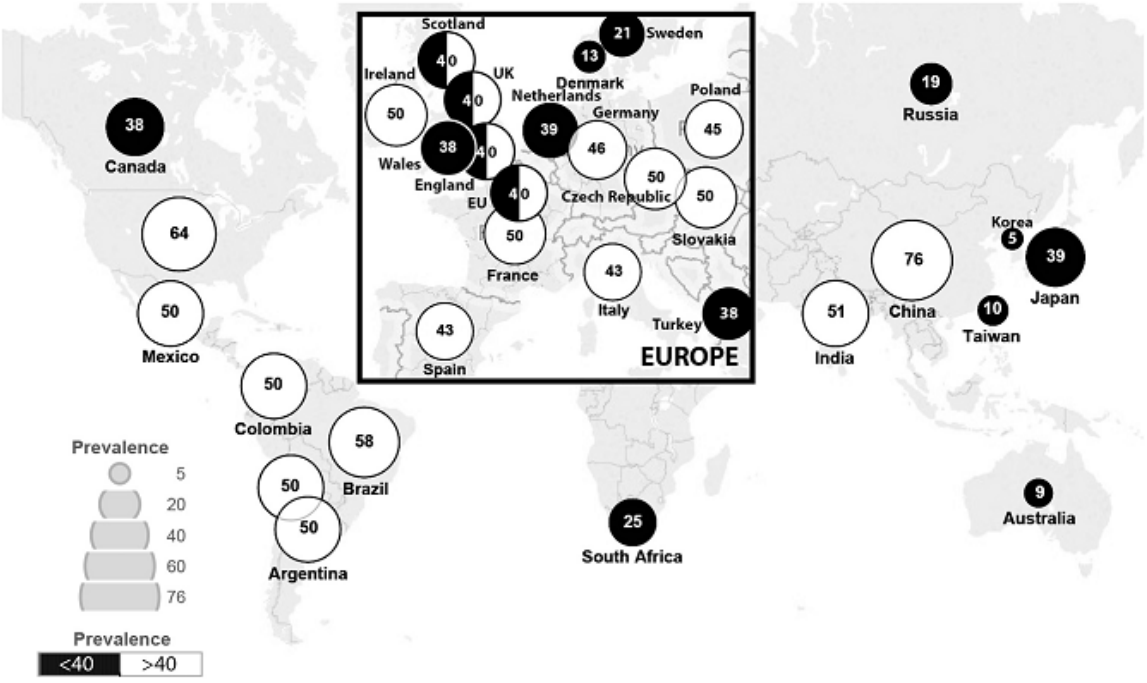
[47] Christopher J. Ryerson et al., "A Global Registry for Idiopathic Pulmonary Fibrosis: The Time Is Now," *European Respiratory Journal* 44, no. 2 (August 1, 2014): 273–76, doi:10.1183/09031936.00051914.
[48] *http://pulmonaryfibrosis.org/our-role/signature-programs/pulmonary-fibrosis-foundation-ambassador-program*

approximately 85 per 100,000) or with little prospect of profitability.[49] The act has resulted in more than 350 drugs being created for rare diseases and brought to the US market.

In 2012, Canada's federal government also committed to developing a regulatory framework for orphan drugs and to launching a Canadian portal to Orphanet, an international network and comprehensive resource for rare diseases. The objectives of the regulatory framework are to improve access to orphan drugs and to facilitate clinical research in the area of rare diseases. In August 2014, the Federal Minister of Health Rona Ambrose announced a pilot project seeking input from Canadians to help inform a rare disease/orphan drug framework.

An interesting aspect of developing frameworks to address rare disease is that there is no standard definition of rare disease. A recent systematic review developed by the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) identified 296 definitions from 1,109 organizations.[50] While two-thirds of international jurisdictions defined rare disease using a threshold between 40 to 50 cases per 100,000, the global average was 40 per 100,000 (see Figure 1).

FIGURE 1: REGIONAL DISTRIBUTION OF PREVALENCE THRESHOLDS FOR JURISDICTIONS



The size of circle corresponds to the average prevalence threshold (number of cases/100,000) for all organizations within a jurisdiction. Black and white circles correspond to jurisdictions in which the average prevalence in definitions of rare disease is lower or higher, respectively, than the average across all jurisdictions in this study of 40 cases/100,000.

Source: [51]

[49] *http://www.fda.gov/regulatoryinformation/legislation/significantamendmentstothefdcact/orphandrugact/default.htm*

[50] Trevor Richter et al., "Rare Disease Terminology and Definitions-A Systematic Global Review: Report of the ISPOR Rare Disease Special Interest Group," *Value in Health: The Journal of the International Society for Pharmacoeconomics and Outcomes Research* 18, no. 6 (2015): 906–14, doi:10.1016/j.jval.2015.05.008.

[51] Ibid.

Reimbursement policy

Although regulatory frameworks for drugs are in development, there are still challenges with payer/population-based decision-making for the coverage of treatments of rare disorders. In Canada, with the delivery of health care services under provincial jurisdictions and with different sizes and mandates, there are province-to-province variations in the provision of services, such as home oxygen and the availability of multidisciplinary care clinics. Other types of non-drug supplies and services will also differ by province and according to special programs such as the Régie de l'assurance maladie du Québec (RAMQ) and the Alberta Aids to Daily Living Program.

For drugs, there are currently no special frameworks or considerations specifically for rare diseases, with the exception of in the province of Ontario (see below). Public drug insurance administrators have created coordinated processes for review and recommendation that are implemented by CADTH. One process, the pan-Canadian Oncology Drug Review (pCODR) provides recommendations for oncology drugs based on considerations of effectiveness (clinical benefit), cost-effectiveness, alignment with patient values, and feasibility of adoption into the health system. The second, the Common Drug Review (CDR), provides recommendations on new outpatient (not oncologic) drugs. Neither mechanism is currently considering a special process for drugs for rare diseases.

In May 2014, a review of the process for funding new treatments for rare diseases concluded that no separate process would be established. The CDR does have a special priority review process for drugs that meet a set of particular criteria; these are: "1) the drug is indicated or anticipated to be indicated for an immediately life-threatening or other serious disease; 2) the drug addresses an unmet medical need; 3) the drug offers substantial improvement in clinically important outcome measures of efficacy and effectiveness, when compared with other appropriate comparators."[52] This priority review procedure, which facilitates a faster review, may or may not apply to drugs for rare diseases.

Provincial frameworks

In British Columbia, a rare disease framework for drug reimbursement has been implemented through the British Columbia Ministry of Health Expensive Drugs for Rare Diseases Advisory committee. However, the committee uses similar standards to evaluate drugs for rare diseases as for other drugs. It provides advice to the Ministry regarding special authorization requests, for drugs that are not otherwise listed.

Alberta similarly established a rare disease program that designates certain diseases allowable for drug coverage, and upon review by the Alberta Rare Diseases Clinical Review Panel. Drugs are only reimbursed if a request is made by a designated rare disease specialist. For the purpose of this program, rare diseases are defined as "genetic, lysosmal storage disorders occurring at a rate of less than [2 per 100,000] for the Canadian population for a specific disease (as determined by Alberta Health)."[53] Alberta has also developed a Short Term Exceptional Drug Therapy (STEDT) program for one-off requests for expensive drugs.

The province of Ontario similarly began to consider how to fund drugs for rare diseases through the establishment of a Citizen's Council in 2008. In 2010, the Council was asked to deliberate on the question of "under what situations and/or conditions should the Ontario Government

[52] *https://www.cadth.ca/media/cdr/filing/CDR_Consultation_Priority-Review_March-20-2014.pdf*
[53] *https://www.ab.bluecross.ca/dbl/pdfs/dbl_sec4.pdf*

(i.e. taxpayers) pay for Drugs for Rare Diseases."[54] The Council recommendations to the Ministry stated that drugs for rare diseases "should have their own set of funding criteria" and that these be different than those for other drugs. It also recommended, among other things, that the definition of "rare" be standardized and that funding should be conditional upon gathering further information and having clear starting and stopping rules. It did suggest that health-related quality and length of life should underpin all listing decisions.

In light of these recommendations, Ontario adopted a rare disease framework for outpatient (non-oncologic) drugs.[55] For the purpose of developing the initial framework, rare was defined as 0.6 per 100,000 live births. The framework was tested with idursulfase for mucopolysaccharidosis II (Hunter syndrome). The framework lays out a number of steps for assessing a rare disease, including: 1) confirming the disease is rare; 2) understanding the disease; 3) understanding the potential clinical benefits of new therapies, including validity of surrogates; 4) using mathematical modelling to deal with shortcomings from existing clinical trial data; 5) evaluating cost-effectiveness and applying similar thresholds of acceptability as for drugs for non-rare conditions; 6) consulting with disease experts regarding the assessment; and 7) reassessing.

The province of New Brunswick has also announced a similar approach, partnering with Ontario. Like Alberta, the rare disease drug plan is for designated diseases. The plan will cover the cost of five drugs for specific rare diseases and drugs (Aldurazyme® for the treatment of Hurler and Hurler-Scheie forms of mucopolysaccharidosis I; Elaprase® for the treatment of Hunter syndrome; Ilaris® for the treatment of cryopyrin-associated periodic syndrome; Myozyme® for the treatment of Pompe disease; and Zavesca® for the treatment of Niemann-Pick type C).[56]

International reimbursement frameworks

United Kingdom

In the UK, in recognizing that standard approaches to HTA may be insufficient, NICE has established a separate committee for "highly specialised technology". In addition to a consideration of clinical effectiveness and costs, the committee also considers the "nature of the condition (including morbidity/clinical disability with current standards of care; effect on caregivers' quality of life; current treatment options)"; impact beyond direct health benefits (are there any such benefits, are costs/savings incurred outside of the NHS [National Health Service] and PSS [Prescribed Specialised Services]); and impact on delivery of the specialized service (staffing and infrastructure requirements such as training, planning for expertise).[57]

Scotland

Scotland has adopted the definition of orphan medicines provided by the European Agency for the Evaluation of Medicinal Products (EMEA): "an orphan medicine is one licensed for treating or

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[54] Ontario Citizens' Council, "A Report Of The Ontario Citizens' Council Considerations For Funding Drugs For Rare Diseases," *http://www.health.gov.on.ca/en/public/programs/drugs/councils/report/report_201003.pdf.*

[55] Eric Winquist et al., "An Evaluation Framework for Funding Drugs for Rare Diseases," *Value in Health: The Journal of the International Society for Pharmacoeconomics and Outcomes Research* 15, no. 6 (October 2012): 982–86, doi:10.1016/j.jval.2012.06.009.

[56] *http://www2.gnb.ca/content/gnb/en/news/news_release.2014.07.0939.html*

[57] *https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-highly-specialised-technologies-guidance/Highly-Specialised-Technologies-Interim-methods-and-process-statements.pdf*

preventing life-threatening rare diseases affecting fewer than 5 in 10,000 people in the European Union." The Scottish Medicines Consortium (SMC) will consider additional factors when compelling clinical evidence is provided along with additional costs that are high. This includes giving consideration to evidence relating to whether the disease is a life-threatening disease; whether life expectancy or quality of life will improve substantially; what other therapeutic options are available; whether specific sub-group of patients will highly benefit; whether a disease condition can be stabilized or reversed; whether the new medicine bridges a gap to a definitive therapy; and whether the drug is an alternative to an unlicensed drug that is the sole treatment in use for a specific condition. Patients and care providers may also make a special request for exceptional access.[58]

Australia

Through Australia's Pharmaceutical Benefits Scheme (PBS), which manages a national formulary and considers whether to list new drugs, Australia has established a "rule of rescue," which considers the following criteria: 1) there are no drug or non-drug treatments available in Australia for patients with the specific medical condition; 2) the medical condition is severe, progressive, and expected to result in premature death; 3) the medical condition applies to a very small number of patients; and 4) the proposed drug qualifies as a rescue from the condition by providing worthwhile clinical improvement.[59] Australia also has a special access program for specific drugs/diseases.

France

France has had a National Plan for Rare Diseases since 2005, but has no specific framework for reimbursement of drugs for rare diseases. However, and similar to CADTH's priority review process, France will expedite a review if the following criteria are met: 1) new therapeutic modality; 2) high unmet need; and 3) demonstrated efficacy/tolerability. France also has provisions for special access.

Spain

Spain has also not adopted a framework specific to rare diseases. However, the Spanish Interterritorial Council of the National Health System, which defines the benefits package of the National Health System, has considered factors beyond clinical and cost-effectiveness such as considerations of severity of indication, needs of patient groups, therapeutic options, and degree of innovation.

Germany

Germany has created a special provision for new medicines for small populations when evaluated by the Institute of Quality and Efficiency in Health Care (IQWiG). The provision states that, "for small sample sizes, it is reasonable to accept a higher than 5% p-value (e.g. 10%) to prove statistical significance and to accept evidence from surrogate endpoints."[60] It also suggests surrogate endpoints must be valid, and that there is no reason to deviate from evidence hierarchies (that is, using randomized controlled trials) when assessing the impact of drugs for small populations.

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[58] *http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Orphan_Drugs*
[59] *http://www.pbac.pbs.gov.au/section-f/f3-other-relevant-factors.html*
[60] *https://www.iqwig.de/download/IQWiG_Methoden_Entwurf-fuer-Version-4-2.pdf*

Section Three: Options for Future Idiopathic Pulmonary Fibrosis Policy

What is clear from the above examples of evaluation frameworks for new medicines is that the size of the eligible population is typically not a consideration in public reimbursement for new treatments. This is consistent with studies of social values that have shown that the public does not value "rarity" per se or the funding of treatments for rare conditions at the expense of treating more common ones.[61]

The criteria that do appear across various frameworks include the following:

1. Consideration of the severity/morbidity of the disease including premature death
2. Evidence of clinical benefit of new treatments (with some flexibility overcome by modelling or less strict statistical standards)
3. Magnitude of clinical benefit
4. Consideration of costs and cost-effectiveness
5. Availability of alternatives
6. Alignment with patient values
7. Wider consultation with stakeholders
8. Reassessment and revisiting decisions
9. Starting and stopping rules

Questions for Consensus Meeting Participants

Given the above, what opportunities and gaps exist and what are some proposed ways forward? Specifically:

1. What minimum set of factors should be considered when implementing treatment programs for IPF (for example, the use of stopping rules, education, multidisciplinary care)?
    a. What factors are currently often not considered?
    b. What factors are most important?
    c. Are these factors based in evidence?

[61] Nick Dragojlovic et al., "Challenges in Measuring the Societal Value of Orphan Drugs: Insights from a Canadian Stated Preference Survey," *The Patient* 8, no. 1 (2015): 93–101, doi:10.1007/s40271-014-0109-5; Warren G. Linley and Dyfrig A. Hughes, "Societal Views on NICE, Cancer Drugs Fund and Value-Based Pricing Criteria for Prioritising Medicines: A Cross-Sectional Survey of 4118 Adults in Great Britain," *Health Economics* 22, no. 8 (August 2013): 948–64, doi:10.1002/hec.2872; Emmanouil Mentzakis, Patricia Stefanowska, and Jeremiah Hurley, "A Discrete Choice Experiment Investigating Preferences for Funding Drugs Used to Treat Orphan Diseases: An Exploratory Study," *Health Economics, Policy, and Law* 6, no. 3 (July 2011): 405–33, doi:10.1017/S1744133110000344; Arna S. Desser, Jan Abel Olsen, and Sverre Grepperud, "Eliciting Preferences for Prioritizing Treatment of Rare Diseases: The Role of Opportunity Costs and Framing Effects," *PharmacoEconomics* 31, no. 11 (November 2013): 1051–61, doi:10.1007/s40273-013-0093-y; Arna S. Desser et al., "Societal Views on Orphan Drugs: Cross Sectional Survey of Norwegians Aged 40 to 67," *BMJ (Clinical Research Ed.)* 341 (2010): c4715.

2. What minimum set of criteria should be considered when deciding to fund IPF treatment (that is, based on an examination of frameworks for rare diseases and how IPF fits into these)?
    a. What are the implications for future drug and non-drug reimbursement decisions?
    b. Are there a set of criteria that should be applied to treatment funding?