Prior Authorization Review Panel
MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review.
Policies submitted without this form will not be considered for review.

Plan: AmeriHealth Caritas Pennsylvania and Keystone First	**Submission Date**: 10/1/2024
Policy Number: ccp.1470	**Effective Date:** 10/2020 **Revision Date:** September 1, 2024
Policy Name: EndeavorRx video for ADHD	

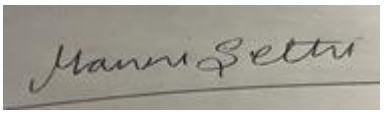
Type of Submission – Check all that apply:

- ☐ **New Policy**
- ☒ **Revised Policy***
- ☐ **Annual Review – No Revisions**
- ☐ **Statewide PDL**

***All revisions to the policy must be highlighted using track changes throughout the document.**

Please provide any clarifying information for the policy below:

See tracked changes below.

Name of Authorized Individual (Please type or print): Manni Sethi, MD, MBA, CHCQM	**Signature of Authorized Individual:** 

Keystone First
Family of Health Plans

EndeavorRx video for ADHD

Clinical Policy ID: CCP.1470

Recent review date: 9/2024

Next review date: 1/2026

Policy contains: Attention deficit and hyperactivity disorder; digital therapeutics; EndeavorRx video.

Keystone First has developed clinical policies to assist with making coverage determinations. Keystone First's clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of "medically necessary," and the specific facts of the particular situation are considered by Keystone First, on a case by case basis, when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Keystone First's clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Keystone First's clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Keystone First will update its clinical policies as necessary. Keystone First's clinical policies are not guarantees of payment.

Coverage policy

EndeavorRx™ video (Akili Interactive Labs Inc., Philadelphia, Pennsylvania) for attention deficit hyperactivity disorder is investigational/not clinically proven and, therefore, not medically necessary.

Limitations

No limitations were identified during the writing of this policy.

Alternative covered services

Medication (stimulants and non-stimulants); behavior management.

Background

Attention deficit hyperactivity disorder is a psychiatric and neurodevelopmental condition that affects a child's ability to function. Symptoms generally include developmentally inappropriate loss of concentration and focus, inattentiveness, hyperactivity, and impulsivity. The disorder is usually first suspected in childhood during elementary school with children demonstrating difficulty completing tasks, becoming disorganized and forgetful, and losing things. A diagnosis is made based on these symptoms before age 12. Symptoms interfere with daily living activities and last six months or longer. Although the condition begins in childhood, it frequently extends into adulthood. The three main subtypes are predominantly inattentive, predominantly hyperactive-impulsive, and a combination of the two (Magnus, 2023).

An estimated 7 million (11.4%) of U.S. children have been diagnosed with attention deficit hyperactivity disorder, typically between ages 3 and 17 years. The disease's prevalence in boys is more than double than that of girls (15% compared to 8%), and 78% of children with the condition has at least one other co-occurring condition (Centers for Disease Control and Prevention, 2024a).

The causes of the condition have remained elusive, but several risk factors have been implicated. Studies of twins have identified a genetic link in some cases. Other suspected risk factors include brain injury; exposure to environmental toxins (e.g., lead) during pregnancy or at a young age; alcohol and tobacco use during pregnancy; and parental mental health and family environment (Centers for Disease Control and Prevention, 2024a).

Treatment is age-specific and can include medication with or without behavioral therapy. Among children with attention deficit hyperactivity disorder, approximately 32% children received both medication treatment and behavior treatment, but 30% received no treatment (Centers for Disease Control and Prevention, 2024b).

Current therapies do not help all children with attention deficit hyperactivity disorder, and alternative treatments are sought. Digital therapeutics (software applications for clinical use) have been proposed to improve attention problems.

In 2020, Akili Interactive Labs, Inc. received regulatory approval to market EndeavorRx as a class II device indicated to improve attention function as measured by computer-based testing in children ages 8 to 12 years old with primarily inattentive or combined-type attention deficit hyperactivity disorder who have a demonstrated attention issue (U.S. Food and Drug Administration, 2020a). EndeavorRx is the first game-based digital therapeutic granted approval by the federal government for the condition intended to be used as an adjunct to clinician-supervised treatment (U.S. Food and Drug Administration, 2020b).

Findings

Guidelines

Current guidelines for treatment of pediatric attention deficit hyperactivity disorder do not include the use of digital therapeutics, including the EndeavorRx video game (Barbaresi, 2020; Wolraich, 2019).

Evidence review

The evidence for EndeavorRx consists of two reported studies performed in children under controlled conditions. EndeavorRx appears safe and well-tolerated and offers short-term improvement in inattention and hyperactivity, but its effectiveness in real world settings and over the long term is unclear.

Before developing EndeavorRx, Akili Interactive tested prototype digital treatments. In one of these, 80 children were randomized into those with and without attention deficit hyperactivity disorder. Significant neuropsychological improvements were observed for the 40 cases, but not for the 40 controls (Davis, 2018).

Regulatory approval for EndeavorRx was based on five studies, with a total of more than 600 participants. The primary study was a controlled trial (n = 348) of children ages 8 to 12 years old. All participants were required to have a definitive diagnosis of attention deficit hyperactivity disorder, scores on several ratings scales indicating attention problems, an intelligence quotient above 80, no comorbid psychiatric conditions, and no use of medications for the disease that could not be discontinued (Kollins, 2020).

Children in the case group played the EndeavorRx video game for five five-minute sessions per day, five days a week for four weeks. The control group played a game whose objective was to find and connect letters on a grid to spell words during the same period. Major findings include:

	Cases (180)	Controls (168)	*P* value	
Test of Variables of Attention	47%	32%	.0058	*
Attention Performance Index	11%	4%	.033	*
ADHD Rating Scale (> 2 points)	74%	73%	.77	
ADHD Rating Scale (> 30%)	24%	19%	.23	
Impairment Rating Scale	48%	37%	.049	*

Clinical Global Impressions (< 2 post-intervention)	17%	16%	.86	
Clinical Global Impressions (1 post-intervention)	1%	1%	.96	
Self-Reported Improvement on Exit (patients)	73%	66%	.15	
Self-Reported Improvement on Exit (parents)	56%	44%	.025	*

* Significance at $P < .05$.

The percentage of patients experiencing intervention-emergent adverse effects during the study period was higher for cases (7%, n = 12) versus controls (2%, n = 3). Ten of the 12 effects on the test patients were frustration (5), headache (3), and emotional reaction (2). No serious adverse effects were experienced by either group, and there were no discontinuations (Kollins, 2020).

An update to this trial (n = 206) of children ages 8 to 14 with attention deficit hyperactivity disorder taking or not taking stimulant medication assessed the impact of AKL-T01, an application and video-game-based treatment for inattention. Subjects used the game for four weeks, followed by non-use for four weeks. Impairment improved in groups taking or not taking medication, both significant at $P < .001$) after four weeks, with no side effects, and improvements persisted up to one month (Kollins, 2021).

A systematic review examined the effects of game-based therapeutics, including EndeavorRx, in randomized controlled trials on children and adolescents with attention deficit hyperactivity disorder. The investigators indirectly compared the outcomes of game-based digital therapeutics, medication, and controls. Outcomes were reported as standard mean difference (95% confidence interval). Both digital therapeutics and controls improved inattention (0.28 [0.14 to 0.41] and 0.21 [0.03 to 0.39], respectively) and hyperactivity/impulsivity (0.28 [0.03 to 0.53] and 0.30 [0.05 to 0.55], respectively). However, medication had outcomes superior to digital therapeutics for these indicators (Oh, 2023).

Video games, such as EndeavorRx, may improve treatment adherence, as they are perceived as enjoyable activities. Drop-out rates for EndeavorRx were 5.45% (Kollins, 2020) and 12.13% (Kollins, 2021), lower than most other video game-based treatments. However, long-term efficacy is uncertain (Caselles-Pina, 2023).

In 2024, we added a systematic review (Caselles-Pina, 2023) and guideline references, and deleted several older references. No policy changes are warranted.

References

On August 1, 2024, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were “attention deficit and hyperactivity disorder,” “digital therapeutics,” and “EndeavorRx video.” We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

Barbaresi WJ, Campbell L, Diekroger EA, et al. Society for developmental and behavioral pediatrics clinical practice guideline for the assessment and treatment of children and adolescents with complex attention-deficit/hyperactivity disorder. *J Dev Behav Pediatr*. 2020;41 Suppl 2S:S35-S57. Doi: 10.1097/DBP.0000000000000770.

Caselles-Pina L, Sujar A, Quesada-Lopez A, Delgado-Gomez D. Adherence, frequency, and long-term follow-up of video game-based treatments in patients with attention-deficit/hyperactivity disorder: A systematic review. *Brain Behav*. 2023;13(11):e3265. Doi: 10.1002/brb3.3265.

Centers for Disease Control and Prevention. About attention-deficit / hyperactivity disorder (ADHD). https://www.cdc.gov/adhd/about/?CDC_AAref_Val=https://www.cdc.gov/ncbddd/adhd/facts.html. Dated June 27, 2024. (a)

Centers for Disease Control and Prevention. Treatment of ADHD. https://www.cdc.gov/adhd/treatment/index.html. Dated May 15, 2024. (b)

Chung W, Jiang S-F, Pakasarian D, et al. Trends in the prevalence and incidence of attention-deficit/hyperactivity disorder among adults and children of different racial and ethnic groups. *JAMA Netw Open*. 2019;2(11):e1914344. Doi: 10.1001/jamanetworkopen.2019.14344.

Davis NO, Bower J, Kollins SH. Proof-of-concept study of an at-home, engaging, digital intervention for pediatric ADHD. *PLoS One*. 2018;13(1):e0189749. Doi: 10.1371/journal.pone.0189749.

Kollins SH, DeLoss DJ, Canadas E, et al. A novel digital intervention for actively reducing severity of paediatric ADHD (STARS-ADHD): A randomized controlled trial. *Lancet Digit Health*. 2020;2(4):E168-E178. Doi: 10.1016/S2589-7500(20)30017-0.

Kollins SH, Childress A, Heusser AC, Lutz J. Effectiveness of a digital therapeutic as adjunct to treatment with medication in pediatric ADHD. *NPJ Digit Med*. 2021;4(1):58. Doi: 10.1038/s41746-021-00429-0.

Magnus W, Nazir S, Anilkumar AC, Shaban K. Attention Deficit Hyperactivity Disorder. In: *StatPearls*. Treasure Island (FL): StatPearls Publishinghttps://www.ncbi.nlm.nih.gov/books/NBK441838/. Last updated August 8, 2023.

Oh S, Choi J, Han DH, Kim EY. Effects of game-based digital therapeutics on attention deficit hyperactivity disorder in children and adolescents as assessed by parents or teachers: A systematic review and meta-analysis. *Eur Child Adolesc Psychiatry*. 2024;33(2):481-493. Doi: 10.1007/s00787-023-02174-z.

U.S. Food and Drug Administration. DEN200026. EndeavorRx. Classification letter to Akili Interactive Labs Inc. % Janice Hogan. https://www.accessdata.fda.gov/cdrh_docs/pdf20/DEN200026.pdf. Dated June 15, 2020. (a)

U.S. Food and Drug Administration. FDA permits marketing of first game-based therapeutic to improve attention function in children with ADHD. https://www.fda.gov/news-events/press-announcements/fda-permits-marketing-first-game-based-digital-therapeutic-improve-attention-function-children-adhd. Published June 15, 2020. (b)

Wolraich ML, Hagan JF, Jr., Allan C, et al. Clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics*. 2019;144(4)Doi: 10.1542/peds.2019-2528.

Policy updates

9/2020: initial review date and clinical policy effective date: 10/2020.

9/2021: Policy references updated.

9/2022: Policy references updated.

9/2023: Policy references updated.

9/2024: Policy references updated.