Policy Number	**PSY301.022**
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Digital Health Technologies for Attention Deficit/Hyperactivity Disorder

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Related Policies (if applicable)
None

Disclaimer

Carefully check state regulations and/or the member contract.
Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Coverage

The use of EndeavorRx **is considered experimental, investigational and/or unproven** for all indications including attention-deficit/hyperactivity disorder.

Policy Guidelines

None.

Description

Digital health technologies is a broad term that includes categories such as mobile health, health information technology, wearable devices, telehealth and telemedicine, and personalized medicine. These technologies span a wide range of uses, from applications in general wellness to applications as a medical device, and include technologies intended for use as a medical product, in a medical product, as companion diagnostics, or as an adjunct to other

medical products (devices, drugs, and biologics). The scope of this review includes only those digital technologies that are intended to be used for therapeutic application and meet the following 3 criteria: 1) Must meet the definition of "Software as a medical device" which states that software is intended to be used for a medical purpose, without being part of a hardware medical device or software that stores or transmits medical information. 2) Must have received marketing clearance or approval by the U.S. Food and Drug Administration (FDA) either through the *de novo* premarket process or 510(k) process or pre-market approval and 3) Must be prescribed by a healthcare provider. This review will assess whether digital therapy in the form of a computer game can improve attention in children with ADHD.

Scope of Policy

Software has become an important part of product development and is integrated widely into digital platforms that serve both medical and non-medical purposes. The 3 broad categories of software use in medical devices are:

1. Software used in the manufacture or maintenance of a medical device (e.g., software that monitors x-ray tube performance to anticipate the need for replacement),
2. Software that is integral to a medical device or software in a medical device (e.g., software used to "drive or control" the motors and the pumping of medication in an infusion pump),
3. Software, which on its own is a medical device referred to as "Software as a Medical Device" (SaMD) (e.g., software that can track the size of a mole over time and determine the risk of melanoma).

The International Medical Device Regulators Forum, a consortium of medical device regulators from around the world led by the U.S. Food and Drug Administration (FDA) defines SaMD as "software that is intended to be used for one or more medical purposes that perform those purposes without being part of a hardware medical device." (1) Such software was previously referred to by industry, international regulators, and health care providers as "standalone software," "medical device software," and/or "health software," and can sometimes be confused with other types of software.

The scope of this policy includes only those digital technologies that are intended to be used for therapeutic application and meet the following 3 criteria:

1. Must meet the definition of "Software as a medical device" (SaMD) which states that software is intended to be used for a medical purpose, without being part of a hardware medical device or software that stores or transmits medical information.
2. Must have received marketing clearance or approval by the U.S. FDA either through the *de novo* premarket process or 510(k) process or pre-market approval and,
3. Must be prescribed by a healthcare provider.

Evaluation Framework for Digital Health Technologies

SaMDs, as defined by the FDA, are subject to the same evaluation standards as other devices. Technology evaluation criterion are as follows:

1. The technology must have final approval from the appropriate governmental regulatory bodies.

2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.
3. The technology must improve the net health outcome.[a]
4. The technology must be as beneficial as any established alternatives.
5. The improvement must be attainable outside the investigational settings.[b]

[a] The technology must assure protection of sensitive patient health information as per the requirements of The Health Insurance Portability and Accountability Act of 1996 (HIPAA).
[b] The technology must demonstrate usability in a real-world setting.

Other regulatory authorities such as the United Kingdom's National Institute for Health and Care Excellence (NICE) have proposed standards to evaluate SaMD. (2)

Regulatory Status
In April 2020, EndeavorRx (Akili Interactive Labs) received marketing clearance by the U.S. Food and Drug Administration (FDA) through the de novo premarket review process (DEN200026). EndeavorRx is a prescription device that is indicated to "improve attention function as measured by computer-based testing in children ages 8-12 years old with primarily inattentive or combined type ADHD, who have a demonstrated attention issue. Patients who engage with EndeavorRx demonstrate improvements in a digitally assessed measure Test of Variables of Attention (TOVA) of sustained and selective attention and may not display benefits in typical behavioral symptoms, such as hyperactivity." EndeavorRx is intended to be used as part of a therapeutic program that may include clinician-directed therapy, medication, and/or educational programs.

Rationale

Medical policies assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be

adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Digital Technologies for Attention-Deficit/Hyperactivity Disorder

Clinical Context and Therapy Purpose

Attention-deficit/hyperactivity disorder (ADHD) is a chronic condition characterized by core symptoms of hyperactivity, impulsivity, and inattention, which are considered excessive for the person's age. Both the International Classification of Mental and Behavioral Disorders 10th edition (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) require that the symptoms are reported or observed in several settings and that the symptoms of ADHD affect psychological, social, and/or educational/occupational functioning. Prevalence estimates for ADHD vary from 7.2% to 15.5% of children. (3)

For children younger than 17 years of age, the DSM-5 requires at least 6 symptoms of hyperactivity-impulsivity or at least 6 symptoms of inattention. The combined type requires a minimum of 6 symptoms of hyperactivity-impulsivity plus at least 6 symptoms of inattention. The symptoms must 1) occur often, 2) be present in more than 1 setting, 3) persist for at least 6 months, 4) be present before 12 years of age, 5) impair function in academic, social, or occupational activities, and 6) be excessive for the developmental level of the child.

Treatment may include environmental adjustments, behavioral and psychological interventions, and medications. In some children, these treatments do not sufficiently address symptoms. In others, there may be resistance by the parents to treat children with medications, or there may be other barriers to obtaining established therapies. EndeavorRx is proposed to address these barriers with improved access to care and minimal side effects. The therapy is based on research showing that impairments in attention and cognitive control are associated with lower activation of frontal, frontoparietal, and ventral attention networks. Previously, a game-like intervention was shown to improve cognitive performance and alter the electroencephalogram in the prefrontal cortex in older adults. (4) The similarity between cognitive control in older adults and attention deficits in ADHD led to the development of EndeavorRx for the treatment of ADHD in children.

The purpose of prescribed therapeutic digital applications is to provide a treatment option that is an alternative to or an improvement on existing therapies for individuals with attention-deficit/hyperactivity disorder (ADHD).

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is children 8 to 12 years of age with ADHD, with primarily inattentive or combined type ADHD.

Interventions

The digital technology being considered is EndeavorRx. It is an interactive video game that requires the user to navigate a character through a game-like space while collecting objects. It is designed to be played on a mobile device at home for approximately 25 minutes a day, 5 days a week. Typical treatment would be for a period of 1 month, with an extension up to 3 months allowed per license.

EndeavorRx uses a proprietary technology platform that adjusts the difficulty level based on the user's prior performance. The adaptive algorithm is intended to encourage the user to surpass their previous performance, so that the user would gradually increase their ability to focus attention. No claims are made for behavioral symptoms such as hyperactivity.

Version 1.5 was reviewed by the U.S. Food and Drug Administration for De Novo marketing clearance. Earlier non-prescription versions were called ProjectEvo and AKL-T01, which was released under the Enforcement Policy for Digital Health Devices For Treating Psychiatric Disorders During the COVID-19 Public Health Emergency.

EndeavorRx is intended to be used as part of a therapeutic program. EndeavorRx is not intended to be used as a stand-alone treatment

Comparators

Established treatments for ADHD in children include educational, environmental, psychological, and behavioral interventions, and medication. Almost two-thirds of children with ADHD take medication, and about half receive behavioral treatment. (3) The following therapies are currently used to treat ADHD, either individually or in combination:

- Educational intervention involves discussion with parents about symptoms and access to services, environmental modifications such as seating arrangements, changes to lighting and noise, reducing distractions, and the benefit of having movement breaks and teaching assistants at school.
- Parent-child behavioral therapy teaches parenting techniques within the principles of behavior therapy. The therapy programs typically last 2 to 3 months and include rewarding positive behavior, identifying unintentional reinforcement of negative behaviors, limiting choices, and using calm discipline.
- Medication with stimulants, such as methylphenidate, is considered first-line therapy for ADHD in school-age children. However, adverse effects of stimulants may include sleep disturbance, decreased appetite, and weight changes. Combination therapy with medication and behavioral interventions can improve both core ADHD symptoms and non-ADHD symptoms such as social skills and parent-child relations.

Outcomes

The general outcomes of interest are change in symptoms of inattention, ability to function at school and home, quality of life, and treatment-related adverse effects.

ADHD-specific rating scales are described in Table 1.

Table 1. ADHD Rating Scales

Rating Scale	Description	Scoring
ADHD Rating Scale (5)	The ADHD-RS-IV is an 18-item, clinician-administered questionnaire for which a parent respondent rates the frequency of occurrence of ADHD symptoms and behaviors as defined by criteria outlined for ADHD in the DSM-IV. Each item is scored on a 4-point scale ranging from 0 (rarely or never) to 3 (very often) with total scores ranging from 0 to 54. The 18 items are grouped into 2 subscales: hyperactivity/impulsivity and inattentiveness.	Each subscale produces a subscale score ranging from 0 to 27. A higher score indicates more severe ADHD symptoms and behaviors and a negative change in total score indicates improvement.
The Clinical Global Impression Scale – Improvement (6)	The CGI-I is a clinician's comparison of the participant's overall clinical condition at follow-up to the overall clinical condition at baseline. It includes an assessment of the change from the initiation of treatment with a rating from 1 to 7.	The 7-point scale is: 1=Very much improved, 2=Much improved, 3=Minimally improved, 4=No change, 5=Minimally worse, 6=Much worse, and 7=Very much worse. A score of 1, 2, or 3 would indicate overall improvement of ADHD severity.
Conners Comprehensive Behavior Rating Scales (7)	Parent and teacher forms are available in full (90-item, 59-item) and abbreviated (27-item, 28-item) versions.	Normative values are provided separately by gender and age.
The Vanderbilt Assessment Scales for parents and teachers (8, 9)	The Vanderbilt Assessment Scales are based on DSM-IV scales. The scale for parents has 55 questions that rate symptoms and their impact on family and school. The teacher scale includes 43 questions on symptoms and school performance.	Normative data and percentile ranks are provided for each subscale by grade and gender.
Test of Variables of Attention, Attention performance index (10)	TOVA® is a validated computerized continuous performance test that presents targets and non-targets as squares that either appear at the top or bottom of the screen. The task consists of two halves: the first half	Clinical meaningfulness for the pivotal trial was defined as: TOVA API improvement greater than 1.4 points, and post-test API score 0 or more (normative range), ADHD-RS

	has a target-to-non-target ratio assessed sustained attention; the second half assesses inhibitory control. The program assesses attention consistency, attentional lapses, and processing speed.	improvement of 2 points or more, CGI-I post-score of 1 (very much improved) or 2 or less (very much or much improved), and any improvement in an Impairment Rating Scale.

ADHD: attention-deficit/hyperactivity disorder; ADHD-RS-IV: ADHD rating scale, version 4; CGI-I: clinical global impression scale-improvement; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders 4th edition; TOVA (API): test of variables of attention (attention performance index).

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Randomized Controlled Trials

Key RCT characteristics and results are described in Tables 2 and 3. Limitations in study relevance and study design and conduct are described in Tables 4 and 5.

Kollins et al. (2020) reported results of the STARS-ADHD (Software Treatment for Actively Reducing Severity of ADHD) randomized double blind trial, which compared treatment with AKL-T01 to a game (EVO Words) that targets cognitive domains other than those targeted by AKL-T01. (11) EVO Words requires the child to spell as many words as possible by connecting letters in a grid in a fixed amount of time. Parents and children were informed that the study was evaluating 2 different investigational interventions for ADHD, and only the study coordinator was aware of which video game the children received. Compliance was monitored by study coordinators, who notified parents by email if the game was not played for more than 48 hours. After 4 weeks, patients were reassessed for attentional functioning, ADHD symptoms, and impairment. The primary outcome was the change in the test of variable of attention, attention performance index (TOVA API). Secondary outcomes included a number of clinician and parent-reported measures such as the ADHD rating scale, Impairment Rating Scale, and Clinical Global Impressions-Improvement. Out of 348 patients who were randomly assigned, 5 were lost to follow-up, 4 were withdrawn by the parent or investigator, and 10 had invalid test results; there was a final sample of 329 children for the primary outcome measure. The 2 children who received the incorrect allocation were included in the intention-to-treat population. The mean change from baseline on the TOVA API was 0.93 in the AKL-T01 group and 0.03 in the control group ($p<.05$). However, there were no between-group differences for secondary measures, which included the clinician and parent ratings of ADHD symptoms; both

groups showed improvement in ADHD ratings from baseline to post-treatment. Treatment-related adverse events AKL-T01 group included frustration (5 [3%] of 180) and headache (3 [2%] of 180) with a mean number of completed sessions of 83%, compared to 96% compliance in the EVO Words group.

Kollins et al. (2021) reported results of the STARS-Adjunct study, a multicenter, open-label study of EndeavorRx as an adjunct to pharmacotherapy in children 8 to 14 years of age with ADHD on stimulant medication (n= 130) or EndeavorRx alone (n=76). (12) This study design does not permit conclusions about the adjunctive treatment effect of EndeavorRx as both study arms received EndeavorRx. An appropriate study design would be comparing EndeavorRx plus stimulant medication versus stimulant medication alone.

Table 2. Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	**Comparator**
Kollins et al. (2020); STARS-ADHD (11) (NCT02674633)	United States	20	2016 to 2017	348 pediatric patients aged 8 to 12 years, with confirmed ADHD, TOVA API scores -1.8 and below, without or with washout of disorder-related medication.	AKL-T01 (EndeavorRx) for 25 min a day on 5 days per week for 4 weeks (n=180)	EVO Words for 25 min a day on 5 days per week for 4 weeks (n=168)
Kollins et al. (2021); STARS-Adjunct (12) (NCT03649074)	United States	15	2018 to 2019	Inclusion • Children ages of 8 to 14 years with confirmed ADHD • Experiencing suboptimal treatment of ADHD (IRS ≥ 3 overall impairments score) • On stimulants cohort participants must have been stable on stimulant medication at an approved dose for ≥ 30 days prior to enrollment and for the no stimulants cohort, participants must be stable off stimulant medication for ≥ 30 days prior to enrollment Primary endpoint • Change in ADHD-related impairment as	AKL-T01 (EndeavorRx) for 25 min a day on 5 days/week for 4 weeks for 4 weeks, followed by a 4-week pause and another 4-week treatment plus stimulant medication (n=130)	AKL-T01 (EndeavorRx) for 25 min a day on 5 days/week for 4 weeks for 4 weeks, followed by a 4-week pause and another 4-week treatment only (n=76)

				measured by the (parent-reported, clinician-rated) from baseline to day 28		

ADHD: attention-deficit/hyperactivity disorder; IRS: Impairment Rating Scale; min: minutes; NCT: national clinical trial; RCT: randomized controlled trial; STARS-ADHD: Software Treatment for Actively Reducing Severity of ADHD; TOVA API: test of variables of attention, attention performance index.

Table 3. Summary of Key RCT Results

Study	**TOVA API Mean Improvement (SD)**	**TOVA API Improvement >1.4 points n/N (%)**	**ADHD-Rating Scale Improvement ≥2 points n/N (%)**	**Impairment Rating Scale n/N (%)**	**Clinical Global Impressions ≤2 n/N (%)**
Kollins et al. (2020); STARS-ADHD (11)					
N	329	329	337	332	339
AKL-T01	0·93 (3.15)	79/169 (47%)	128/173 (74%)	82/171 (48%)	29/175 (17%)
EVO Words	0·03 (3.16)	51/160 (32%)	119/164 (73%)	60/161 (37%)	26/164 (16%)
p-value	<.05	.006	.77	.049	.86
Kollins et al. (2021); STARS-Adjunct (12)	**ADHD-IRS Total (Change mean ±SD)**	**ADHD-IRS Inattention subscale (Change mean ±SD)**	**ADHD-IRS Hyperactivity-Impulsivity subscale**	**CGI-I (Change mean ±SD)**	**IRS overall responder[a], n/N (%)**
N	128	74	74	74	-
AKL-T01 + stimulants	-6.1 (±7.18)	-3.4 (±4.43)	-2.7 (±3.92)	3.3 (±0.84)	Day 28: 71/128 (55.5%) Day 84: 77/113 (68.1%)
AKL-T01 only	-7.4 (±9.92)	-3.9 (±5.60)	-3.4 (±5.13)	3.4 (±0.83)	Day 28: 30/74 (40.5%) Day 84: 46/67 (68.7%)
p value between groups	Not reported	Not reported	Not reported	Not reported	Not reported

ADHD: attention deficit/hyperactivity disorder; CGI-I: clinical global impressions scale-improvement; IRS: impairment rating scale; RCT: randomized controlled trial; SD: standard deviation; STARS-ADHD: Software Treatment for Actively Reducing Severity of ADHD; TOVA API: test of variables of attention, attention performance index.

[a] Proportion of children with ≥1 point improvement on IRS Overall Score

The purpose of the study limitations tables (Tables 4 and 5) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of evidence supporting the position statement.

STARS-ADHD was well-designed and well conducted. However, several limitations affect its relevance to clinical practice. First, the study population was not representative of intended use. The trial eligibility criteria only allowed inclusion of children not taking ADHD medication, while EndeavorRx is intended to be used as part of a therapeutic program that may include clinician-directed therapy, medication, and/or educational programs. Additionally, the 4-week study duration was insufficient to evaluate long-term effects on ADHD-related impairment and functioning, which is critical given the chronic nature of the condition. Lastly, the clinical significance of an improvement in a computerized test of attention without a detectable improvement in behavior by parents and clinicians is uncertain.

Major limitations identified in the STARS-Adjunct study related to the use of an inappropriate comparator. The study compared EndeavorRx plus stimulant medication versus Endeavor Rx alone. This design permits drawing conclusions only about the adjunctive effect of stimulant medication rather than EndeavorRx. Comparing EndeavorRx plus stimulant medication versus stimulant medication alone would be the design to inform the treatment effect of adjunctive EndeavorRx. In addition, the trial did not report statistical comparisons between arms and only reported pre- and post- differences within each arm. Lastly, the study duration was not sufficient to assess long-term impact on ADHD-related impairment and functioning as ADHD is a chronic condition and understanding long-term treatment effects is critically important.

Table 4. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Kollins et al. (2020); STARS-ADHD (11)	3. Study population not representative of intended use			7. Other (improvement on computerized tests of attention is weakly associated with classroom attention)	1. Not sufficient duration for benefit
Kollins et al. (2021); STARS-Adjunct (12)			5. Other (Study design compared EndeavorRx plus stimulant medication versus EndeavorRx alone)	5 and 6. Clinically significant difference not prespecified and not supported	1. Not sufficient duration for benefit

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest; 5. Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. No establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 5. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Kollins et al. (2020); STARS-ADHD (11)				2. Missing data was not included in the intention-to-treat analysis.		
Kollins et al. (2021); STARS-Adjunct (12)	1. Participants not randomly allocated; 4. Inadequate control for selection bias	1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician				4. Other (comparative treatment effects not reported; results report only within-group effect)

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician; 4. Other.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6.

Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

Section Summary: Digital Therapies for Attention-Deficit/Hyperactivity Disorder

The pivotal STARS-ADHD RCT compared outcomes of EndeavorRx with a word game that targeted different cognitive abilities (digital control intervention). The experimental treatment group had significantly greater improvement on a computerized test of attention, but the experimental and control groups improved to a similar extent on parent and clinician assessments. STARS-ADHD was well-designed and well conducted. However, several limitations affect its relevance to clinical practice. First, the study population was not representative of intended use. The trial eligibility criteria only allowed inclusion of children not taking ADHD medication, while EndeavorRx is intended to be used as part of a therapeutic program that may include clinician-directed therapy, medication, and/or educational programs. Additionally, the 4-week study duration was insufficient to evaluate long-term effects on ADHD-related impairment and functioning, which is critical given the chronic nature of the condition. Lastly, the clinical significance of an improvement in a computerized test of attention without a detectable improvement in behavior by parents and clinicians is uncertain. A second open label study STARS-Adjunct compared EndeavorRx plus stimulant medication with EndeavorRx alone. This study design does not permit conclusions about the adjunctive treatment effect of EndeavorRx as both study arms received EndeavorRx. An appropriate study design would be comparing EndeavorRx plus stimulant medication versus stimulant medication alone.

Summary of Evidence

For individuals who are children ages 8-12 years with attention-deficit/hyperactivity disorder (ADHD) who receive EndeavorRx, the evidence includes a pivotal randomized controlled trial (RCT) and an open label study. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. The pivotal STARS-ADHD RCT compared outcomes of EndeavorRx with a word game that targeted different cognitive abilities (digital control intervention). The experimental treatment group had significantly greater improvement on a computerized test of attention, but the experimental and control groups improved to a similar extent on parent and clinician assessments. STARS-ADHD was well-designed and well conducted. However, several limitations affect its relevance to clinical practice. First, the study population was not representative of intended use. The trial eligibility criteria only allowed inclusion of children not taking ADHD medication, while EndeavorRx is intended to be used as part of a therapeutic program that may include clinician-directed therapy, medication, and/or educational programs. Additionally, the 4-week study duration was insufficient to evaluate long-term effects on ADHD-related impairment and functioning, which is critical given the chronic nature of the condition. Lastly, the clinical significance of an improvement in a computerized test of attention without a detectable improvement in behavior by parents and clinicians is uncertain. A second open label study STARS-Adjunct compared EndeavorRx plus

stimulant medication with EndeavorRx alone. This study design does not permit conclusions about the adjunctive treatment effect of EndeavorRx as both study arms received EndeavorRx. An appropriate study design would be comparing EndeavorRx plus stimulant medication versus stimulant medication alone. A number of questions remain concerning the efficacy of this treatment, and additional studies to assess the effect of the digital therapy in adolescents and in children on stimulant medication have recently been completed but not yet published. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements

American Academy of Pediatrics

In 2019, the American Academy of Pediatrics (AAP) updated their 2011 clinical practice guideline on the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder (ADHD) in children and adolescents. (3)

The guidelines were based on a systematic evidence review by the Agency for Healthcare Research and Quality. The AAP gave strong recommendations based on level A evidence for medications and training and behavioral treatment for ADHD implemented with the family and school.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and/or unpublished trials that might influence this policy are listed in Table 6.

Table 6. Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date
NCT05991167	EndeavorRx® Prospective Product Registry ("Expedition EndeavorRx")	150	Dec 2025
NCT02828644	Software Treatment for Actively Reducing Severity of ADHD - Follow Up (STARS-ADHD2)	175	Feb 2018
NCT05183919	Software Treatment for Actively Reducing Severity of ADHD in Adults (STARS ADHD Adult)	223	Jan 2023
NCT04897074	Software Treatment for Actively Reducing Severity of ADHD in Adolescents (STARS-ADHD-Adolescents)	165	Sep 2022
NCT03310281	Software Treatments for Actively Reducing Severity of Cognitive Deficits in MDD (STARS-MDD)	84	Nov 2018
NCT03649074	Software Treatment for Actively Reducing Severity of ADHD as Adjunctive Treatment to Stimulant	203	Sep 2019

NCT: national clinical trial.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	99199
HCPCS Codes	A9291, G0552, G0553, G0554

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
12/15/2025	Document updated. Coverage unchanged. No new references added.
10/15/2024	Reviewed. No changes.
01/01/2024	Document updated with literature review. Coverage statement changed from “Prescription digital therapy is considered experimental, investigational and/or unproven for the treatment of attention-deficit/hyperactivity disorder” to “The use of EndeavorRx is considered experimental, investigational and/or unproven for all indications including attention-deficit/hyperactivity disorder”; intent unchanged. Added references 1, 2, and 12. Title changed from “Digital Health Therapies for Attention Deficit/Hyperactivity Disorder”.
10/01/2022	Reviewed. No changes.
04/15/2022	New medical document. Prescription digital therapy is considered experimental, investigational and/or unproven for the treatment of attention-deficit/hyperactivity disorder.