Rare & Developmental Disorders Toolkit Guideline v2.0

Instruments

Toolkit Purpose

A collection of measures to capture essential phenotypes associated with Rare & Developmental (R&D) Disorder biomedical research.

Guideline Description

The R&D toolkit can be used to collect essential phenotypes associated with R&D related research, including: Birth History, Neurodevelopmental History, Epilepsy and System Anomalies. The following document establishes guidelines (particularly applicable in Africa) on how to use the toolkit and collect detailed, relevant and harmonized phenotype and exposure data for research.

As listed below, the R&D toolkit consists of 7 Instruments, labelled Instruments 1 to 7:

Instrument	**Phenotypes**
1	Biological Parents And Grandparents
2	Participant Birth History
3	Developmental Milestones
4	Neurodevelopmental Assessment
5	Developmental Disorders
6	Epilepsy Screener
7	Rare Disorders

Important Notes

1. The toolkit employs branching logic, therefore, we recommend that it is completed in order, as some variables may or may not appear OR accept input based on the input of previously listed variables.

2. Some branching logic (specifically related to date of birth/age and current pregnancy) affects the display of items relevant to adult or paediatric participants across multiple instruments.

3. Any addition or removal of variables may also affect branching logic so editing of variables should be carefully positioned so as not to interrupt branching logic conditions with related variables.

4. The toolkit is recommended to be used in conjunction with the Core Phenotypes toolkit (https://github.com/h3abionet/h3aphenstds).

5. Although not highlighted below, each instrument requires a collection date, which can be collected either manually or automatically.

6. Consistent codes are recommended for the identification of missing data, and these are incorporated into all Instruments discussed below.

7. Codes for Missing Data are specified below:

Code	Value Label
-991	No information
-992	Asked but unknown
-993	Temporarily unavailable
-994	Not asked
-995	Refused
-998	Not applicable

8. We recommend that when a participant responds with an "I don't know" to a question that the interviewer firstly ensures that the participant understands the question clearly and secondly is gently encouraged to reconsider their response if possible. If "I don't know" is still the response we make use of the 'Asked but unknown' missing code. Questions where "I don't know" is a highly anticipated and valid response will have a checkbox for Unknown included - it should be noted that this will not be recognised as missing data in statistical software.

Recommendations

Instrument 1: Biological Parents And Grandparents

The instrument enables the recording of possible consanguinity with regards to the research participant’s biological parents and grandparents.

Questions	What is the degree of relatedness (consanguinity) between the participant's biological parents? **Response Options**: First degree; Second degree; Third degree; Other degree of relatedness; Unrelated (If Other) Specify other degree of relatedness (consanguinity) between the biological parents: What is the degree of relatedness (consanguinity) between the participant's maternal biological grandparents? **Response Options**: First degree; Second degree; Third degree; Other degree of relatedness; Unrelated What is the degree of relatedness (consanguinity) between the participant's paternal biological grandparents? **Response Options**: First degree; Second degree; Third degree; Other degree of relatedness; Unrelated Have either of the participant's biological parents previously experienced pregnancy loss? **Response Options**: Yes; No (If Yes) How many pregnancy losses?

Notes	- Relatedness Definitions:
	  - **First Degree** - include an individual's parents, siblings, and children.
	  - **Second Degree** - include an individual's grandparents, grandchildren, uncles, aunts, nephews, nieces, and half-siblings.
	  - **Third Degree** - include an individual's great-grandparents, great grandchildren, great uncles/aunts, and first cousins.
	- **Pregnancy loss** refers to a common complication of pregnancy, resulting in spontaneous abortion before the fetus has reached viability.
	- Interviewers need to be sensitive to the participant's culture and religion and be aware that some participants may be reluctant to answer these questions truthfully.
	- Participants should be reassured that their answers will be kept confidential.

Instrument 2: Participant Birth History

The instrument enables the retrospective collection of extensive information related to the participant's birth history i.e. information about the delivery and health status at birth typically elicited as a part of the past medical history.

Questions	Did the participant's birth mother have any illnesses during pregnancy? **Response Options**: Yes; No (If Yes) Specify type of illness/es during pregnancy: **Response Options**: Chronic Hypertension; Diabetes Mellitus Type 1; Diabetes Mellitus Type 2; Epilepsy; Gestational Diabetes; HIV/AIDS; Pregnancy induced hypertension Thyroid Dysfunction; Other

<table>
<tr><td></td><td>(If Other) Specify other type of illness/es during pregnancy:</td></tr>
<tr><td>Notes</td><td>- Illnesses descriptions (specific to pregnancy of the enrolled research participant):
<table>
<tr><th>Illness</th><th>Description</th></tr>
<tr><td>Gestational Diabetes</td><td>Carbohydrate intolerance first diagnosed during pregnancy.</td></tr>
<tr><td>Diabetes Mellitus Type 1</td><td>A chronic condition in which the pancreas produces little or no insulin. Type I diabetes mellitus is manifested by the sudden onset of severe hyperglycemia with rapid progression to diabetic ketoacidosis unless treated with insulin.</td></tr>
<tr><td>Diabetes Mellitus Type 2</td><td>A type of diabetes mellitus initially characterized by insulin resistance and hyperinsulinemia and subsequently by glucose intolerance and hyperglycemia.</td></tr>
<tr><td>Pregnancy Induced Hypertension</td><td>A blood pressure elevation after 20 weeks of gestation in the absence of either proteinuria or systemic findings like thrombocytopenia, impaired liver function, progressive renal insufficiency, pulmonary edema or the new-onset of cerebral or visual disturbances.</td></tr>
<tr><td>Chronic Hypertension</td><td>Persistently high systemic arterial BLOOD PRESSURE. Based on multiple readings (BLOOD PRESSURE DETERMINATION), hypertension is currently defined as when SYSTOLIC PRESSURE is consistently greater than 140 mm Hg or when DIASTOLIC PRESSURE is consistently 90 mm Hg or more.</td></tr>
<tr><td>Epilepsy</td><td>A disorder in which brain activity becomes abnormal, causing seizures or periods of unusual behavior, sensations, and sometimes loss of awareness.</td></tr>
<tr><td>Thyroid Dysfunction</td><td>A medical condition that keeps the thyroid from making the appropriate amount of thyroid hormone.</td></tr>
<tr><td>HIV/AIDS</td><td>A syndrome resulting from the acquired deficiency of cellular immunity caused by HIV. It is characterized by the reduction of T-lymphocytes in the peripheral blood and the lymph nodes.</td></tr>
</table></td></tr>
<tr><td>Questions</td><td>[Did the participant's birth mother receive any vaccinations during pregnancy?
Did the participant's mother take any medication during pregnancy?]
Response Options:
Yes; No
(If Yes) Specify type/s of medication used during pregnancy:
Response Options:
Anti-convulsants; Anti-depressants; Anti-anxiety; Antibiotics; Anti-hypertensives; Anti-microbials; Anti-retrovirals; Anti-thyroid; Anti-inflammatory; Other
(If Other) Specify other type of medication used during pregnancy:</td></tr>
<tr><td>Notes</td><td>- Medication Descriptions:
- Anti-retrovirals: medication used to treat retrovirus infection, such as medications used to treat HIV/AIDS.
- Anti-convulsants: medication used in treatment of epileptic seizures.</td></tr>
</table>

	- **Anti-depressants**: medications used to treat major depressive disorder, some anxiety disorders, some chronic pain conditions, and to help manage some addictions. - **Anti-anxiety**: medication that reduces anxiety. - **Anti-hypertensives**: medication used in treatment of hypertension. - **Antibiotics**: medications used to fight infections caused by bacteria. - **Anti-microbials**: medication used to treat a microbial infection, including antibiotics, antifungals, antiprotozoals, and antivirals. - **Anti-thyroids**: medication that inhibits thyroid hormone production. - **Anti-inflammatory**: medication which reduces pain, decreases inflammation, decreases fever, and prevents blood clots.
Questions	[Did the participant's birth mother smoke cigarettes during pregnancy? Did the participant's birth mother consume alcohol during pregnancy? Did the participant's birth mother use illicit substances during pregnancy?] **Response Options**: Yes; No (If Yes) Specify substances used during pregnancy: **Response Options**: Sedatives or tranquilizers; Painkillers; Marijuana; Cocaine or crack; Stimulants; Club drugs; Hallucinogens; Inhalants or solvents; Heroin; Other (If Other) Specify other substances used during pregnancy:
Notes	- For illicit substances descriptions, See **Core Phenotypes**.
Questions	Was the participant's birth mother exposed to any environmental or work related toxins during pregnancy? **Response Options**: Yes; No (If Yes) Specify environmental or work toxins exposed to during pregnancy: **Response Options**: Arsenic: Lead; Mercury; Nickel; Oil-based paints; Organic paint thinners; Pesticides; Solvents ;Other (If Other) Specify other environmental or work toxins exposed to during pregnancy:
Notes	- Environmental Toxins Descriptions: - **Lead; Mercury; Arsenic; Nickel**: a group of toxic heavy metals which can affect human health. - **Oil-based paints**: Oil-based paint contains natural/synthetic oil as a base, and has become common due to its lower price and higher strength. - **Paint thinners**: any of the solvents used to thin oil-based paints or clean up after their use, including mineral spirits, acetone, turpentine, dimethylformamide, and more. - **Pesticides**: agents used to control, repel, or kill unwanted organisms. - **Organic Solvents**: carbon-based substances capable of dissolving or dispersing other substances, including benzene, carbon tetrachloride, and trichloroethylene.
Questions	[Did the participant's birth mother have medical X-Rays conducted during pregnancy? Did the participants' birth mother have a CT scan conducted during pregnancy? Did the participant's birth mother have ultrasound scans done during pregnancy?] **Response Options**: Yes; No

	(If Yes) Specify ultrasound findings: **Response Options**: Abnormalities or irregularities detected; No abnormalities or irregularities detected (If abnormalities or irregularities detected) Specify ultrasound findings:

Notes	- Relevant definitions:
	  - **X-ray**: low radiation used to create images of the inside of the body.
	  - **Dental X-rays**: radiation-created images of the teeth.
	  - **CT scan**: a medical imaging technique used to produce cross-sectional images of a body, allowing user to see inside the body without cutting.
	  - **Ultrasound scans**: a medical test that uses high-frequency sound waves to capture live images of the inside of the body.

Questions	Did the participant's birth mother experience any bleeding during pregnancy? **Response Options**: Yes; No (If Yes) Specify the trimester during which bleeding was experienced: **Response Options**: 1st trimester; 2nd trimester; 3rd trimester What was the participant's gestational age at birth (weeks)? Was intensive/special neonatal care required? **Response Options**: Yes; No (If Yes) What number of days were spent in intensive/neonatal care? (If Yes) What was the reason for intensive care? **Response Options**: Cardiac anomalies; Feeding difficulties; Hypoxic Ischaemic Encephalopathy Neonatal sepsis Prematurity Respiratory difficulties Other (If Other) Specify other reason for intensive care:

Notes	- Trimester Descriptions:
	  - **1st trimester**: Pregnancy period that ranges from the 1st day of the last menstrual period to the 12th week.
	  - **2nd trimester**: Pregnancy period that ranges from the 13th to 27th week.
	  - **3rd trimester**: Pregnancy period that ranges from the 28th week until delivery.
	- **Gestational Age**: a measure of the age of a pregnancy which is taken from the beginning of the woman's last menstrual period.
	- **Neonatal**: refers to infants from the period immediately succeeding birth and continuing through the first 28 days of extrauterine life.
	- Neonatal Complications Descriptions:
	  - **Hypoxic Ischemic Encephalopathy**: ischemic brain damage in which the entire brain is deprived of oxygen.
	  - **Prematurity**: condition of an infant born viable but before 37 weeks of gestation.
	  - **Neonatal sepsis**: infectious disorder of newborn infants, characterized by a systemic inflammatory response most commonly caused by bacteria.
	  - **Feeding difficulties**: impaired ability to eat related to problems gathering

	food and getting ready to suck, chew, or swallow it. - **Cardiac anomalies**: Birth defects in the heart. - **Respiratory difficulties**: Difficult or laboured breathing

Instrument 3: Developmental Milestones

The instrument enables the recording of a research participant's developmental milestones.

Questions	**Gross Motor Milestones:** Is the participant able to sit unsupported? **Response Options:** Yes; No; Not anymore At what age did the participant first sit unsupported? Is the participant able to crawl? **Response Options:** Yes; No; Not anymore At what age did the participant first crawl? Is the participant able to walk unassisted? **Response Options:** Yes; No; Not anymore At what age did the participant first walk unassisted?
Notes	- **Gross Motor Skills**: those skills which require whole body movement and which involve the large (core stabilising) muscles of the body to perform everyday functions
Questions	**Fine Motor Milestones** Is the participant able to dress themselves? **Response Options:** Yes; No; Not anymore At what age could the participant dress themselves?
Notes	- **Fine Motor Skills**: those skills which require the coordination of small muscles in movement with the eyes, usually involving the synchronisation of hands and fingers.
Questions	**Social / Language Milestones** Is the participant able to smile when prompted? **Response Options:** Yes; No; Not anymore At what age did the participant smile when prompted? Is the participant able to speak with words? **Response Options:** Yes; No; Not anymore At what age did the participant say their first words? Is the participant's speech intelligible (would a foreign speaker e.g. someone that doesn't live with the participant, understand the participant)? **Response Options:** Yes; No; Not anymore

Instrument 4: Neurodevelopmental Assessment

The instrument enables the collection of information related to a participant's neurodevelopmental history. As the instrument involves clinical assessment, it needs to be conducted by or the

information needs to be retrieved from a trained and qualified neurodevelopmental healthcare specialist.

Questions	Has the participant undergone a neurodevelopmental assessment by a clinician? **Response Options:** Yes; No (If Yes) Age neurodevelopmental assessment carried out? (If Yes) What was the result of the neurodevelopmental ID/DD assessment? **Response Options**: No ID/DD; Mild ID/DD; Moderate ID/DD; Severe ID/DD Has the participant ever repeated years at school? **Response Options:** Yes; No; Never attended school (If Yes) How many additional years has the participant spent in school?
Notes	- **ID:** Intellectual disability - **DD:** Developmental disability
Questions	Is the participant exhibiting any of the following abnormal behaviours? **Response Options:** Yes; No; Not anymore (If Other) Specify abnormal behaviour/s: Abnormal Behaviours: Aggression Autistic behaviour Hyperactivity Repetitive behaviour Ritualistic behaviour Self harming behaviour Other abnormal behaviour
Notes	- Behaviour Descriptions: - **Aggression**: A type of behaviour intending to cause physical or mental harm. - **Repetitive behaviours**: abnormal behaviors that are characterized by repetition, rigidity, inappropriateness, and lack of adaptability. - **Ritualistic behaviours**: also known as obsessive behaviour, examples Include physical routines, needing to fix something that is not their version of correct, staying on a strict schedule etc. - **Hyperactivity**: abnormally or extremely active. - **Autistic behaviour**: Repetitive body movements (hand flapping, rocking, spinning); moving constantly. Obsessive attachment to unusual objects (rubber bands, keys, light switches). - **Self harming behaviour**: behaviours in which a person deliberately physically hurts themselves.

Instrument 5: Developmental Disorders

The instrument enables the collection of information related to a participant's developmental disorder history.

<table>
<tr><td>Questions</td><td>Has the participant ever been diagnosed with Fetal alcohol syndrome?
Response Options: Yes; No; Not anymore
(If Yes) At what age?
Has the participant ever been diagnosed with a developmental genetic disorder?
Response Options: Yes; No; Not anymore
(If Yes) At what age?
(If Yes) Specify developmental genetic disorder:
Response Options: Down Syndrome; Fragile X; Other
(If Other) Specify other genetic disorder:
Has the participant ever been diagnosed with an Autism spectrum disorder?
Response Options: Yes; No; Not anymore
(If Yes) At what age?
Has the participant ever been diagnosed with Attention Deficit/Hyperactivity Disorder (ADHD)?
Response Options: Yes; No; Not anymore
(If Yes) At what age?
Has the participant ever been diagnosed with a Learning disorder?
Response Options: Yes; No; Not anymore
(If Yes) At what age?
(If Yes) Specify ALL diagnosed learning disorders:
Response Options: Math (Dyscalulia); Reading (Dyslexia); Writing (Dysgraphia); Processing deficits
Has the participant ever been diagnosed with a language/speech disorder?
Response Options: Yes; No; Not anymore</td></tr>
<tr><td>Notes</td><td>- Disease Descriptions:<table><tr><td>Learning Disability</td><td>Description</td></tr><tr><td>Fetal Alcohol Syndrome</td><td>A disorder caused by a prenatal exposure to maternal consumption of alcohol leading to a range of behavioral, cognitive and neurological deficits in the offspring. It is characterized by physical growth problems, distinct facies, and varying psycho-neurological issues.</td></tr><tr><td>Down Syndrome</td><td>A chromosomal dysgenesis syndrome resulting from a triplication or translocation of chromosome 21. Down syndrome occurs in approximately 1:700 live births. Abnormalities are variable from individual to individual and may include slowed mental development, slowed growth, flat hypoplastic face with short nose, prominent epicanthic skin folds, small low-set ears with prominent antihelix, fissured and thickened tongue, laxness of joint ligaments, pelvic dysplasia, broad hands and feet, stubby fingers, transverse palmar crease,</td></tr></table></td></tr>
</table>

	lenticular opacities and heart disease.
Fragile X Syndrome	A genetic syndrome caused by mutations in the FMR1 gene which is responsible for the expression of the fragile X mental retardation 1 protein. This protein participates in neural development. This syndrome is manifested with mental, emotional, behavioral, physical, and learning disabilities.
Genetic Disorder	A disorder whose etiology involves an abnormality in the nucleotide sequence of an organism's genome.
Autism Spectrum Disorder	A disorder beginning in childhood. It is marked by the presence of markedly abnormal or impaired development in social interaction and communication and a markedly restricted repertoire of activity and interest. Manifestations of the disorder vary greatly depending on the developmental level and chronological age of the individual.
ADHD	A disorder that can cause above-normal levels of hyperactive and impulsive behaviors. People with ADHD may also have trouble focusing their attention on a single task or sitting still for long periods of time
Dyslexia	A disorder that involves difficulty reading due to problems identifying speech sounds and learning how they relate to letters and words (decoding)
Dyscalculia	A disability that impairs an individual's ability to learn number-related concepts, perform accurate math calculations, reason and problem solve, and perform other basic math skills.
Dysgraphia	A disorder of written expression that impairs writing ability and fine motor skills.
Processing deficits	Problems with the processes of recognizing and interpreting information taken in through the senses. The two most common areas of processing difficulty associated with learning disabilities are visual and auditory perception.

Instrument 6: Epilepsy Screener

This instrument enables the retrospective collection of information related to a participant's history of seizures and epilepsy.

Questions	[Has the participant ever had a seizure or convulsion caused by a high fever? Has the participant ever been diagnosed with a seizure disorder or epilepsy?] **Response Options**: Yes; No
Notes	- **Epilepsy** is a brain disease that is characterized by the occurrence of at least two unprovoked seizures resulting from a persistent epileptogenic abnormality of the brain that is able to spontaneously generate paroxysmal activity and

	typically manifested by sudden brief episodes of altered or diminished consciousness, involuntary movements, or convulsions.
Questions	[(If No) Has the participant ever experienced... - A seizure, convulsion, fit or spell under any circumstances? - Uncontrolled movements of part or all of the body such as twitching, jerking, shaking or going limp? - An unexplained change in mental state or level of awareness; or an episode of "spacing out" that could not be controlled? - Daydreaming or staring into space more often than peers? - Unusual body movements or feelings when exposed to strobe lights, video games, flickering lights, or sun glare? - Uncontrollable jerking or clumsiness, such as dropping things, shortly after waking up? - Any other type of repeated unusual spells?] **Response Options**: Yes; No
Notes	- The above questions specifically interrogate epilepsy symptoms in participants, and should be collected for both participants with and without epilepsy.

Instrument 7: Rare Disorders

The instrument enables the self-reported collection of a participant's rare disorder diagnosis.

Questions	Has the participant ever been diagnosed with a rare disorder? **Response Options**: Yes; No (If Yes) Specify the rare disorder: (If Yes) Is the participant undergoing treatment for the rare disorder? **Response Options**: Yes; No (If Yes) Specify treatment participant is undergoing for rare disorder:

Notes	- A **rare disorder** refers to any disorder that affects a small percentage of the investigated population.
	- **Examples of rare disorders include:**
	  - Cystic Fibrosis.
	  - Muscular Dystrophy
	  - Spina bifida
	  - Haemophilia
	  - Multiple sclerosis
	  - Narcolepsy

Abbreviations

ADHD: Attention Deficit Hyperactivity Disorder
AIDS: Acquired Immunodeficiency Syndrome
CT scan: Computerized Tomography scan
DD: Developmental Disability

HIV: Human Immunodeficiency Virus
ID: Intellectual Disability

Administration

Mode of Administration

	Instruments						
	1	2	3	4	5	6	7
Interview OR Self-administered questionnaire	X	X	X		X	X	X
Clinical assessment			X	X			
Bioassay/Lab- based assessment							

Life Stage

	Instruments						
	1	2	3	4	5	6	7
Infancy (0 - 12 months)	X	X	X		X		X
Toddler (13 - 24 months)	X	X	X		X		X
Childhood (2-11 years)	X	X	X	X	X	X	X
Adolescence (12 - 18 years)	X	X	X	X	X	X	X
Adult (18 and older)	X	X	X	X	X	X	X

Personnel and Training Required

Instruments 1, 2, 3, 5, 6 and 7 may be implemented as either self-reported questionnaires or interviewer- administered questionnaires. If interviewer- administered, interviews should be conducted by trained or study coordinators or data collectors who speak the native/local language of the target population. Information can also be recorded from or verified using hospital and(or) patient records. Information in **Instrument 4** needs to be recorded from a clinical assessment conducted by a qualified and trained healthcare worker. This may also apply to **Instrument 3**.

References

The R&D toolkit is based on and aligned with several existing standards, to facilitate data harmonisation. These resources are listed below:

1. H3Africa DDD-Africa Case Report Forms
2. H3Africa Rare Diseases WG Case Report Forms
3. Instrument - Epilepsy Screener - Adult (https://www.phenxtoolkit.org/protocols/view/130401)
4. Instrument - Epilepsy Screener - Child/Proxy (https://www.phenxtoolkit.org/protocols/view/130402)

Contributors

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Contact Us

For queries related to this standard and guideline, users can log a ticket to the Phenotypes Standards queue in the H3ABioNet Helpdesk. User feedback and improvements on the current toolkit are welcome and encouraged. These can also be submitted through the Helpdesk, or on our GitHub Issues page.