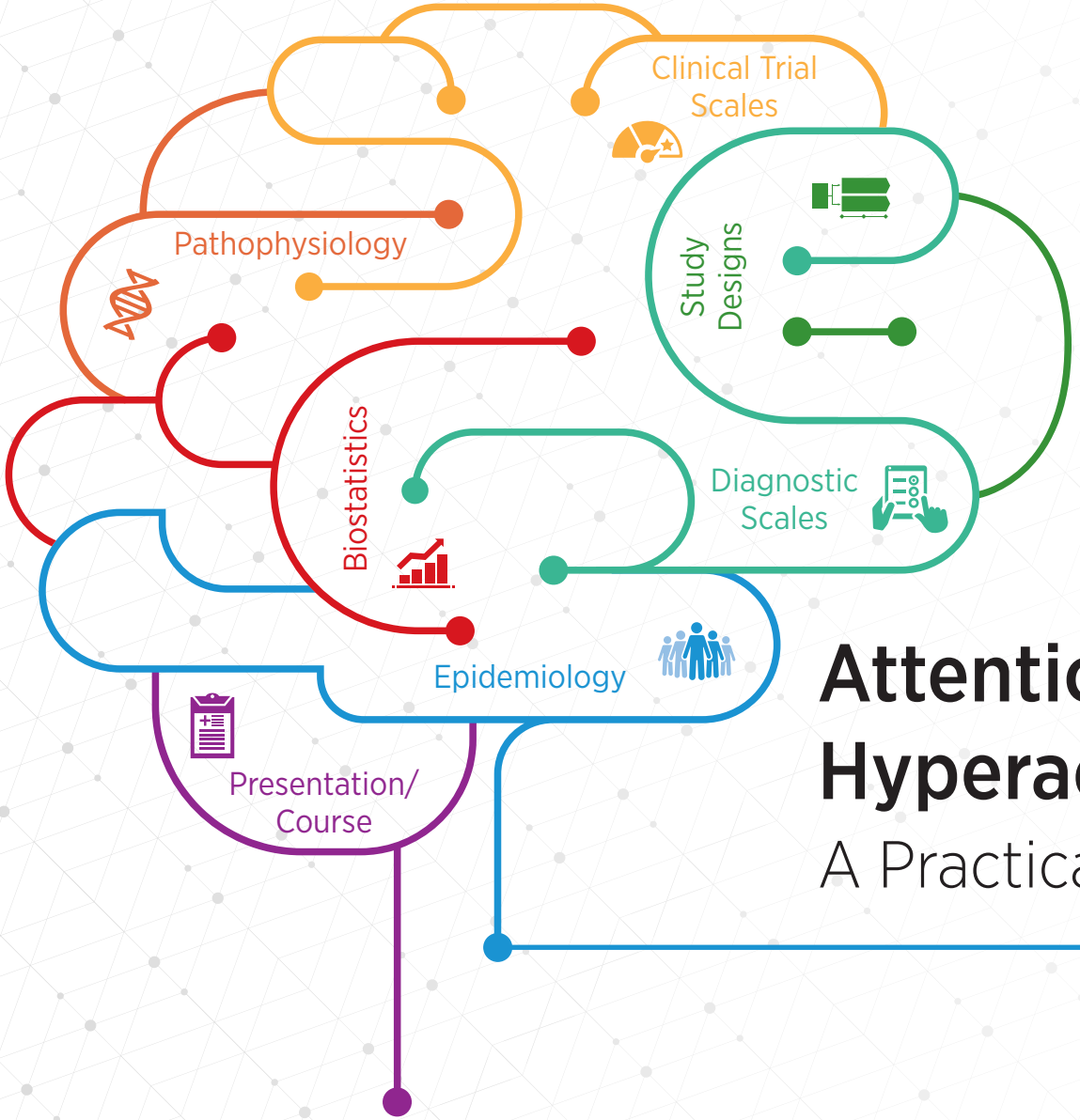



# Attention Deficit Hyperactivity Disorder

## A Practical Guide

TrisADHDBooksforHCPs.com

Tris PHARMA

# Introduction

The purpose of this informational booklet is to provide healthcare professionals with current diagnostic and disease-state information about attention deficit hyperactivity disorder (ADHD) in an easy-to-use, handy format.

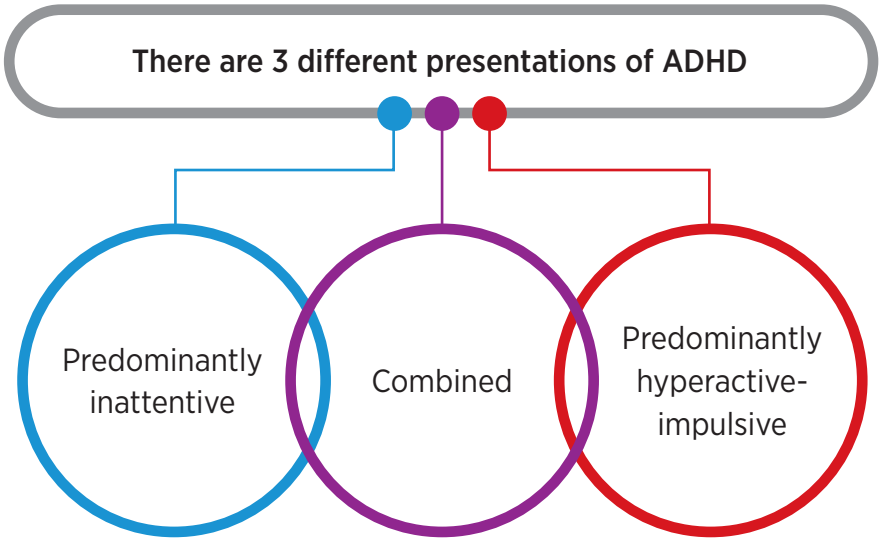
The current epidemiology of ADHD in children, adolescents, and adults is provided, along with a basic outline of ADHD pathophysiology and theories of ADHD causation. This booklet outlines important ADHD measurement tools and scales that are commonly used in the biomedical literature to report clinical trial efficacy and safety data. Methods of reporting and interpreting pharmacokinetic data are also included. Finally, to provide an aid in understanding the body of evidence related to ADHD research, a review of various techniques commonly used in the reporting of inferential and descriptive statistics associated with ADHD clinical trials is provided.

Compliments of Tris Pharma, Inc.
Produced by Medica Communications, LLC.

# Epidemiology

# What is ADHD?

- ADHD is the most common childhood neurodevelopmental disorder[1]
- The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5®) defines ADHD as "A persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development."[2]



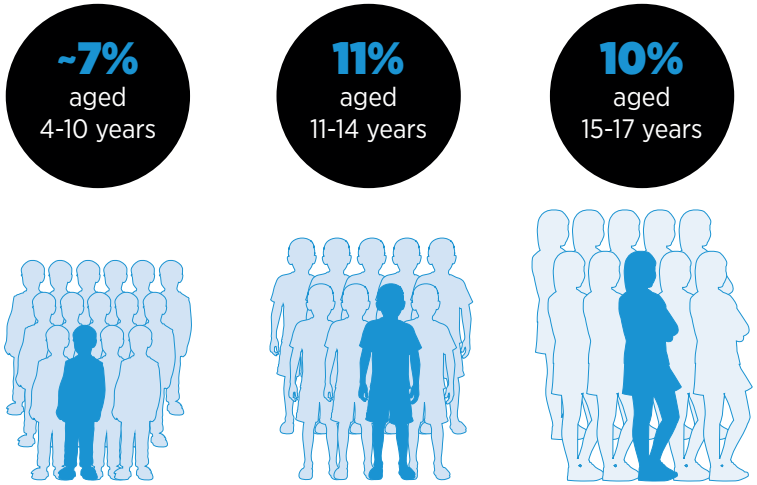

- In order to meet the diagnostic criteria for ADHD, there must be clear evidence of interference with, or the reduced quality of, social, academic, or occupational functioning attributable to the symptoms[2]
  - Several inattentive or hyperactive-impulsive symptoms present prior to age 12 years
  - Several inattentive or hyperactive-impulsive symptoms present in two or more settings (e.g., at home, school, or work; with friends or relatives; in other activities)

# The estimated prevalence of diagnosed ADHD in the US varies, but epidemiological studies suggest it may be increasing among children, adolescents, and adults

## In 2016, ~6.1 million (9.4%) children aged 2–17 years had ever received an ADHD diagnosis[3]

- 2% aged 2-5 years[3]
- 9.6% aged 6-11 years[3]
- 13.6% aged 12-17 years[3]
- Girls, 5.6%[3]; Boys, 12.9%[3]

### Children and adolescents with ADHD diagnosis in 2011[4]




## History of ADHD diagnoses by a healthcare provider as reported by parents increased by approximately 5% per year between 2003 and 2011 among children and adolescents aged 4-17 years[5]

- 7.8% in 2003
- 9.5% in 2007
- 11.0% in 2011

**As many as 60% of individuals with ADHD symptoms in childhood continue to have ADHD symptoms as adults[6]**

## Adults with ADHD diagnosis

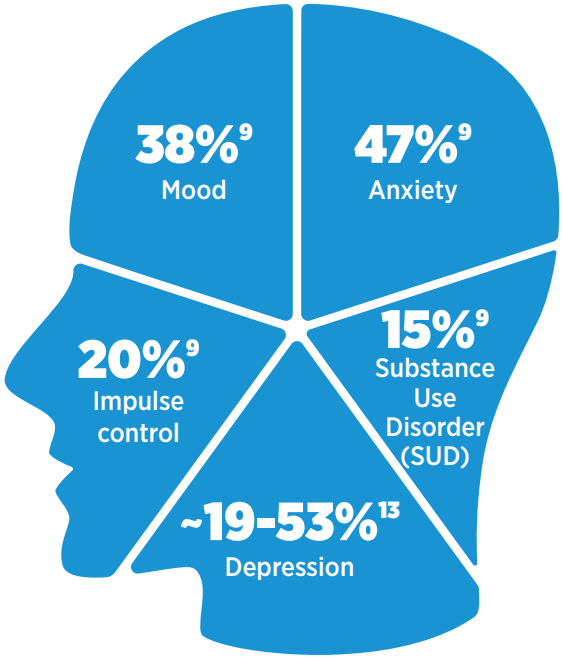
- 4.4-5.2% aged 18-44 years[7-9]
- 2.8-3.5% aged 50 years or older[10]

**More adults >50 years who are experiencing symptoms of ADHD are seeking assessment for the first time[11]**

# Individuals with ADHD often have psychiatric comorbidities

## Adults

- Up to 80% of adults with ADHD have at least one coexisting psychiatric disorder[12,13]
  - Lifetime psychiatric lifetime comorbidity is ~77% in patients with ADHD compared to ~46% in patients without ADHD[13]




## Children and Adolescents

- ~50% of children and adolescents aged 4-17 years have at least 1 comorbid psychiatric condition[14]
- Behavioral problems are the most common comorbidity in children[14,15]
  - 25-75% have comorbid oppositional defiant disorder[15]
  - 16.5% have comorbid conduct disorder[14]
- Children with ADHD are more likely to have general anxiety and subtypes[15]
- Children with ADHD may experience a depressive illness[16]

# Pathophysiology

# Neuroimaging shows ADHD is associated with dysfunctions in several areas of the brain

**Imaging studies suggest ADHD is associated with dysfunction in the following areas[17]:**

- Frontostriatal
- Anterior cingulum
- Dorsolateral and ventrolateral prefrontal cortex
- Orbitofrontal cortex
- Superior parietal regions
- Caudate nucleus
- Thalamus
- Amygdala
- Cerebellum

**Changes in neuronal plasticity may be behind persisting brain changes in ADHD**

**Three key regions in the networks mediating the control of attention and action sometimes show structural differences between groups with and without ADHD.[18]**

- The prefrontal cortex, the striatum (the caudate and the putamen), and the cerebellum hubs.[18]
- The white matter tracts that form the physical connections in these 3 hubs may differ in the brains of individuals with impaired attention.[18]

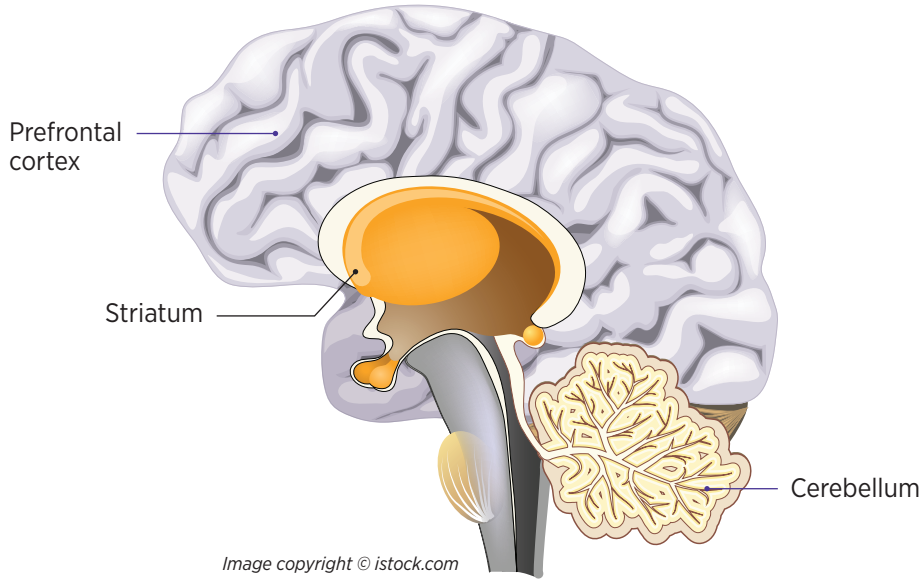
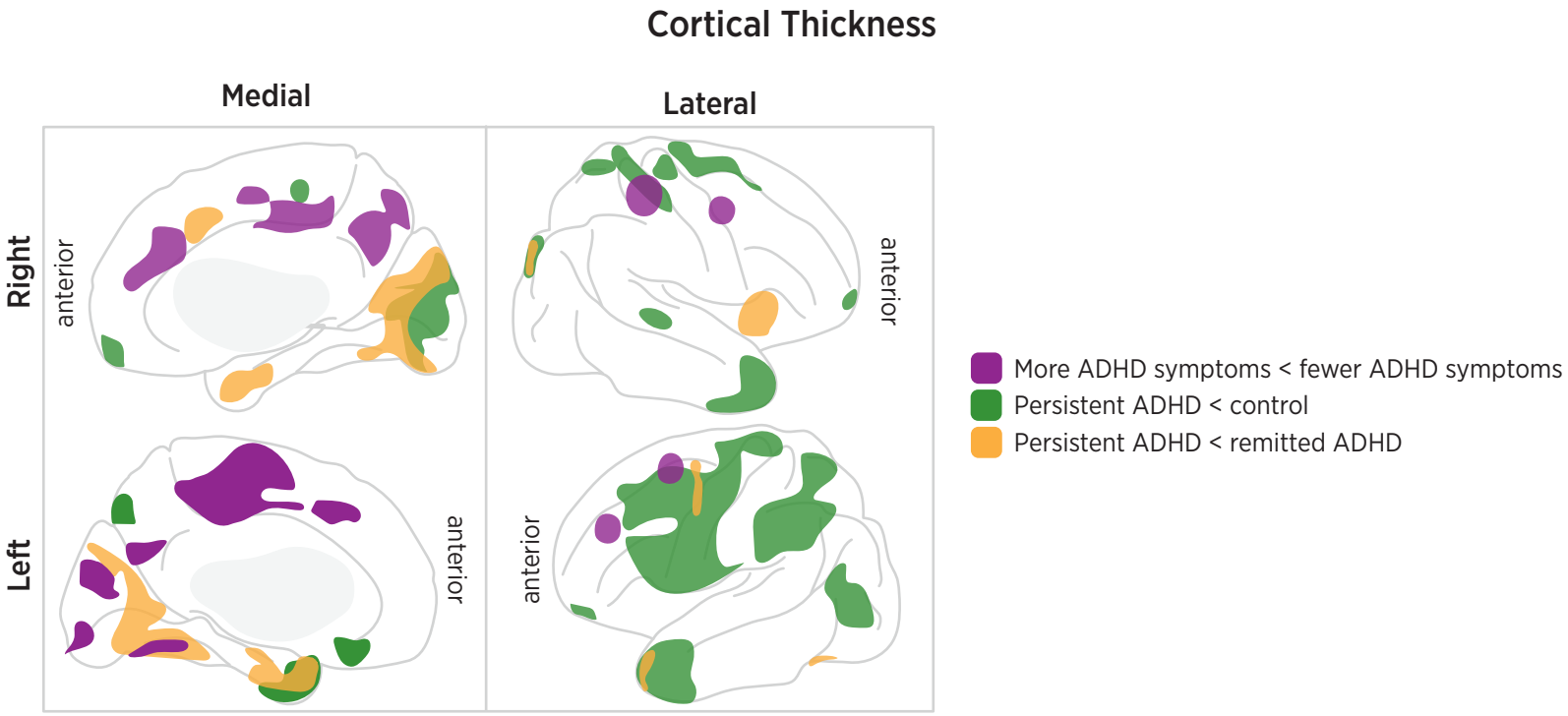



*Image copyright © istock.com*

# Specific structural, functional, and neurotransmitter changes in the brain may be associated with ADHD

## Structural

Structural imaging studies include volumetric measurements of gray or white matter of the whole brain (including or excluding the cerebellum) and its lobes, and fine-grained measurements (e.g., cortical thickness, density of gray matter) acquired from individual voxels in the brain or across the cortical surface.[19]




Adapted from Jadidian A, Hurley RA, Taber KH. Neurobiology of adult ADHD: Emerging evidence for network dysfunctions. *J Neuropsychiatry Clin Neurosci*. 2015;27(3):173-178.

# Specific structural, functional, and neurotransmitter changes in the brain may be associated with ADHD (continued)

## Individuals with ADHD have structural differences in their brains compared with individuals without ADHD

### Gray matter density is lower[20,21]

- Localized volumetric gray matter abnormalities in the basal ganglia[20]
- Reduced right globus pallidus and putamen volumes and decreased caudate volumes in manual tracing studies in children with ADHD[20]
- Volume reduction in the anterior cingulate cortex of adults with ADHD[20]

### Smaller volume overall and in specific structures[19,20,23]

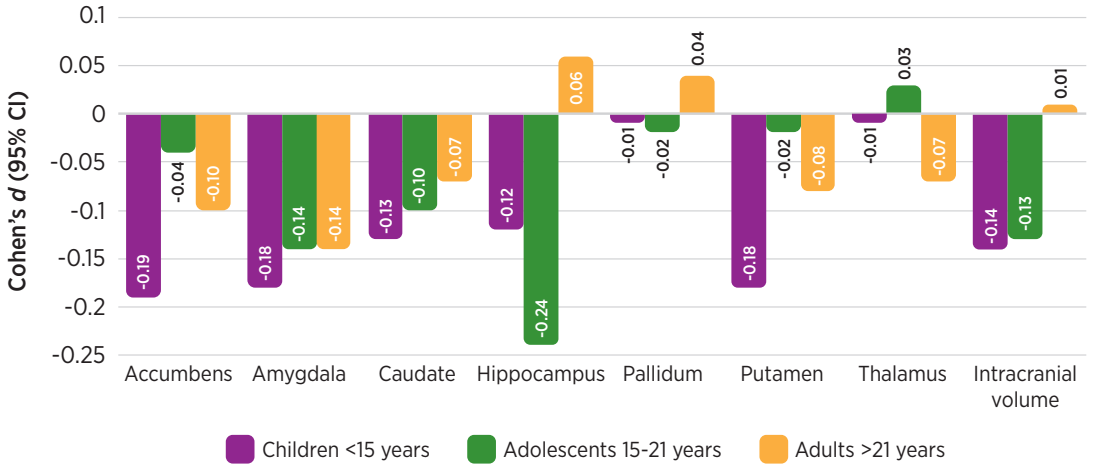
- Large MRI study showed volumes of various brain structure were slightly smaller in children, adolescents, and adults with ADHD (N=1,713) compared with controls (N=1,529)[23]

### White matter abnormalities

- Lobar white matter volume reduced ~4% in children and adolescents (N=152) with ADHD aged 5-18 years[19,22]
- Abnormally high fractional anisotropy in frontal networks in adolescents (N=14) with ADHD[19]

### Cortical differences

- Delayed cortical maturation in children and adolescents (N=223) aged 7-13 years[24]
- Reduced cortical thickness in adults.[20,25]



# Specific structural, functional, and neurotransmitter changes in the brain may be associated with ADHD (continued)

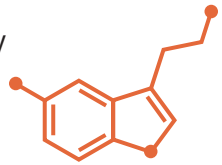
## Functional

**Regions of the brain that are associated with ADHD correspond to networks involving frontal regions, executive function, and attention.[26]**

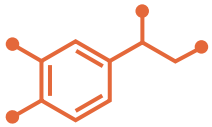
- Functional neuroimaging studies have shown variation in activation/suppression of networks in ADHD
  - Under-activation of frontostriatal and frontoparietal circuits, and other frontal brain regions[20,27-29]
  - Under-activation of systems involved in executive function and attention[34,44]
  - Over-activation (reduced suppression) of the default mode network during task performance[30,31]

## Neurotransmitters

- Neuromodulatory influences over catecholamines in the fronto-striato-cerebellar regions play important roles in high-level executive functions[32]
- ADHD symptoms may be related to dysregulation of basal, tonic catecholaminergic levels[30,33]
  - Too low: distractibility
  - Too high: hyperactivity and anxiety
- Dopamine[18,30,34]
  - Deficit in dopaminergic signaling[30]



- Noradrenaline
  - Noradrenergic signaling[34,35]



- Glutamate[36,37]
  - Levels of glutamate/glutamine are significantly reduced in the caudate/putamen of adults with ADHD compared to adults without ADHD

# Hereditary and genetic factors associated with ADHD

- Several genes associated with the catecholaminergic system—including the dopamine receptor genes (*DRD4* and *DRD5*), the dopamine transporter gene, and the gene for dopamine beta-hydroxylase, which catalyzes conversion of dopamine to norepinephrine—have been implicated in ADHD.[33]
- Serotonin transport gene polymorphism was associated with behavioral response to methylphenidate in children with ADHD aged 6-12 years (N=157)[38]

# Presentation/Course

# Clinical presentations

**Diagnosis in children:** ≥6 of the symptoms that have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities[2]

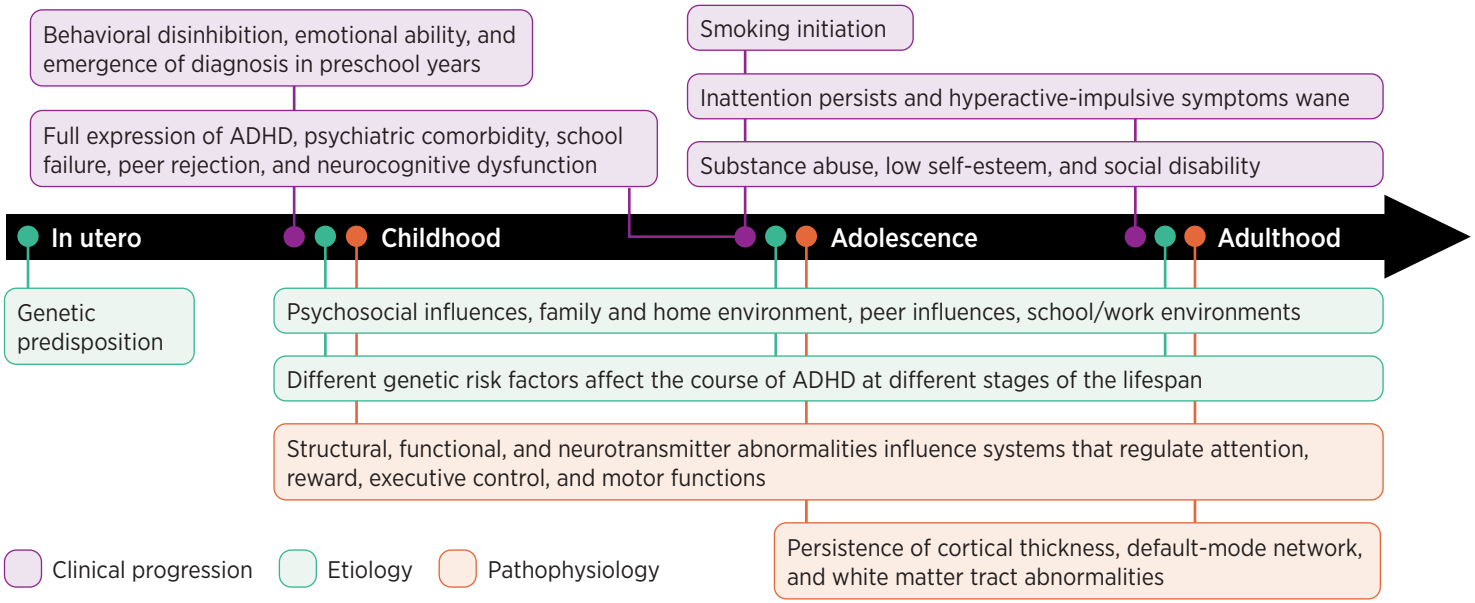
**Diagnosis in individuals aged 17 and older:** ≥5 of the symptoms[2]

**The DSM-5 describes three different presentations of ADHD[2]**

| Symptoms of ADHD subtypes[2,53,54] | | |
|---|---|---|
| **Inattentive** | **Hyperactive/Impulsive** | **Combined** |
| • More common in adults | • More common in children | • ≥6 more symptoms inattentive |
| • Careless mistakes | • Fidgety | • ≥6 more symptoms of hyperactive/impulsive |
| • Short attention span | • Moves frequently | |
| • Poor listening skills | • Restless | |
| • No follow through | • Noisy | |
| • Disorganization | • Always on the go | |
| • Appearing lazy or apathetic | • Talkative | |
| • Routinely misplaces essential items (e.g., keys, wallet, backpack, etc.) | • Impulsive reactions | |
| • Distractibility | • Has trouble waiting their turn | |
| • Forgetfulness | • Disruptive | |

# Longitudinal course of ADHD

- Hyperactivity tends to decrease with age[41,42]
- Inattention symptoms tend to increase with age[41,42]
- Trajectories of hyperactivity and inattention in early childhood are significantly associated with each other; higher measures on one predict higher measures on the other[41]
- Large prospective studies have followed children with ADHD and healthy controls into adolescence and adulthood; however, assessment and diagnostic (e.g., earlier and later DSM criteria) metrics have not been consistent[41]
- Functional adult outcomes vary, including impact on educational attainment, job performance, income, marriage and family relationships, and social interactions[41]




Adapted from Faraone SV, et al. Attention-deficit/hyperactivity disorder. *Nature Reviews. Disease Primer*. 2015;1:Article number 15020.

# Longitudinal course of ADHD (continued)

### Early life/preschool age[41,42]

- Most ADHD preschoolers present with the combined presentation
- Hyperactive-impulsive more common; inattentive presentation is rare and more likely in girls
- Hard to diagnose at this stage because some manifestations are also part of normal developmental stages
- Comorbid conditions such as oppositional defiant disorder (ODD), communication disorders, and anxiety disorders are common and cause greater impairment
- Preschool ADHD persists into school age in 60-80% of children

### School age[41,42]

- Most ADHD diagnoses made at this stage
- Academic achievement, family interactions, and peer relationships are impaired
- Higher rates of psychiatric comorbidity; the most common comorbidities are ODD, anxiety disorders, and learning disorders
- ~70% have ≥1 comorbid disorder

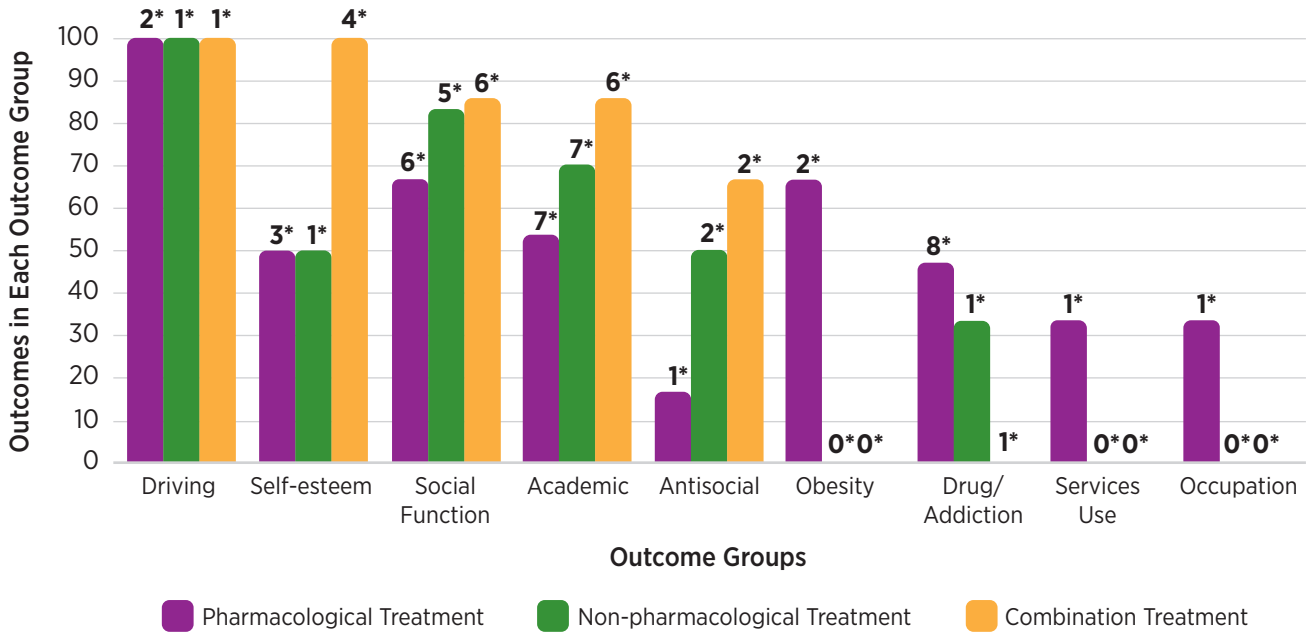
### Adolescence/Adulthood[41,42]

- Roughly two-thirds of children with ADHD continue to have symptoms of ADHD into adulthood
- ADHD as a syndrome persists in ~15% by age 25; impairing symptoms persist in ~65%
- Inattention symptoms are more persistent and decline more slowly with age than symptoms of hyperactivity and impulsivity

# Longitudinal course of ADHD (continued)

## The majority of long-term outcomes of ADHD improve with all treatment modalities[43]

- In the figure, each bar represents the % of outcomes reported to exhibit benefit (either significantly improved from untreated baseline or significantly improved compared with a group of untreated individuals with ADHD) with each treatment modality[43]




*Number of studies used to generate the data.

# Diagnostic Scales

# Scales used for diagnosis of ADHD

- ADHD-specific rating scales focus directly on the symptoms of ADHD[44]
- Are used to determine if core symptoms of ADHD are present[44]
- Reliability varies depending upon the age of the child, the scale that is used, and who is providing the information (e.g., parent, teacher, adolescent)[44]

## Key aspects of ADHD rating scales[45]

### Assessment measures


- Frequency or severity of ADHD symptoms
- Levels of functional impairment
- Impact on quality of life and finances

### Population

- Children
  - Only the Conners Comprehensive Behavior Rating Scales and the ADHD Rating Scale-IV (ADHD-RS-IV) have been validated in preschool-aged children.[44]
  - The Vanderbilt Assessment Scales were not designed for preschool children but may be used in children ≥4 years[44]
- Adolescents
- Adults

### Administration

- Clinician
- Parent
- Teacher
- Self-reported

### Scoring methods

- Different scales employ different scoring methods; examples include Likert scale, yes/no, or free-text responses
- Threshold values for improvement following treatment vary between rating scales

### Availability and cost

- Some are freely available to clinicians
- Some require online purchase
- Copyright restrictions vary

# ADHD rating scales (ADHD-RS)[46-48]

## ADHD Rating Scale-5 (ADHD-RS-V)

https://www.guilford.com/books/ADHD-Rating-Scale-5-for-Children-and-Adolescents/DuPaul-Power-Anastopoulos-Reid/9781462524877

- What is assessed:
  - Frequency and severity of ADHD symptoms
  - 6 functional impairment domains (relationships with significant others, peer relationships, academic functioning, behavioral functioning, homework performance, and self-esteem)

| Age | Administration | Content | Scoring | Use |
|---|---|---|---|---|
| • 5-10 years<br>• 11-17 years | • Parent/caregivers<br>• Teachers | • Home/school versions<br>• Two 9-item symptom subscales (inattention and hyperactivity-impulsivity) and an 18-item total scale corresponding to the 18 items in the DSM-V criteria, plus a 6-domain functional impairment assessment<br>• Separate scoring profiles for impairment in boys and girls | • 4-point frequency scale<br>– 0 = never/rarely<br>– 3 = very often<br>• Scoring templates convert raw scores to percentile scores, as a function of gender and age group | • Screening<br>• Diagnosis<br>• Treatment evaluation |

## ADHD Rating Scale-IV (ADHD-RS-IV) with adult prompts

https://psychology-tools.com/test/adult-adhd-self-report-scale

- What is assessed:
  - Frequency and severity of ADHD symptoms
  - 18 items: 9 assess inattentive symptoms, and 9 assess hyperactive-impulsive symptoms
- Scoring is based on a 4-point frequency scale ranging from 0 (never) to 3 (very often)

Website links are true and correct at the time of publication.

# Adult ADHD self-report scale (ASRS)[49]

## Adult ASRS Symptom Checklist

| Age | Administration | Content | Scoring | Use |
|---|---|---|---|---|
| • ≥18 years | • Self | • 18 items<br>– 1 to 9 cover inattention symptoms;<br>– 10 to 18 cover hyperactivity and impulsivity symptoms | • 5-point frequency scale<br>– 0 = never/seldom<br>– 4 = very often | • Screening<br>• Diagnosis |

## Adult ASRS v1.1

https://add.org/wp-content/uploads/2015/03/adhd-questionnaire-ASRS111.pdf

- Developed as a 6-question subset of the ADHD ASRS Symptom Checklist
- Used as an initial self-assessment tool in primary care
- Consists of 6 items: 4 for inattentive symptoms and 2 for hyperactive-impulsive symptoms
- Scoring is based on symptom frequency

Website links are true and correct at the time of publication.

# Parent and teacher rating scales

## Child Behavior Checklist/Teacher Report Form[50,51]

https://www.apa.org/obesity-guideline/child-behavior-checklist.pdf
https://aseba.org/wp-content/uploads/2019/02/trf.pdf

| Age | Administration | Content | Scoring | Use |
|---|---|---|---|---|
| **1.5-5 years: CBCL/1.5–5**<br>• A parent-rated version for preschool children<br><br>**Child & Adolescent (6-18 years)**<br>• Wide range of behavioral, emotional, and social problems and competencies<br>• Can also be used to screen for any additional physical problems | • Parent<br>• Teacher<br>• Self | • Assesses somatic complaints, social/thought/attention problems, anxiety/depression, aggressive/delinquent behavior, withdrawal<br>• 20 competence items obtain parents' reports of the amount and quality of participation in sports, hobbies, games, activities, jobs and chores, and friendships; how well the child gets along with others and plays and works alone; and school functioning | • Each of the 118 specific problem items and 2 open-ended problem items are scored on a 3-step response scale<br>• Mixture of free text, yes/no, multiple choice, and Likert scales<br>• Raw scores can also be converted to T-scores, for comparisons with normative samples | • Screening<br>• Evaluation in children and adolescents (6-18 years): Wide range of behavioral, emotional, and social problems and competencies<br>• Diagnosis<br>• Treatment evaluation |

Website links are true and correct at the time of publication.

# Parent and teacher rating scales (continued)

## Conners[52]

https://www.pearsonclinical.com/psychology/products/100000523/conners-3rd-edition-conners-3.html

| Age | Administration | Content | Scoring | Use |
|---|---|---|---|---|
| • 6-18 years | • Parent<br>• Teacher<br>• Self | • Parent: 203 items<br>• Teacher: 205 items<br>• Self-Report: 179<br>• 27/28 questions (short versions of the scale) divided into 4 subscales: oppositional problems, cognitive problems, hyperactivity, and an ADHD index | • 4-point scale | • Screening<br>• Diagnosis<br>• Treatment evaluation |

## Vanderbilt[53,54]

https://psychology-tools.com/vadrs-vanderbilt-adhd-diagnostic-rating-scale

| Age | Administration | Content | Scoring | Use |
|---|---|---|---|---|
| • 6-12 years | • Parent<br>• Teacher | • Parent: 55 questions on a parent's perception of social functioning and school performance<br>• Teacher: 43 questions on school performance (academic and classroom behavioral) and ADHD symptoms | • 4-point scale for symptom assessment; 5-point scale for performance<br>• High scores indicate more severe symptoms, except for the performance section, where higher scores indicate better performance in classroom behavior and academic achievement | • Screening<br>• Diagnosis<br>• Treatment evaluation |

Website links are true and correct at the time of publication.

# ICD-10[55]

- In Europe, the diagnosis of hyperkinetic disorder (HKD) is defined by the International Statistical Classification of Diseases and Related Health Problems, 10th edition (ICD-10) criteria
- The ICD-10 criteria for HKD are more restrictive than the DSM-5 criteria for ADHD, requiring ≥6 symptoms of inattention, ≥3 symptoms of hyperactivity, and ≥1 symptom of impulsivity in more than one setting
  - Subtypes are HKD with and without conduct disorder

# Examples of the variety of scales used to assess children, adolescents, and adults with ADHD

## Children and Adolescents

| Symptom Scales | Executive Function and Health-Related Quality of Life (HRQOL) Scales |
|---|---|
| **ADHD-RS-IV** http://pcptoolkit.beaconhealthoptions.com/wp-content/uploads/2016/ 01/ cms-quality-child_adhd_rating_scale_screener.pdf | **AIM-C** https://www.healthactchq.com/surveys/pdf/overviews/AIM-C_Overview.pdf |
| **ADHD-RS-5** https://www.guilford.com/books/ADHD-Rating-Scale-5-for-Children- and-Adolescents/DuPaul-Power-Anastopoulos-Reid/9781462524877 | **BEFARS** https://www.pearsonclinical.ca/en/products/product-master.html/item-589 |
| **ASEBA*** https://aseba.org<br>*includes CBCL | **BFSQ** https://eprovide.mapi-trust.org/instruments/before-school-functioning-questionnaire |
| **BEFARS** https://www.pearsonclinical.ca/en/products/product-master.html/item-589 | **BRIEF** https://www.parinc.com/Products/Pkey/23 |
| **CGI-I** https://www.psywellness.com.sg/docs/CGI.pdf | **CHIP-AE** https://eprovide.mapi-trust.org/instruments/child-health-and-illness-profile |
| **CGI-S** https://www.psywellness.com.sg/docs/CGI.pdf | **CHIP-CE** https://eprovide.mapi-trust.org/instruments/child-health-and-illness-profile |
| **K-SADS-PL** https://www.pediatricbipolar.pitt.edu/resources/instruments | **CONNERS 3™** https://www.pearsonclinical.co.uk/Psychology/ChildMentalHealth/ ChildADDADHDBehaviour/Conners3rdEdition(Conners3)/Conners3rdEdition(Conners3).aspx |
| **MINI kid** https://harmresearch.org/index.php/mini-international-neuropsychiatric-interview-mini/ | **DPREMB-R** https://eprovide.mapi-trust.org/instruments/daily-parent-rating-of-evening-and-morning-behavior-scale-revised |
| **SDQ** https://www.sdqinfo.org/ | **PedsQL™** https://eprovide.mapi-trust.org/instruments/pediatric-quality-of-life-inventory |
| **SKAMP** https://eprovide.mapi-trust.org/instruments/swanson-kotkin-agler-m-flynn-and-pelham-rating-scale | **PERMP** https://eprovide.mapi-trust.org/instruments/permanent-product-measure-of-performance |
| **SNAP-IV 26** https://www.caddra.ca/pdfs/caddraGuidelines2011SNAP.pdf | **WFIRS-P*** ** https://www.caddra.ca/canadian-adhd-practice-guidelines/<br>***The WFIRS scales can be found within the CADDRA ADHD Guidelines |
| **SWAN**** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4618695/<br>**available as Table 3 of the referenced citation | **WISC-V** https://www.pearsonassessments.com/store/usassessments/en/Store/ Professional-Assessments/Cognition-%26-Neuro/Gifted-%26-Talented/Wechsler-Intelligence-Scale-for-Children-%7C-Fifth-Edition-/p/100000771.html |
| | **YQOL-R** https://depts.washington.edu/seaqol/ |

Website links are true and correct at the time of publication.

# Examples of the variety of scales used to assess children, adolescents, and adults with ADHD (continued)

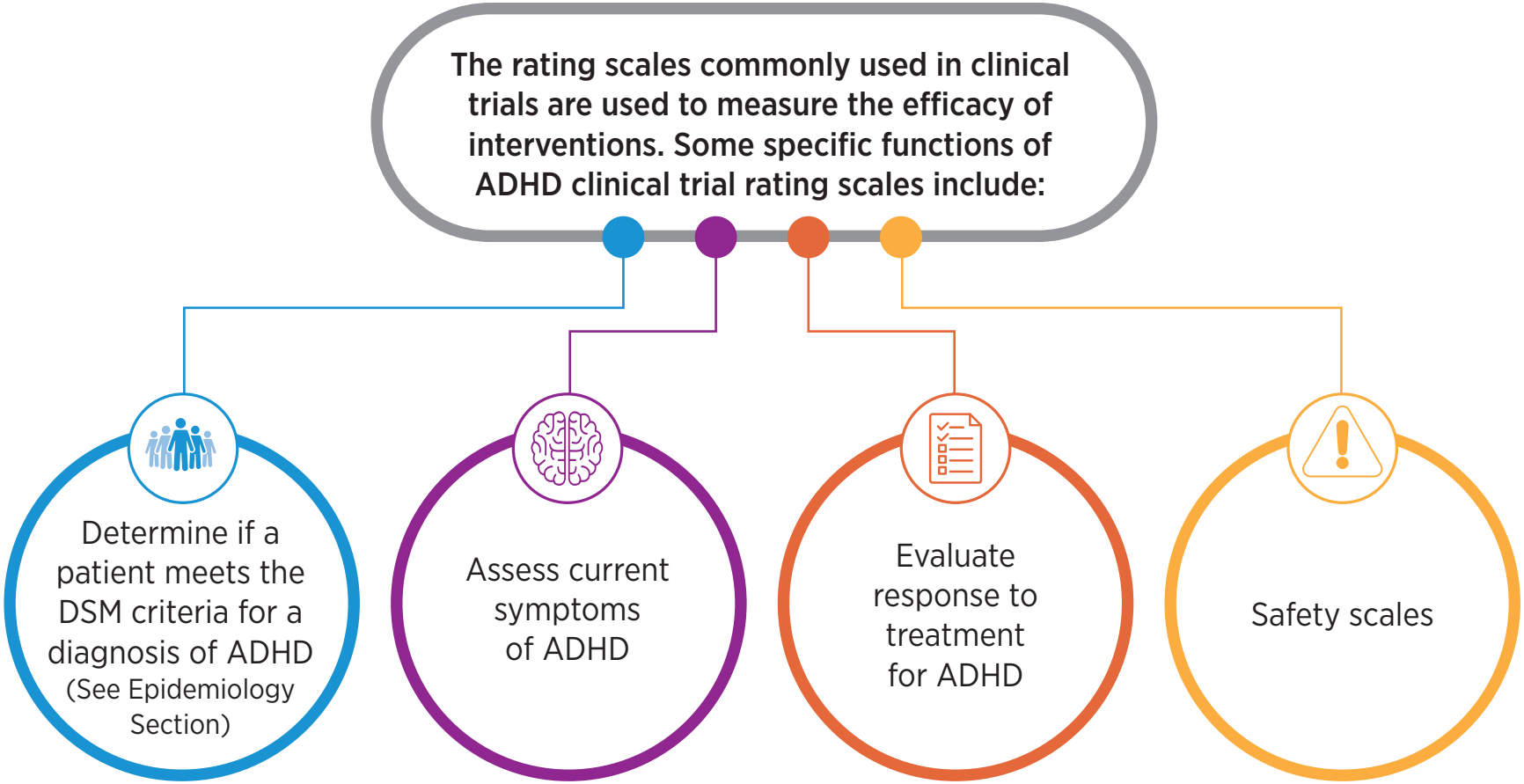
## Adults

| Symptom Scales | Executive Function and Health-Related Quality of Life (HRQOL) Scales |
|---|---|
| **ADHD-RS-IV with adult prompts** https://www.qandadhd.com/Content/pdf/ADHD-RS-IV_Tear-Pad-with-Adult-Prompts.pdf | **AAQoL** https://pubmed.ncbi.nlm.nih.gov/16411036/ |
| **AISRS** https://eprovide.mapi-trust.org/instruments/adult-adhd-investigator-rating-scale | **AIM-A™** https://www.healthactchq.com/surveys/pdf/overviews/AIM-A_Overview.pdf |
| **ASEBA*** https://aseba.org *includes ABCL | **BDEFS** https://www.guilford.com/books/Barkley-Deficits-Executive-Functioning-Scale-BDEFS-Adults/Russell-Barkley/9781606239346 |
| **ASRS-5** https://www.hcp.med.harvard.edu/ncs/ftpdir/adhd/ASRS-5_English.pdf | **BEFARS** https://www.pearsonclinical.ca/en/products/product-master.html/item-589 |
| **BEFARS** https://www.pearsonclinical.ca/en/products/product-master.html/item-589 | **BRIEF-A** https://www.parinc.com/Products/Pkey/25 |
| **CAARS** https://www.pearsonclinical.co.uk/Psychology/AdultMentalHealth/AdultMentalHealth/ConnersAdultADHDRatingScales(CAARS)/ConnersAdultADHDRatingScales(CAARS).aspx | **PERMP** https://eprovide.mapi-trust.org/instruments/permanent-product-measure-of-performance |
| **CGI-I** https://www.psywellness.com.sg/docs/CGI.pdf | **WFIRS-S**** https://www.caddra.ca/canadian-adhd-practice-guidelines/ **The WFIRS can be found within the CADDRA ADHD Guidelines |
| **CGI-S** https://www.psywellness.com.sg/docs/CGI.pdf | |
| **MINI** https://harmresearch.org/index.php/mini-international-neuropsychiatric-interview-mini/ | |
| **SKAMP-R** https://eprovide.mapi-trust.org/instruments/swanson-kotkin-agler-m-flynn-and-pelham-rating-scale | |
| **WURS** http://www.attentiondeficit-info.com/pdf/wender-utah-rating-scale.pdf | |

Website links are true and correct at the time of publication.

# Clinical Trial Scales

# Scales used in clinical trials of ADHD



# Scales used in clinical trials of ADHD (continued)

## Adult ADHD Clinical Diagnostic Scale (ACDS)[56,57]

@ Available from L. Adler, MD at: adultADHD@med.nyu.edu

| Age | Administration | Content | Scoring | Use |
|---|---|---|---|---|
| • Adults | • Clinician | • Semi-structured interview<br>• First part is a retrospective assessment of childhood ADHD symptoms<br>• Second part is a prompted, adult-specific assessment of the 18 ADHD symptoms that have been present in the past 6 months | • Subjective | • Diagnosis<br>• Symptom assessment |

## ADHD Rating Scale-5 (ADHD-RS-5)[46,48]

https://www.guilford.com/books/ADHD-Rating-Scale-5-for-Children-and-Adolescents/DuPaul-Power-Anastopoulos-Reid/9781462524877

| Age | Administration | Content | Scoring | Use |
|---|---|---|---|---|
| • 6-12 years | • Parent/caregivers<br>• Teachers | • Home/school versions<br>• 18-item scale divided into subscales for hyperactivity/impulsivity and inattentiveness<br>• Assesses symptoms of ADHD according to DSM-V criteria[62]<br>• Separate scoring profiles for impairment in boys and girls | • 4-point frequency scale<br>• 0 = never/rarely to 3 = very often<br>• Raw scores are converted to percentiles | • Screening<br>• Diagnosis<br>• Treatment evaluation |

- For preschoolers and adults, ADHD-RS-IV can be used (See Diagnostic Scales section)
- A non-official version for adults called ADHD-RS-DSM V has been used in clinical studies[58]

Website links are true and correct at the time of publication.

# Scales used in clinical trials of ADHD (continued)

## ADHD Investigator Symptom Rating Scale (AISRS)[59]

@ Available from L. Adler, MD at: adultADHD@med.nyu.edu

| Age | Administration | Content | Scoring | Use |
|---|---|---|---|---|
| • Adults | • Clinician | • Semi-structured interview assesses each symptom domain of ADHD<br>• Captures symptoms of ADHD as they present in adulthood<br>• Suggested prompts for each item to improve interrater reliability<br>• 9 inattentive items alternate with 9 hyperactive-impulsive items<br>• Each item includes a series of additional questions that the interviewer can use to further prompt the participant | • 0 (none), 1 (mild), 2 (moderate), 3 (severe)<br>• The maximum total score for the scale is 54 points, with 27 points for each subscale<br>• The total score is the sum of the inattentive and hyperactive-impulsive subscales | • Symptom assessment |

Website links are true and correct at the time of publication.

# Scales used in clinical trials of ADHD (continued)

## Clinical Global Impression (CGI) Scale (CGI-Severity [CGI-S] and CGI-Improvement [CGI-I])[60]

https://www.psywellness.com.sg/docs/CGI.pdf

| Age | Administration | Content | Scoring | Use |
|---|---|---|---|---|
| • Children<br>• Adults | • Physician | • Two companion 1-item measures assess severity of symptoms and improvement<br>• CGI-S assesses the severity of ADHD at a given point in time: Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?<br>• CGI-I provides a "global" or "holistic" change in severity from the initiation of treatment (baseline) over one specified time period: Compared with the patient's condition at admission to the project [prior to medication initiation], this patient's condition is [score]?<br>– Rating of "minimal improvement" (CGI-I score = 3) | **CGI-S**<br>• 0 = not assessed<br>• 1 = normal, not at all ill<br>• 2 = borderline mentally ill<br>• 3 = mildly ill<br>• 4 = moderately ill<br>• 5 = markedly ill<br>• 6 = severely ill<br>• 7 = among the most extremely ill patients<br>**CGI-I**<br>• 1 = very much improved since the initiation of treatment<br>• 2 = much improved<br>• 3 = minimally improved<br>• 4 = no change from baseline (the initiation of treatment)<br>• 5 = minimally worse<br>• 6 = much worse | • Treatment evaluation |

- Brief, easy to use, and captures clinical impressions when administered by an experienced clinician

Website links are true and correct at the time of publication.

# Scales used in clinical trials of ADHD (continued)

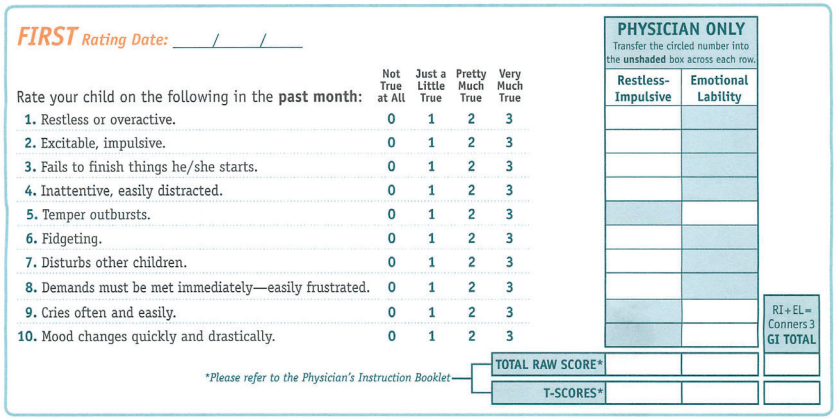
## Conners' Global Index

https://www.pearsonclinical.com/psychology/products/100000523/conners-3rd-edition-conners-3.html

| Age | Administration | Content | Scoring | Use |
|---|---|---|---|---|
| • 6-18 years | • Parent/caregivers<br>• Teachers<br>• Self-report | • 10 items designed to evaluate the frequency and severity (as observed over the preceding week) of the child's impulsivity, emotional outbursts, and motor hyperactivity | • Age- and gender-specific<br>• Scores >65 are in the clinical range for ADHD | • Screening<br>• Diagnosis<br>• Treatment evaluation |

## Conners' Global Index Parent form[75]

https://ehr.wrshealth.com/live/shared/practice-documents/2037330/2716_conners.pdf



*FIRST* Rating Date: ____/____/____

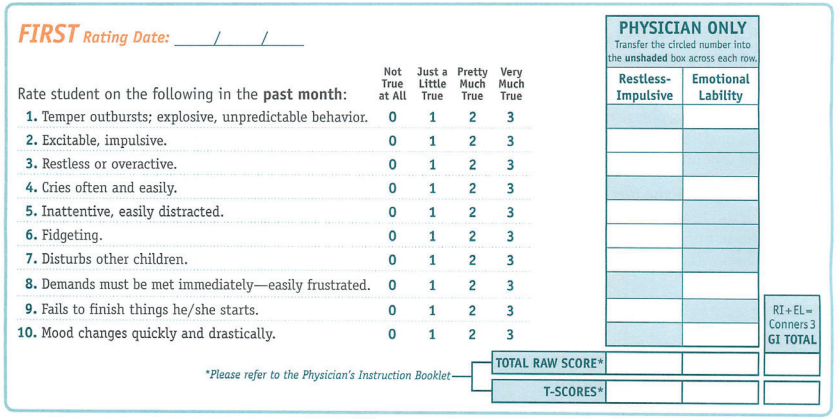
| Rate your child on the following in the **past month:** | Not True at All | Just a Little True | Pretty Much True | Very Much True | PHYSICIAN ONLY (Transfer the circled number into the **unshaded** box across each row.) Restless-Impulsive | Emotional Lability |
|---|---|---|---|---|---|---|
| **1.** Restless or overactive. | 0 | 1 | 2 | 3 | | |
| **2.** Excitable, impulsive. | 0 | 1 | 2 | 3 | | |
| **3.** Fails to finish things he/she starts. | 0 | 1 | 2 | 3 | | |
| **4.** Inattentive, easily distracted. | 0 | 1 | 2 | 3 | | |
| **5.** Temper outbursts. | 0 | 1 | 2 | 3 | | |
| **6.** Fidgeting. | 0 | 1 | 2 | 3 | | |
| **7.** Disturbs other children. | 0 | 1 | 2 | 3 | | |
| **8.** Demands must be met immediately—easily frustrated. | 0 | 1 | 2 | 3 | | |
| **9.** Cries often and easily. | 0 | 1 | 2 | 3 | | |
| **10.** Mood changes quickly and drastically. | 0 | 1 | 2 | 3 | | |
| | | | | | TOTAL RAW SCORE* | |
| | | | | | T-SCORES* | |

RI+EL= Conners 3 GI TOTAL

*Please refer to the Physician's Instruction Booklet

## Conners' Global Index Teacher form[76]

https://ehr.wrshealth.com/live/shared/practice documents/2037330/2716_conners.pdf



*FIRST* Rating Date: ____/____/____

| Rate student on the following in the **past month:** | Not True at All | Just a Little True | Pretty Much True | Very Much True | PHYSICIAN ONLY (Transfer the circled number into the **unshaded** box across each row.) Restless-Impulsive | Emotional Lability |
|---|---|---|---|---|---|---|
| **1.** Temper outbursts; explosive, unpredictable behavior. | 0 | 1 | 2 | 3 | | |
| **2.** Excitable, impulsive. | 0 | 1 | 2 | 3 | | |
| **3.** Restless or overactive. | 0 | 1 | 2 | 3 | | |
| **4.** Cries often and easily. | 0 | 1 | 2 | 3 | | |
| **5.** Inattentive, easily distracted. | 0 | 1 | 2 | 3 | | |
| **6.** Fidgeting. | 0 | 1 | 2 | 3 | | |
| **7.** Disturbs other children. | 0 | 1 | 2 | 3 | | |
| **8.** Demands must be met immediately—easily frustrated. | 0 | 1 | 2 | 3 | | |
| **9.** Fails to finish things he/she starts. | 0 | 1 | 2 | 3 | | |
| **10.** Mood changes quickly and drastically. | 0 | 1 | 2 | 3 | | |
| | | | | | TOTAL RAW SCORE* | |
| | | | | | T-SCORES* | |

RI+EL= Conners 3 GI TOTAL

*Please refer to the Physician's Instruction Booklet

Website links are true and correct at the time of publication.

# Scales used in clinical trials of ADHD (continued)

## Permanent Product Measure of Performance (PERMP-A and PERMP-C)[63]

https://eprovide.mapi-trust.org/instruments/permanent-product-measure-of-performance

| Age | Administration | Content | Scoring | Use |
|---|---|---|---|---|
| • Preschool and school-aged children<br>• Adult version (Adult workplace environment PERMP1) | • Teachers<br>• Clinicians<br>• Investigator | • To assess compliance and academic productivity in school children (children/adolescents) or workplace environment (adults)<br>• Assesses the time course of medication effect over the course of a day<br>• 10-minute timed test in which the number of problems attempted and number of problems correct are recorded<br>• Math test that measures effortful performance in preschool and school-aged children<br>• Series of 10-minute, skill-adjusted math tests comprising five pages of 80 math problems each (400 in total) to investigate impairments seen in the home and academic setting as a result of ADHD<br>• Administered in classroom setting (laboratory classroom) | • Determines the number of problems attempted and the number of problems correctly answered<br>• Total PERMP score for each test is calculated by adding the number of math problems attempted (PERMP-A) plus the number answered correctly (PERMP-C)<br>• A higher PERMP score indicates better performance<br>• Tailored to a child's math ability level | • Screening/placement test<br>• Treatment evaluation |

Website links are true and correct at the time of publication.

# Scales used in clinical trials of ADHD (continued)

## Swanson, Kotkin, Agler, M-Flynn, and Pelham Scale (SKAMP)[64]

https://eprovide.mapi-trust.org/instruments/swanson-kotkin-agler-m-flynn-and-pelham-rating-scale

| Age | Administration | Content |
|---|---|---|
| • School-aged children and adults | • Teachers<br>• Other raters | • Assesses functional impairment related to ADHD in the classroom, including the performance of academic tasks, following class rules, and interacting with peers and adults in the classroom |

| Scoring | Use |
|---|---|
| **Level of impairment on a scale of 0 to 6**<br>• 0 = none<br>• 1 = slight<br>• 2 = mild<br>• 3 = moderate<br>• 4 = severe<br>• 5 = very severe<br>• 6 = maximal impairment | • Used to assess the time course of treatment effects in laboratory classroom studies or adult workplace environment |

Website links are true and correct at the time of publication.

# Scales used in clinical trials of ADHD (continued)

## Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADDS)[65,66]

Available by contacting: Fred W. Reimherr, MD, Mood Disorders Clinic, Department of Psychiatry, University of Utah Health Science Center, Salt Lake City, UT 84132.

| Age | Administration | Content |
|---|---|---|
| • Adults | • Investigator<br>• Self | **61 questions in 7 symptom categories:**<br>• Attention difficulties<br>• Hyperactivity/restlessness<br>• Temper<br>• Affective lability<br>• Emotional overreactivity<br>• Disorganization<br>• Impulsivity |

| Scoring | Use |
|---|---|
| **Scoring scale is 0 to 2**<br>• 0 = not present<br>• 1 = mild<br>• 2 = clearly present<br>**Summarizes each of the 7 categories on a 0-to-4 scale**<br>• 0 = none<br>• 1 = mild<br>• 2 = moderate<br>• 3 = quite a bit<br>• 4 = very much | • Measures severity of target symptoms of adults with ADHD using the Utah Criteria, which Wender developed |

## Subset of 25 questions associated with ADHD

| | As a child I was (or had) |
|---|---|
| 3 | concentration problems easily distracted |
| 4 | anxious worrying |
| 5 | nervous fidgety |
| 6 | inattentive daydreaming |
| 7 | hot- or short-tempered low boiling point |
| 9 | temper outbursts tantrums |
| 10 | trouble with stick-to-it-tiveness not following through. failing to finish things started |
| 11 | stubborn strong-willed |
| 12 | sad or blue depressed unhappy |
| 15 | disobedient with parents rebellious sassy |
| 16 | low opinion of myself |
| 17 | irritable |
| 20 | moody ups and downs |
| 21 | angry |
| 24 | acting without thinking impulsive |
| 25 | tendency to be immature |
| 26 | guilty feelings regretful |
| 27 | losing control of myself |
| 28 | tendency to be or act irrational |
| 29 | unpopular with other children didn't keep friends for long didn't get along with other children |
| 40 | trouble seeing things from someone else's point of view |
| 41 | trouble with authorities trouble with school visits to principal's office |
| | **As a child in school I was (or had)** |
| 51 | overall a poor student slow learner |
| 56 | trouble with mathematics or numbers |
| 59 | not achieving up to potential |

- May be particularly useful in assessing mood lability symptoms of ADHD.

Website links are true and correct at the time of publication.

# Safety scales

## Columbia-Suicide Severity Rating Scale (C-SSRS)[67,68]

http://cssrs.columbia.edu/wp-content/uploads/C-SSRS_Pediatric-SLC_11.14.16.pdf

| Age | Administration | Content | Scoring | Use |
|---|---|---|---|---|
| • Adults | • Clinician following patient interview | • 3 pages<br>• Risk and protective factors that may apply<br>• Formal assessment of 5 subtypes of suicidal ideation, 5 subtypes of suicidal behavior, and self-injurious behavior without suicidal intent | • Likert scales generate suicide ideation scores (0-5) and suicide ideation intensity score (aggregate, 0-25) | • Suicide risk assessment |

## Pittsburg Sleep Quality Index (PSQI)[69]

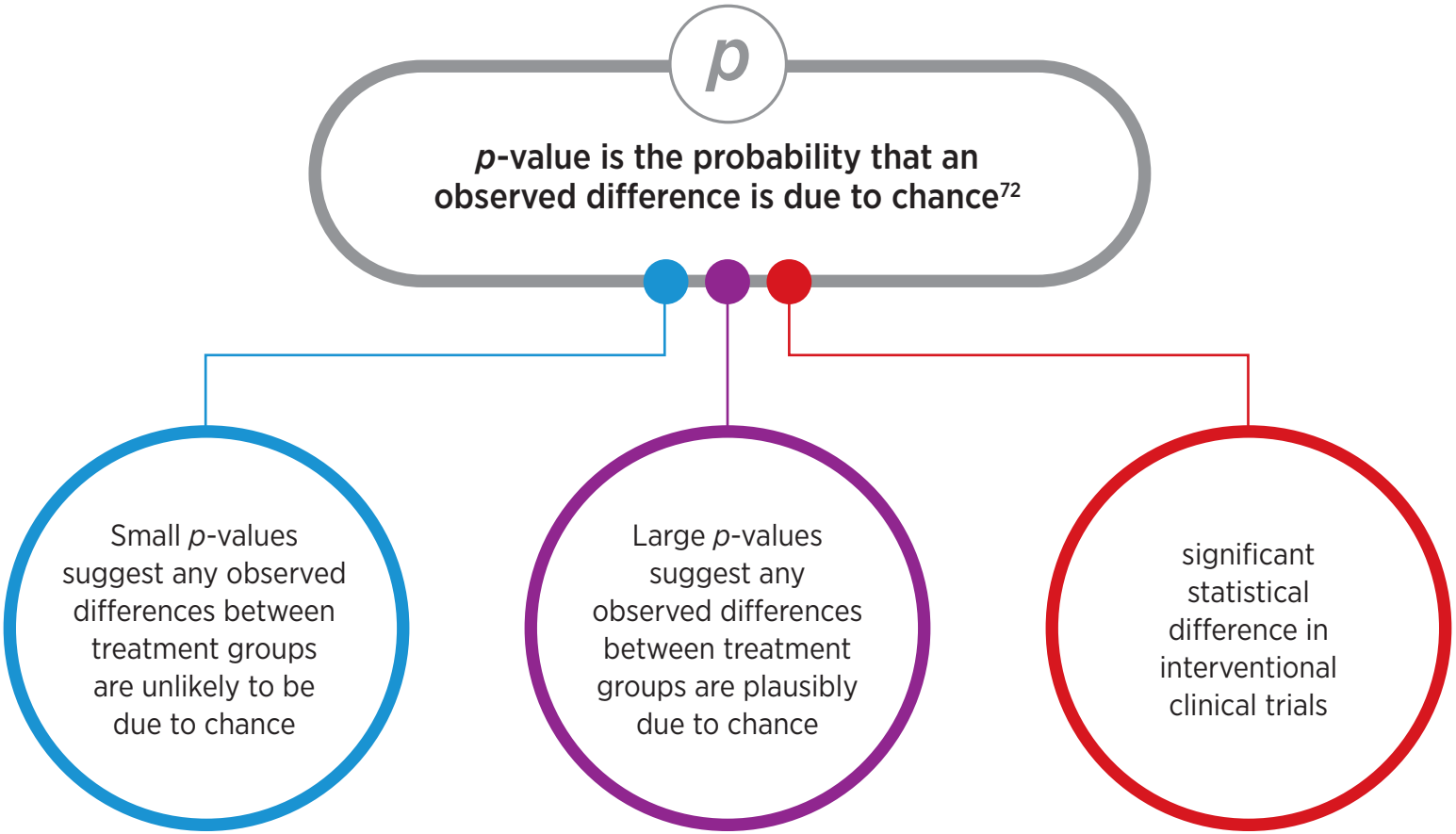
http://www.goodmedicine.org.uk/files/assessment,%20pittsburgh%20psqi.pdf

| Age | Administration | Content | Scoring | Use |
|---|---|---|---|---|
| • Adults | • Self | • Differentiates “poor” from “good” sleep quality<br>• 19 items measure 7 areas: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction over the last month | • Scores for 7 components are summed to generate one global score | • Measures quality and patterns of sleep |

Website links are true and correct at the time of publication.

# Biostatistics

# What is a *p*-value?[70,71]



# What is a confidence interval (CI)?[71]


A CI calculated for a measure of treatment effect shows the range within which the true treatment effect is likely to lie

- A CI that includes zero (or the value of "no effect") indicates that the treatment under investigation is not significantly different from the control

CIs put upper and lower limits on the likely size of any true effect

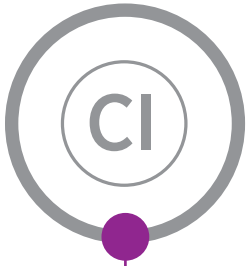
- A narrow CI captures only a small range of effect sizes and infers a large study and a precise effect size
- A wide CI capture a range of effect sizes and infers a small study and an imprecise effect size

CIs are preferable to *p*-values

- CIs provide a range of values within which the true value is certain to exist with a given level of confidence[70]
- A wide CI suggests an imprecise result, and results should be interpreted with caution regardless of statistical significance[70]

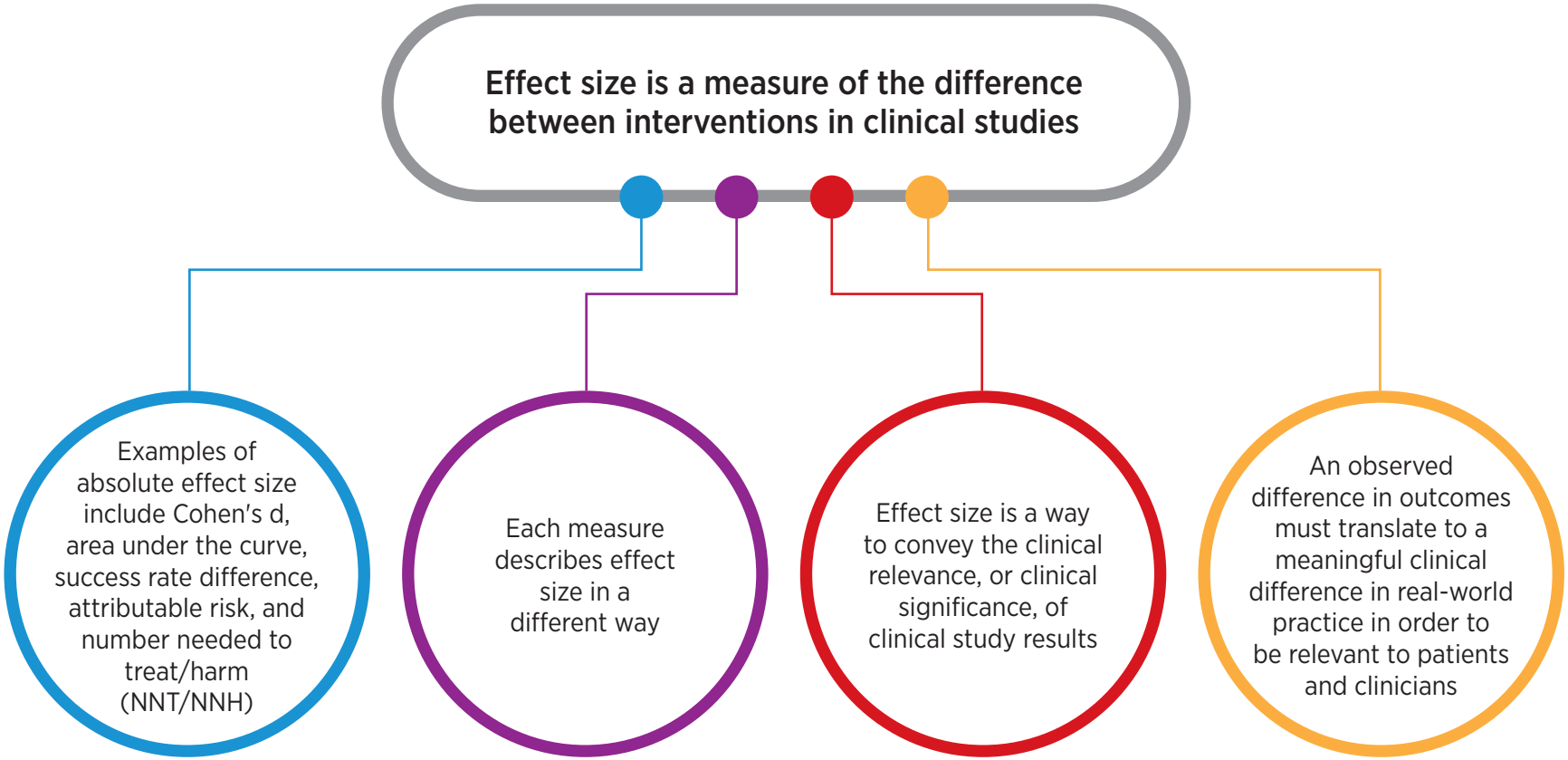
# Limitations of *p*-values and CIs[70-72]


- Statistical significance does not necessarily signify clinical significance
  - For example, a very small *p*-value (<0.000001) may be statistically significant, but it may be clinically meaningless if most patients can expect to experience a serious adverse event
- Non-significance does not necessarily signify "no effect"




- Because *p*-values and CIs don't really measure "clinical relevance," clinicians need other metrics to help them interpret clinical trial data, and to better place the results into a clinically meaningful context

# What is an effect size, and how is it interpreted?[72]



# What are number needed to treat (NNT) and number needed to harm (NNH)?

NNT

**Number Needed to Treat (NNT)[70,72]**

- NNT offers a method for clinicians to use to interpret clinical significance of an intervention
- NNT conveys an estimate of a treatment's clinical effect[81]
- Typically, NNT is applied to a primary endpoint in a study, or one that has clinical relevance
- NNT answers the question: *How many patients would you need to treat with Intervention X before 1 patient would experience a benefit?*

NNH

**Number Needed to Harm (NNH)[72]**

- Conveys an estimate of the potential for a treatment to cause harm
- NNH answers the question: *How many patients would you need to treat with Intervention X before 1 patient would experience harm?* (e.g., an adverse event [AE])

# How are NNT and NNH interpreted?[72]


- A single-digit NNT is usually "good enough" for randomized, placebo-controlled clinical studies that evaluate response/non-response to treatment
  - For example, the treatment is at least 10% better than placebo, resulting in an NNT of less than 10, and the lower the number the better.
- Important to know rates of outcomes used to calculate NNT, not just the difference
  - For example, both 20% vs. 10% and 80% vs. 70% will produce the same NNT, but the clinical treatment scenarios are very different


- An acceptable NNH for drug vs. placebo depends on the outcome in question
  - Outcome must be clinically significant to the patient
    - Some patients may be more at risk for AEs
  - NNHs of 10–100 may be acceptable for AEs that lead to discontinuation but that are not associated with serious immediate health risks
  - NNHs of ≥1,000 are usually required for AEs that pose a significant health risk
- Generally want NNH > NNT so that the benefits occur more frequently than the harm
- Lower NNHs may be acceptable in certain situations. For example, NNH may be lower than NNT when comparing a beneficial outcome with a mild-moderate, temporary AE that does not lead to discontinuation (e.g., a mild dry mouth vs. response to an antidepressant medication)

# Calculating NNT[72]

NNT

***f*X = Frequency of outcome for Intervention X**
***f*Y = Frequency of outcome for Intervention Y**

**Attributable Risk (AR) = *f*X – *f*Y**
**NNT = 1/AR (Rounded up so that it is a whole number)**

**Example**

In a clinical trial, remission rates were 50% with Drug A and 20% with Drug B.

To answer the question *How many patients would you need to treat with Drug A instead of Drug B before you would expect to have one additional patient in remission?* requires calculation of NNT.

*f*A = 0.50

*f*B = 0.20

AR = 0.30

NNT = 1/0.30 = 3.33; rounded is 4

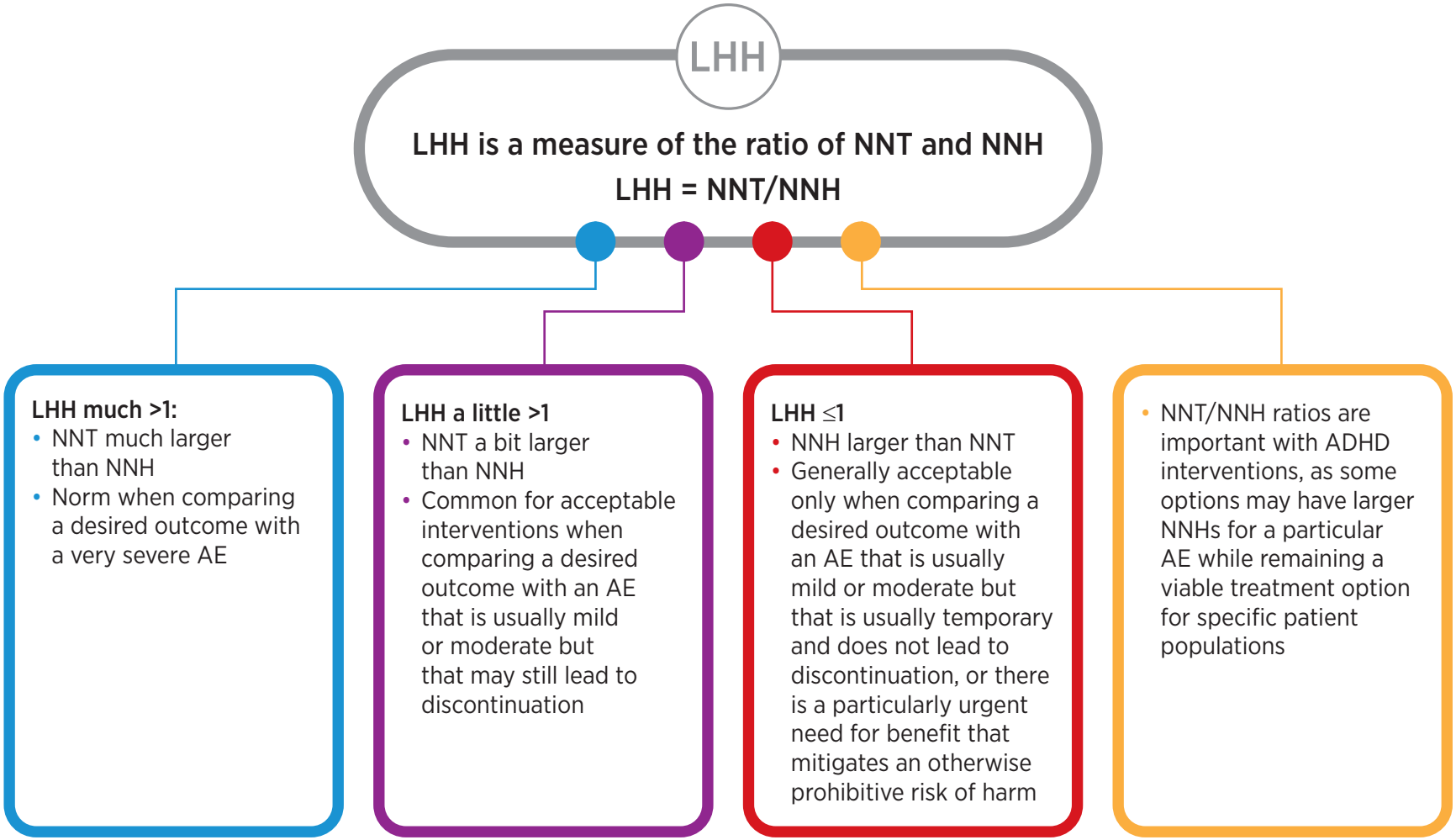
This NNT suggests that a therapeutic advantage may be expected in every fourth patient (frequent) treated with Drug A compared with Drug B

# Calculating NNT[72] (continued)

NNT

- Successful interventions for “very treatable” acute conditions (e.g., acute agitation) are generally expected to have NNTs vs. placebo in the range of 2–3; those for “somewhat treatable” conditions (e.g., osteoarthritis pain) are generally expected to be in the 4–6 range
- Higher NNTs may be acceptable in certain situations such as difficult-to-treat conditions where other interventions have failed and few options remain (e.g., treatment-resistant major depressive disorder)

# Likelihood to be helped or harmed (LHH)[72]



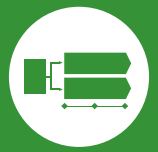
# Controlling for biases[72]

**Bias refers to systematic errors that result from the way the study was designed, executed, or interpreted**

**Common sources of bias in clinical trials include**

- Lack of (or failure in) randomization, leading to unbalanced groups
  - Patients in each group should not be significantly different demographically and with respect to medications, comorbidities, medical histories, etc.
- Poor blinding, leading to unfair treatment and biased assessments
- Large numbers of patients lost to follow-up

- Bias must be assessed before CIs can be interpreted
- Even very large samples and very narrow CIs can be misleading if the studies were biased



# Study Designs

# Overview and terminology

**Clinical studies of treatments in humans are classified into phases**[73,74]

## Phase I

- Small number of healthy volunteers who are closely monitored in a clinical setting
- Determines a safe dosage range and identifies any common side effects or readily apparent safety concerns
- May also be used to develop pharmacokinetics (PK) and pharmacodynamics (PD), to assess the half-life of the drug, estimate the maximum tolerated dose (MTD), or evaluate the effects of multiple dose levels

## Phase II

- May be >100 subjects
- Investigates preliminary evidence of efficacy and continues to monitor safety
- May be the first time the agent is administered to patients with the disease of interest to answer questions such as: What is the correct dosage for efficacy and safety in the patient type? What is the probability a patient treated with the compound will benefit from the therapy or experience an adverse effect?

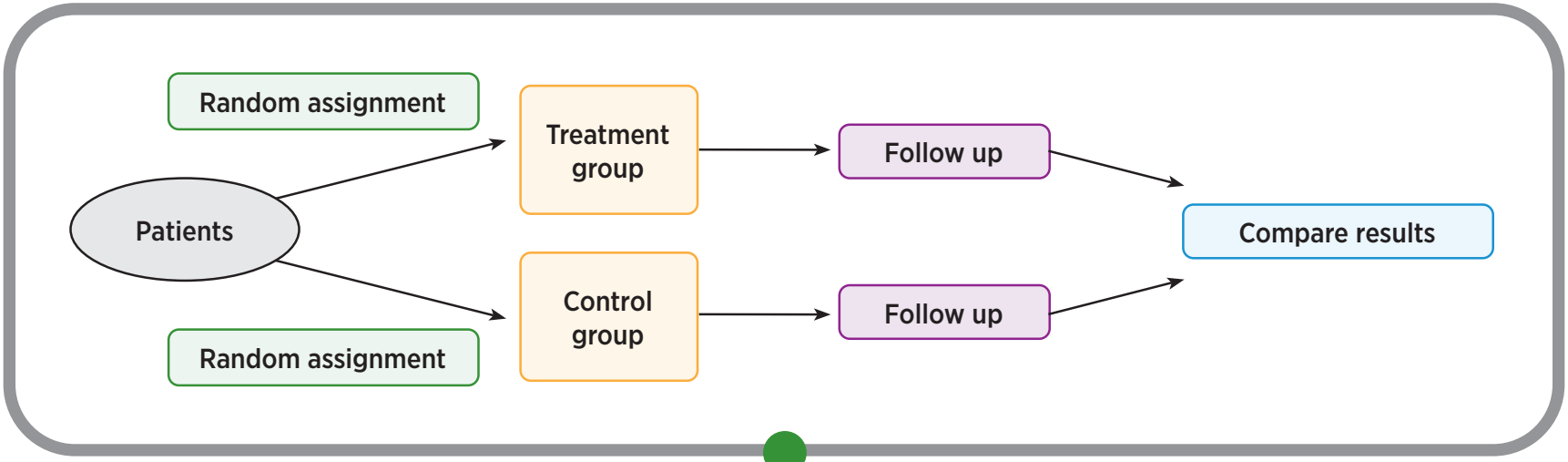
## Phase III

- May be >1,000 subjects
- Rigorous clinical trial with randomization, one or more control groups, and definitive clinical endpoints
- Address questions of comparative treatment efficacy
  - Involves a placebo and/or active control group in order to assess the precise and valid estimates of differences in clinical outcomes attributable to the investigational therapy agent

## Phase IV

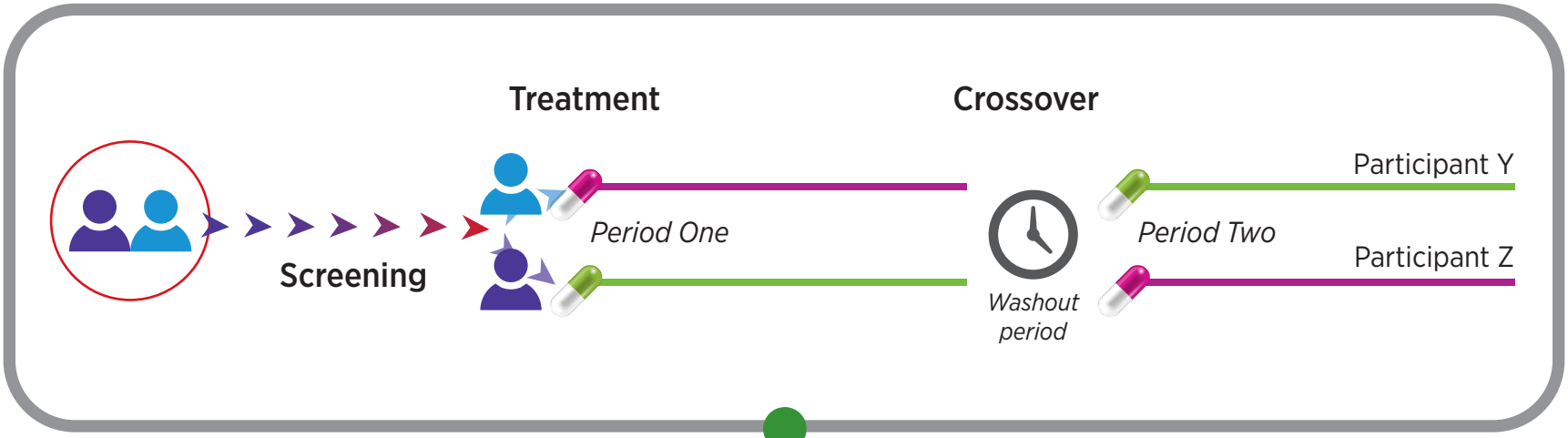
- Very large; may be >10,000 patients
- Postmarketing surveillance (PMS) occurs after regulatory approval of the new agent
- Opportunity to learn about rare side effects and interactions with other therapies
- Can provide important information that was not apparent during the drug development

# Parallel double-blind placebo-controlled[75]




- Subjects are randomly assigned to either treatment or control arms, and they remain in that arm for the duration of the study
- Double-blinded: both investigators and subjects are masked to the treatment
- Advantages include reducing bias through randomization, experiments can be run simultaneously in a number of groups, and groups can be in separate locations

# Crossover[75]




- Patients are randomized to a sequence of treatments, and they cross over from one treatment to another during the course of the trial
- Each treatment occurs in a time period with a washout period in between
- Each patient serves as their own control, which reduces the potential for mean variability; however, there are potential problems with carryover effects (i.e., residual effects)

# Laboratory school protocol (LSP)[76] (Also called the analogue laboratory classroom)

**The application of the LSP to the development of stimulant treatments for ADHD is well documented**

- Uses "cycles of time" to equally expose subjects to different settings in a repeated way across the day
  - For ADHD studies, subjects cycle between the analogue classroom and structured activities
  - Uses age and developmentally appropriate activities and environmental modifications for preschool and school-aged children

- Allows for systematic collection of information deemed to be critical in the standard clinical practice of treating disruptive behavior disorders with medication
  - Dosing, safety, attention, behavior, and classroom productivity

- Pharmacodynamic (PD) and pharmacokinetic (PK) information can be collected simultaneously
- Safety measurements include pulse rate, blood pressure, electrocardiogram, and side effect ratings

# Adult workplace environment (AWE)[76]

**The AWE is similar to the LSP and provides a setting to monitor subjects' response to medication**

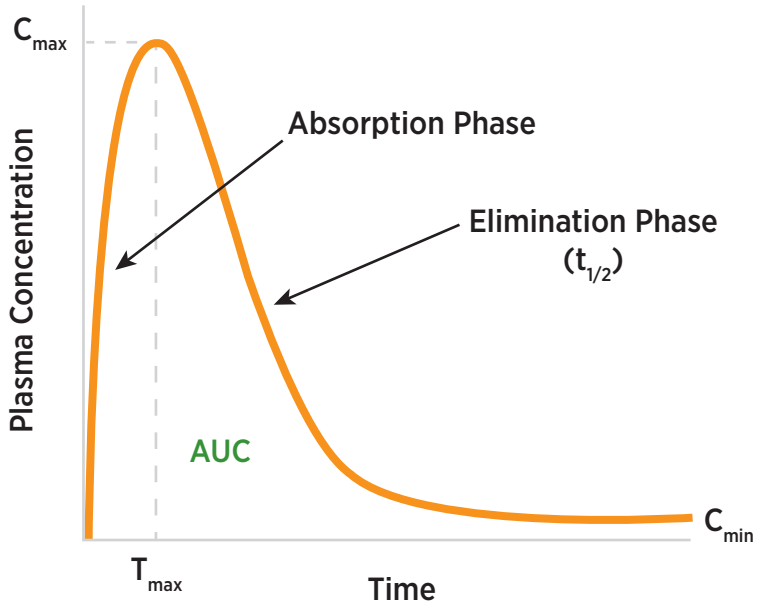
3 cycles of workplace sessions are repeated across the day

Timing is controlled for medication dosing, recreational activities, meals, and safety measurements including vital signs, blood pressure, temperature, laboratory specimens, and electrocardiograms

# Pharmacokinetic studies[77]

Pharmacokinetics (PK) studies investigate what the body does to a drug and provide detailed data regarding the concentration of the drug and any of its metabolites in plasma and other parts of the body over a long enough period of time for almost all of the drug to be eliminated from the body

- Describes the time course over which a drug is absorbed, distributed, metabolized, and eliminated



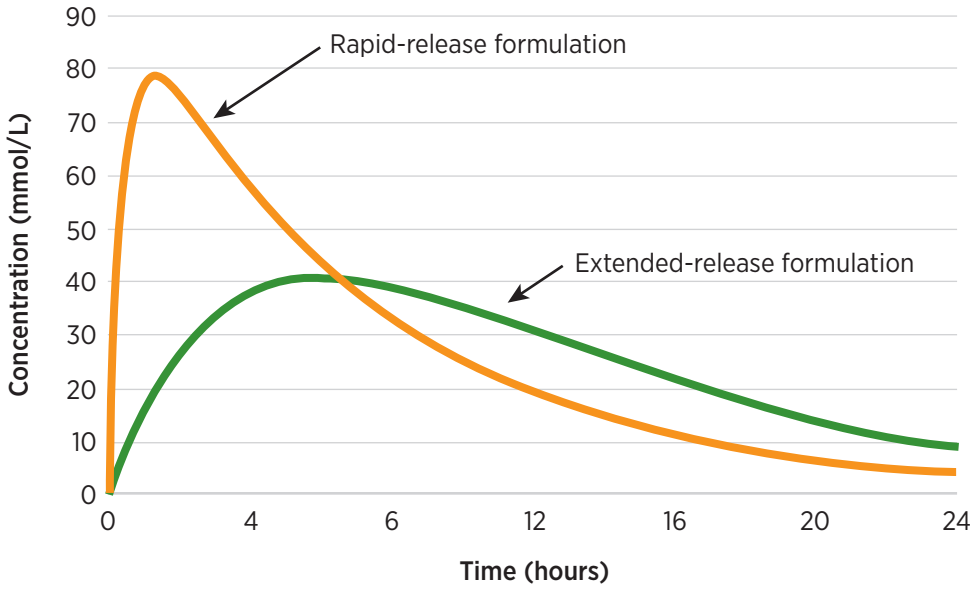
# Basic PK concepts and measurements[77]

**Area under the curve (AUC)**

- The overall amount of drug in the bloodstream after a dose
- Generating an AUC requires collecting many blood samples (usually every one or two hours) right after a person takes a dose up until the next dose is due

**Bioavailability[78]**

- Measures of the amount of intact drug that reaches the systemic circulation
- Provides information about the dose/dosage regimen and performance of different formulations



# Basic PK concepts and measurements[77] (continued)

## Bioequivalence[78]

- Formulations containing the same dose of the same chemical entity, generally in the same dosage form, and that are intended to be interchangeable are deemed bioequivalent
- This information may be useful for evaluating formulation changes (tablet vs. capsule) and comparing generic and branded drugs
- Drugs that are bioequivalent are not expected to differ in clinical and adverse events

## $C_{max}$ (maximum concentration)

- The highest concentration of drug in the blood that is measured after a dose
- $C_{max}$ usually happens within a few hours after the dose is taken
- The time that $C_{max}$ happens is referred to as $T_{max}$

## $C_{min}$ or trough (minimum concentration)

- The lowest concentration of the drug in the blood that is measured after a dose
- It happens right before a patient takes the next usual dose

## Half-life ($t_{½}$)

- The amount of time it takes for the drug concentration in the blood to decline by half.
- $t_{1/2}$ is one of the most important PK measurements for how often a drug has to be dosed

# References

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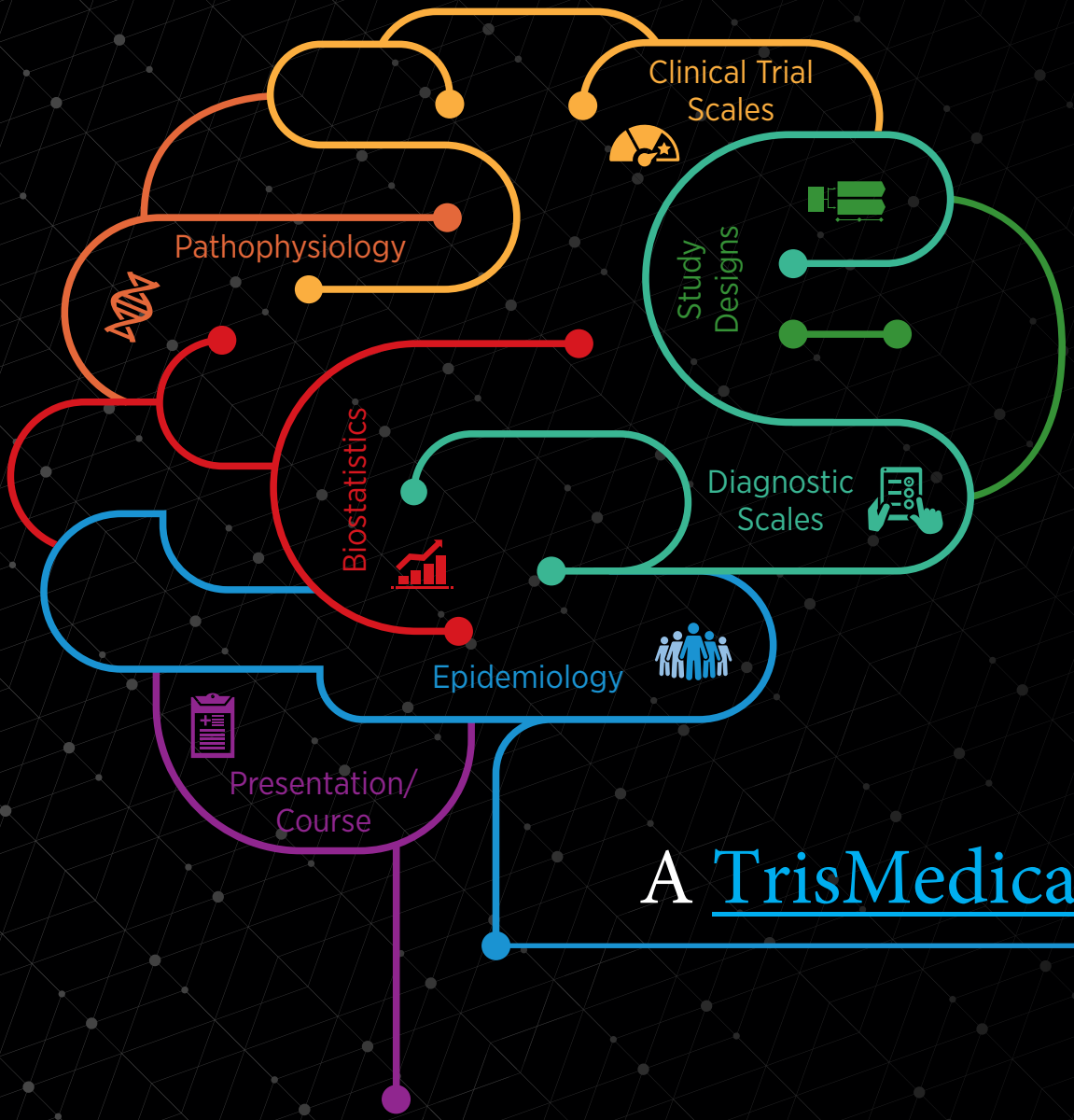


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