3.03.03 Digital Health Technologies for Attention Deficit/Hyperactivity Disorder			
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Section:	3.0 Mental Health	**Page:**	Page 1 of 14

Policy Statement

I. The use of EndeavorRx is considered **investigational** for all indications including attention-deficit/hyperactivity disorder.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

The following CPT code represents reSET by Pear Therapeutics. Per the manufacturer, reSET is prescription digital therapeutics and is a cognitive behavioral therapy, indicated for patients 18 years of age and older who are enrolled in outpatient treatment under the supervision of a clinician.

- **A9291**: Prescription digital behavioral therapy, FDA-cleared, per course of treatment

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 a digital therapy in the form of a computer game can improve attention in children with ADHD.

Related Policies

- N/A

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

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

Background

Scope of Review

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 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" (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.

BCBSA Evaluation Framework for Digital Health Technologies

SaMDs, as defined by the FDA, are subject to the same evaluation standards as other devices. The Blue Cross and Blue Shield Association 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,]

Literature Review

Evidence reviews 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.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

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 review.

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 a 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 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 one 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 includes rewarding positive behavior, identifying unintentional reinforcement of negative behaviors, limiting choices, and using calm discipline.
- Medication with stimulants, such as methylphenidate, are 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 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.	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 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.

Review of Evidence

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 that 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, resulting in 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. The study was well-designed and conducted, but there are a number of limitations in study relevance due to the limited age range, limited follow-up, and most importantly the uncertainty of the association of computerized tests with observable behavior. There are also questions regarding what might be the most effective treatment schedule and characteristics of the patients who might benefit from this intervention. As was also noted by the trial authors "the results of the current trial are not sufficient to suggest that AKL-T01 should be used as an alternative to established and recommended treatments for ADHD."

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)	US	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)

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
Kollins et al (2021); STARS-Adjunct[12], (NCT03649074)	US	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 measured by the (parent-reported, clinician-rated) from baseline to day 28	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)

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

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[13],	**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%)

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 (%)
					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. Major limitations identified in the STARS-ADHD study were 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. Further, the study duration of 4 weeks 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. 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. Major limitations in the study design and conduct are summarized in detailed in Table 5.

Table 4. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Kollins et al (2020)[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[13],			5. Other (Study design compared EndeavorRx plus stimulant medication versus Endeavor Rx alone)	5 and 6. Clinical 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. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 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 (e.g., proposed as an adjunct but not tested as such); 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. Incomplete reporting of harms; 4. Not 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)[11],				2. Missing data was not included in the intention-to-treat analysis.		
Kollins et al (2021); STARS-Adjunct[13],	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. Participants or study staff not blinded; 2. Outcome assessors not blinded; 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 single RCT compared outcomes of EndeavorRx® (AKL-T01) with a word game that targeted different cognitive abilities (digital control intervention). Although the experimental treatment group had significantly greater improvement on a computerized test of attention, both the experimental and control groups improved to a similar extent on parent and clinician assessments. 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 compared EndeavorRx plus stimulant medication with EndeavorRx alone. This study design does not permit conclusions about 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.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

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.

U.S. Preventive Services Task Force Recommendations

Not applicable

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 6.

Table 6. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
Unpublished			
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.
[a] Denotes industry-sponsored or cosponsored trial.

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Documentation for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	None	
HCPCS	A9291	Prescription digital behavioral therapy, FDA-cleared, per course of treatment

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
06/01/2022	New policy.
09/01/2022	Annual review. No change to policy statement. Literature review updated.
10/01/2023	Annual review. Policy statement, guidelines and literature review updated. Policy title changed from Digital Health Therapies for Attention Deficit/ Hyperactivity Disorder to current one.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE Red font: Verbiage removed	AFTER Blue font: Verbiage Changes/Additions
Digital Health Therapies for Attention Deficit/Hyperactivity Disorder 3.03.03 Policy Statement: I. Prescription digital therapy is considered **investigational** for the treatment of attention-deficit/hyperactivity disorder.	Digital Health Technologies for Attention Deficit/Hyperactivity Disorder 3.03.03 Policy Statement: I. The use of EndeavorRx is considered **investigational** for all indications including attention-deficit/hyperactivity disorder.