Cytisinicline for Smoking Cessation

Draft Background and Scope

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Background

Smoking cigarettes remains the number one cause of preventable deaths in the United States (US). Approximately half a million people die each year from smoking-related illnesses in the US.[1] The major causes of death are cardiovascular (strokes and heart attacks), cancer (lung, pancreatic, esophageal, bladder, colorectal, renal, and other cancers), and pulmonary (chronic obstructive lung disease [COPD], pneumonia, bronchitis). The economic costs of smoking in the US were estimated to be more than $600 billion in 2018, including $240 billion in direct healthcare costs and $372 billion in lost productivity.[2] This does not include the cost of tobacco products to consumers, which was estimated to be $75.9 billion in 2021.[3]

Since 1965, the percentage of Americans who smoke has declined from 42.6% to 11.6%.[4] The majority of current smokers (68%) want to quit, and each year more than half try (53% in 2022), but fewer than 10% succeed.[5] Smoking is more common in people who are male, middle-aged, White, less educated, low-income, and suffer from psychological distress (Table 1.1).[2]

Table 1.1. Smoking Prevalence in 2022 in the United States by Selected Characteristics[2]

Characteristic	Percentage
Sex	
Male	13.1
Female	10.1
Age	
18-24	5.3
25-44	12.6
45-64	14.9
65+	8.3
Race/ethnicity	
Asian	5.4
Black	11.7
Hispanic	7.7
White	12.9

Characteristic	Percentage
Education	
GED	30.7
High School Diploma	17.1
Bachelor's Degree	5.3
Graduate Degree	3.2
Income	
Low	18.3
Middle	12.3
High	6.7
Psychological Distress	
Yes	28.1
No	10.9

GED: General Educational Development

There are several treatment approaches that have been shown to help patients quit smoking. Primary care providers are encouraged to ask all patients about tobacco use, advise those who smoke to stop smoking, and offer all patients help with both medications and counseling.[6] Smoking quit lines offer free counseling, and many centers offer in-person counseling as well. The two most effective medical therapies that are available in the US are varenicline (previously Chantix®) and dual nicotine therapy (a long-acting patch combined with short-acting gum or lozenges). Other options include single nicotine replacement therapy (NRT) and bupropion (previously Zyban®).

The focus of this review is a potential new therapy, cytisinicline, also known as cytisine. It is derived from the seeds of an acacia bush that grows in eastern Europe. It has been used for smoking cessation in a different formulation for more than 50 years. It is a partial agonist of nicotinic acetylcholine receptors that helps to block the craving for cigarettes and blunts the short-term rewards that come from smoking a cigarette. The formulation by Achieve Life Sciences is a 3 mg pill given orally three times a day for 6 to 12 weeks.

Stakeholder Input

This draft scoping document was developed with input from diverse stakeholders, including patients and their families, clinicians, researchers, and manufacturers of the agents of focus in this review. This document incorporates feedback gathered during preliminary calls with stakeholders and open input submissions from the public. A revised scoping document will be posted following a three-week public comment period. ICER looks forward to continued engagement with stakeholders throughout its review and encourages comments to refine our understanding of the clinical effectiveness and value of preventive treatments.

We heard from stakeholders that there remains an unmet need for therapies to assist patients in quitting smoking. The availability of a new therapy may spur patients to make another quit attempt. The last FDA approval of a therapy for smoking cessation was in 2006. In addition, a plant-derived product may be attractive to patients who prefer therapies that are natural.

Report Aim

This project will evaluate the health and economic outcomes of cytisinicline for smoking cessation. The ICER value framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms – including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs – are considered in the judgments about the clinical and economic value of the interventions.

Scope of Clinical Evidence Review

The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and uncommon adverse events. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see ICER's grey literature policy).

All relevant evidence will be synthesized qualitatively or quantitatively. Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. Data permitting, we will also consider combined use of direct and indirect evidence in network meta-analyses of selected outcomes. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis will be provided after the revised scope in a research protocol published on the Open Science Framework website (https://osf.io/7awvd/).

Populations

The primary population for the review is individuals who are interested in quitting cigarettes.

In addition, we will explore data in the population of individuals, youth and adults, interested in quitting electronic cigarettes (vaping).

Data permitting, we will evaluate the evidence for treatment effect modification by subpopulations defined by:

- Sociodemographic factors (e.g., sex, race/ethnicity, education, income)
- Age
- Psychiatric disorders (e.g., schizophrenia and depression)

Interventions

- Cytisinicline with behavioral support

Comparators

Data permitting, we intend to compare cytisinicline to the following:

- No pharmacotherapy/behavioral therapy alone
- Nicotine replacement therapy (NRT) products (e.g., nicotine patch plus a short-acting NRT such a gum or lozenge)
- Electronic cigarettes containing nicotine (for smoking cessation)
- Varenicline
- Varenicline plus NRT
- Bupropion

Outcomes

The outcomes of interest are described in the list below.

- Patient-Important Outcomes
    - Abstinence from cigarette smoking or a decrease in cigarettes smoked per day
    - Adverse events including
        - Nausea
        - Headaches
        - Sleep disturbances (e.g., vivid dreams, insomnia)
        - Serious adverse events
        - Adverse events leading to treatment discontinuation
        - Adverse effects of quitting smoking

Timing

Evidence on intervention effectiveness and harms will be derived from studies of at least six months duration.

Settings

All relevant settings will be considered.

Benefits Beyond Health and Special Ethical Priorities

Our reviews seek to provide information on benefits beyond health and special ethical priorities offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These general elements (i.e., not specific to a given disease) are listed in the table below.

Table 1.2. Benefits Beyond Health and Special Ethical Priorities

Benefits Beyond Health and Special Ethical Priorities*
There is substantial unmet need despite currently available treatments.
This condition is of substantial relevance for people from a racial/ethnic group that have not been equitably served by the healthcare system.
The treatment is likely to produce substantial improvement in caregivers' quality of life and/or ability to pursue their own education, work, and family life.
The treatment offers a substantial opportunity to improve access to effective treatment by means of its mechanism of action or method of delivery.

*Benefits beyond health and special ethical priorities shape to some extent how the value of any effective treatments for a particular condition will be judged and are meant to reflect the broader effects of a specific treatment on patients, caregivers, and society. For additional information, please see the ICER Value Assessment Framework.

ICER encourages stakeholders to provide input on these elements in their public comment submissions.

Scope of Comparative Value Analyses

A detailed economic model analysis plan with proposed methodology, model structure, model parameters, model inputs, and model assumptions will be published on August 25, 2025. This scoping document provides early thoughts about the overall model structure.

As a complement to the evidence review, we will develop an economic model to assess the lifetime cost-effectiveness of the treatments of cytisinicline with behavioral support compared to relevant comparator treatments (e.g. NRT, varenicline, varenicline + NRT, etc., each with behavioral

support), data permitting. The model structure will be based in part on a literature review of prior published models of smoking cessation. Analyses will be conducted from the health care system perspective and the modified societal perspective. The base case analysis will take a health care system perspective (i.e., focus on direct medical care costs only). Societal impacts (e.g., patient and caregiver productivity, interactions with the criminal justice system) and other indirect costs will be considered in a separate modified societal perspective analysis. In addition, relevant direct nonmedical costs, such as the cost of cigarettes to patients, may also be evaluated as part of the modified societal perspective analysis. This analysis will be considered as a co-base case when (a) direct data on indirect costs are available, (b) the societal costs of care are large relative to direct health care costs, and (c) the impact of treatment on these costs is substantial. This will most often occur in cases where the incremental cost-effectiveness ratio changes by greater than 20%, greater than $200,000 per QALY, and/or when the result crosses the threshold of $100,000-$150,000 per QALY gained. If direct data are lacking on patient and/or caregiver productivity, we will implement a method to capture the potential impacts of cytisinicline on productivity (patient and caregiver) as well as certain other impacts (e.g., patient time in treatment).

The target population will consist of individuals who are interested in quitting cigarettes. The model will consist of health states including current smoker, former smoker, and death. A cohort of patients will transition between states during predetermined cycles (of one year) over a lifetime time horizon, modeling patients from treatment initiation until death. In addition, cost-effectiveness will be estimated for shorter time horizons (e.g., five years).

Key model inputs will include clinical probabilities, quality of life values, and health care costs. Probabilities, costs, and other inputs will differ to reflect varying effectiveness between interventions. Treatment effectiveness will be estimated using continuous smoking abstinence results from clinical trials.

Health outcomes and costs will be dependent on time spent in each health state, clinical events, adverse events (AEs), and direct medical costs. The health outcome of each intervention will be evaluated in terms of smoking-attributable condition avoided (e.g. COPD, coronary heart disease, stroke, and lung cancer), life-years gained, quality-adjusted life years (QALYs) gained, and equal value of life years gained (evLYG). Quality of life weights will be applied to each health state, including quality of life decrements for serious adverse events. The model will include direct medical costs, including but not limited to costs related to drug administration, drug monitoring, condition-related care, and serious adverse events. In addition, patient and caregiver productivity changes and other indirect costs will be included in a separate analysis, as available data allow. Relevant pairwise comparisons will be made between treatments, and results will be expressed in terms of the marginal cost per QALY gained, cost per evLYG, cost per life-year gained, and cost per smoking-attributable condition avoided.

In separate analyses, we will explore the potential health care system budgetary impact of treatment over a five-year time horizon, utilizing published or otherwise publicly-available information on the potential population eligible for treatment and results from the economic model for treatment costs and cost offsets. This budgetary impact analysis will indicate the relation between treatment prices and level of use for a given potential budget impact, and will allow assessment of any need for managing the cost of such interventions. More information on ICER's methods for estimating potential budget impact can be found here.

Identification of Low-Value Services

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see ICER's Value Assessment Framework). These services are ones that would not be directly affected by cytisinicline (e.g., costs of treating lung cancer), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of smoking beyond the potential offsets that arise from a new intervention. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

References

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