NVPO Definitions Project
DATA COLLECTION v1.0 (June 28, 2018)
MICROCEPHALY (MCP)

ADMINISTRATIVE INFORMATION

Initials of person performing the review: __ __

Outcome code: **MCP**

Country code: **US, AU, UK:** **__ __**

Site code: **BC, CC, EM, UW, MO, SG, SU:** **__ ___**

Origin code **CT=clinical trial** **MR= medical record:** **__ __**

Subject ID number **MCP** _____ _____ _____ _____
Country **Site** **Origin** **Number (starting with 01)**

Which ICD-9/ICD-10/MEDDRA code was used to identify the chart as a case of MCP:
(from case identification log): _____

COMMON VARIABLES

1. **If case from clinical trial (tick and list study drug/vaccine):**
   - ☐ **Vaccine ____**
   - ☐ **Drug _____**
   - ☐ **Epidemiologic _____**
   - ☐ **Other _____**

2. **Year of event:** **_____** (full year)

3. General pregnancy variables

a. Maternal Age (whole years) at time of delivery

_____ (number if uknown fill UNK)

b. **Race (**tick one, please tick other and state UNK, if unknown/uncertain)

☐ Black

☐ White

☐ Asian

☐ Other ____

c. **Ethnicity (**tick one, please tick other and state UNK if unknown/uncertain)

d. ☐ Hispanic

☐ Not Hispanic

☐ Native Population

☐ Other _____

e. **Infant gender (**tick one, please tick other and state UNK if unknown/uncertain)

☐ Male

☐ Female

☐ Other _____

f. Mode of delivery (tick one, please tick other and state UNK if unknown/uncertain)

☐ Vaginal

☐ C-section:

☐ Other: _____

g. Singleton pregnancy (tick one, please tick other and state UNK, if unknown/uncertain)

☐ Yes

☐ No

☐ Other: _____

h. **Parity (fill 1-4 each with full number based on the status at start of this pregnancy). Gravidity is defined as the number of times that a woman has been pregnant and parity is defined as the number of times that she has given birth to a fetus, regardless of whether the child was born alive or was stillborn**

(fill what you see in chart, if absent state UNK)

Gravidity/Parity reported G…. P…..

1. **Prior** Term Pregnancies_____ (number or fill UNK if unknown)
2. **Prior** Preterm Pregnancies (<37 wk) _____ (number or fill UNK if unknown)
3. Abortions/miscarriage (<20 wk)_____ (number or fill UNK if unknown)
4. Born Alive _____ (number or fill UNK if unknown)

GESTATIONAL AGE ASSESSMENT

4. Recorded gestational age (from chart)

_____ (Number: weeks/days, if absent or unknow state UNK)

5. **How was reported gestational age above assessed (**tick one, and if unknown tick other and state UNK)

- ☐ Antenatal Maternal US
- ☐ LMP
- ☐ Infant Exam,
- ☐ Other (describe) _____

6. **Elements of GA available in the neonatal record (**including copy of maternal/delivery record in the neonatal chart: *only if available in neonatal chart, it is not the intention to find the maternal chart*). (tick one option on each line for a-l)

	Recorded	NOT recorded	Incomplete/ uncertain	Comments/Issues
a. **Intrauterine insemination**	☐	☐	☐	_____
b. **Embryo transfer**	☐	☐	☐	_____
c. **Certain LMP (LMP known)**	☐	☐	☐	_____
d. **Uncertain LMP (LMP not known)**	☐	☐	☐	_____
e. **First trimester US**	☐	☐	☐	_____
f. **Second trimester US**	☐	☐	☐	_____
g. **Third trimester US**	☐	☐	☐	_____
h. **Fundal height (any)**	☐	☐	☐	_____
i. **Fundal height in 2nd trimester**	☐	☐	☐	_____
j. **Maternal physical exam in 1st trimester**	☐	☐	☐	_____
k. **Birth weight**	☐	☐	☐	_____
l. **Newborn GA by physical exam**	☐	☐	☐	_____

7. Assessment of Gestational Age LOC based on GAIA Definition (Use Case Definition Checklist:see appendix 2):

a. Level of certainty ____ (1,2,3,4,5 or UNK: unable to assess)

b. If unable to assign GA LOC, describe the reason(s):

Reason _____

MCP CASE DEFINITION SPECIFIC VARIABLES

8. **Recorded infant birth weight (earliest at birth) (**please complete if unknown/not recorded state UNK)

   _____ (in grams)

9. **Recorded Head Circumference ((**please complete if unknown/not recorded state UNK)

   _____ **(in cm)**

10. **Recorded Percentile of Head Circumference (**please complete if unknown/PERCENTILE not recorded state UNK, THERE IS NO NEED TO CALCULATE)

    _____ **(..th percentile)**

11. **Enter name of reference chart utilized to assess percentile ((**please complete with name of chart if unknown tick no reference chart available)

    ☐ _____

    ☐ no reference chart available /listed

12. **Was subject diagnosed with microcephaly at any point in time? (tick one)**

    ☐ Yes

    ☐ No

    ☐ Uncertain /not recorded

13. **Was diagnosis of microcephaly made postnatally? (tick one)**

    ☐ Yes

    ☐ No

    ☐ Uncertain/not recorded

14. **Was diagnosis of microcephaly made antenatally? (tick one)**

    ☐ Yes

    ☐ No

    ☐ Uncertain /not recorded

15. Elements of the MICROCEPHALY case definition in clinical or study record:

Parameter	Evidence in Medical Record or Study record			
	Yes*	No*	Uncertain/ not recorded	Comments
a. Live birth	☐	☐	☐	
b. Stillbirth	☐	☐	☐	
c. Spontaneous or therapeutic abortion	☐	☐	☐	
d. Documented Gestational Age	☐	☐	☐	
e. Gestational Age ≥ 24 weeks	☐	☐	☐	
f. Fetus ≥ 24 weeks gestation (if antenatal diagnosis)	☐	☐	☐	
g. Head circumference (HC) measurement recorded	☐	☐	☐	
h. HC measurement in cm (metric system)	☐	☐	☐	
i. HC documented to be in the normal range for GA and gender according to reference charts	☐	☐	☐	
j. HC 2 SD below the mean for GA and gender according to reference charts	☐	☐	☐	
k. HC < 3rd percentile for GA and gender according to reference charts	☐	☐	☐	
l. Reference charts used to determine mean and percentile of HC are described	☐	☐	☐	
m. Post-natal reference charts used	☐	☐	☐	
n. Prenatal US reference charts used	☐	☐	☐	
o. HC measured within the first 24 h of life	☐	☐	☐	
p. HC measured between 24-36 hr after birth or end of pregnancy	☐	☐	☐	
q. HC measured > 36 hr and up to 6 weeks after birth or end of pregnancy	☐	☐	☐	
r. HC measured up to 6 weeks after birth or end of pregnancy	☐	☐	☐	
s. No evidence of post-natal insult resulting in microcephaly	☐	☐	☐	

t. Diagnosis of microcephaly based on ICD-9/ICD-10 codes using a validated algorithm for diagnosis of microcephaly	☐	☐	☐
u. Elements of validated algorithm included: **- ICD9-CM code 742.1** **- ICD10-CM code Q02** **AND** **- 1 inpatient diagnosis OR** **- 2 outpatient diagnoses OR** **- 1 outpatient diagnosis AND death in the first year**	☐	☐	☐
v. Diagnosis of microcephaly based on ICD-9/ICD-10 codes without a validated algorithm	☐	☐	☐
w. Diagnosis of microcephaly based on physical exam without HC measurement	☐	☐	☐
x. Confirmatory prenatal ultrasound (fetus) after 24 weeks of gestation and at least one week after first US	☐	☐	☐
y. Prenatal fetal ultrasound showed concordance of femur length and abdominal circumference with GA assessment	☐	☐	☐

*Yes means recorded evidence, No means evidence of absence

QUALITY ASSESSMENT CASE DEFINITION

16. Case abstractor's best assessment of LOC for MICROCEPHALY (Use Case Definition Checklist in appendix 1):

a. Level of certainty ____ (1A/B,2, 3A/B,4,5 or UNK: unable to assess)

b. If unable to assign LOC, describe the reason(s):

Reason _____

17. PI's assessment of LOC for MICROCEPHALY (Use Case Definition Checklist in appendix 1):

a. Level of certainty ____ (1A/B, 3A/B,4,5 or UNK: unable to assess)

b. If unable to assign LOC, describe the reason(s):

Reason _____

18. Other comments

Appendix 1: Microcephaly (MCP)
Guide for LOC assignment for Microcephaly (MCP) (check all that are present)

Congenital Microcephaly is a clinical syndrome based on head circumference (HC) measurements. Depending on when the diagnosis is made, congenital microcephaly is stratified into the following categories:
A. Postnatally diagnosed (after birth) congenital microcephaly
B. Prenatally diagnosed (in utero) congenital microcephaly

CLASSIFICATION OF DIAGNOSTIC CERTAINTY

POST NATAL DIAGNOSIS

It is necessary to first obtain an accurate HC measurement using a flexible, non-stretchable measuring tape. The metric system should be used and marked by 0.1 cm increments. utilization of appropriate HC reference charts is recommended such as WHO Child Growth Standards and Intergrowth 21st charts. It is recommended to record the actual measurement of the head circumference in addition to the percentile.

Level 1
□ 1. Live birth, stillbirth, or spontaneous or therapeutic abortion (SAB) of at least 24 weeks GA*
AND
□ 2. HC 2 SD below the mean or < 3rd percentile according to GA and gender, using the proper reference charts for the population
AND
□ 3. HC measured within 24 to 36 hrs after birth

*GA Assessed based on certain LMP with confirmatory 1st or 2nd trimester US, IUI or embryo transfer date

Level 2A
□ 1. Live birth, stillbirth or SAB of at least 24 weeks GA*
AND
□ 2. HC 2 SD below the mean or < 3rd percentile according to GA and gender, using the proper reference charts for the population
AND
□ 3. Measured within the first 24 hrs of birth
OR
□ 3. Measured > 36 hr and up to 6 weeks after birth or end of pregnancy with no apparent post-natal insult resulting in microcephaly

*GA assessed based on certain LMP with confirmatory 1st trimester or 2nd trimester US scan, IUI, or embryo transfer date

Level 2B

□ 1. Live birth, stillbirth or SAB of at least 24 weeks GA*
AND
□ 2. HC 2 SD below the mean or < 3rd percentile according to GA and gender, using the proper reference charts for the population
AND
□ 3. Measured within the first 24 hr of birth
OR
□ 3. Measured > 36 hr and up to 6 weeks after birth or end of pregnancy with no apparent post-natal insult resulting in microcephaly

*GA based on uncertain LMP with 2nd trimester US

Level 3A

□ 1. Live birth, stillbirth or SAB of at least 24 weeks GA*
AND
□ 2. HC 2 SD below the mean or < 3rd percentile according to GA and gender, using the proper reference charts for the population
AND
□ 3. Measured within the first 24 hr of birth
OR
□ 3. Measured > 36 hr and up to 6 weeks after birth or end of pregnancy with no apparent post-natal insult resulting in microcephaly

*GA based on LMP without confirmatory 1st or 2nd trimester US

Level 3B

□ 1. Live birth, stillbirth or SAB
AND
□ 2. Case meets criteria for microcephaly using a validated algorithm:
1 inpatient diagnosis OR 2 outpatient diagnoses OR 1 outpatient diagnosis
AND
Death in first year using the following diagnostic codes ICD-9-CM code 742.1 or ICD-10-CM code Q02

Level 4

□ 1. Live birth, stillbirth or SAB
AND
□ 2. Diagnosis of congenital microcephaly based on physical inspection without HC measurement
OR

□ 2. Diagnosis of congenital microcephaly based on ICD-9-CM or ICD-10-CM code that does not meet validated algorithm criteria above.

PRENATAL DIAGNOSIS OF MICROCEPHALY

In order to apply the case definition of prenatally diagnosed congenital microcephaly, it is necessary to obtain an **accurate HC measurements via prenatal ultrasound (US) scan** by a sonographer or a health professional trained in sonography. A fetal HC measurement can be obtained starting at approximately 14 weeks estimated gestational age. **Accurate gestational age (GA) determination is vital** when determining congenital microcephaly based on prenatal US. Ideally, dating is based on or confirmed by a first trimester US using crown-rump length for measurement. If after the 1st trimester, gestational age has not yet been confirmed and congenital microcephaly is suspected, HC should not be used to determine gestational age.

There are currently several fetal growth standards in use for HC measurements including those from the Fetal Growth Longitudinal Study of the INTERGROWTH-21st Project, the WHO Multicentre Growth Reference Study (MGRS), the National Institute of Child Health and Human Development (NICHD) Fetal Growth Studies, and those referenced by the United States Society for Maternal-Fetal Medicine (SMFM) based on Hadlock growth curves.

Level 1A
□ 1. Fetus of at least 24 weeks GA based on certain LMP with confirmatory 1st trimester or 2nd trimester US scan IUI, or embryo transfer date
AND
□ 2. HC 2 SD below mean or <3 percentile according to fetal US scan using appropriate standardized reference charts according to GA and gender for the population
AND
□ 3. Confirmation of microcephaly (i.e., HC 2 SD below mean or <3 percentile) in fetus by at least one additional US scan after 24 weeks and at least one week after first US
OR
□ 3. Confirmation of microcephaly by HC measurement with standard tape measure at birth or autopsy

Level 1B
□ 1. Fetus of at least 24 weeks GA based on uncertain LMP with 2nd trimester US
AND
□ 2. HC 2 SD below mean or <3 percentile according to fetal US using appropriate standardized reference charts according to GA and gender for the population
AND
□ 3. Confirmation of microcephaly (i.e., HC 2 SD below mean or <3 percentile) in fetus by at least one additional US scan after 24 weeks and at least one week after first US
OR

□ 3. Confirmation of microcephaly by HC measurement with standard tape measure at birth or autopsy

Level 2

□ 1. Fetus of at least 24 weeks GA based on certain or uncertain LMP with fundal height and no confirmatory 1st or 2nd trimester US
AND
□ 2. HC 2 SD below mean or <3 percentile according to fetal US scan using appropriate standardized reference charts according to GA and gender for the population, with femur length and abdominal circumference concordant with GA assessment
AND
□ 3. Confirmation of microcephaly (i.e., HC 2 SD below mean or <3 percentile) in fetus by at least one additional US scan after 24 weeks and at least one week after first US
OR
□ 3. Confirmation of microcephaly by HC measurement with standard tape measure at birth or autopsy

Level 3A

□ 1. Fetus of at least 24 weeks GA based on certain LMP with confirmatory 1st or 2nd trimester US, or uncertain LMP with 2nd trimester US, IUI or embryo transfer date
AND
□ 2. HC 2 SD below mean or <3 percentile according to fetal US scan using appropriate standardized reference charts according to GA and gender for the population, with femur length and abdominal circumference concordant with GA assessment
AND
□ 3. No additional data to confirm microcephaly

Level 3B

□ 1. Fetus of at least 24 weeks GA based on certain or uncertain LMP with fundal height and no confirmatory 1st or 2nd trimester US
AND
□ 2. HC 2 SD below mean or <3 percentile according to fetal US scan using appropriate standardized reference charts according to GA and gender for the population, with femur length and abdominal circumference concordant with GA assessment
AND
□ 3. No additional data to confirm microcephaly

Level 4

□ 1. Fetus of at least 24 weeks GA based on certain LMP with confirmatory 1st trimester or 2nd trimester US, uncertain LMP with 2nd trimester US, IUI, embryo transfer date, or certain or uncertain LMP with fundal height and no confirmatory 1st or 2nd trimester US
AND

□ 2. HC 2 SD below mean or <3 percentile according to fetal US scan using appropriate standardized reference charts according to GA and gender for the population
AND
□ 3. HC at birth or autopsy is in the normal range using appropriate standardized reference charts according to GA and gender for the population, which means that this is NOT a case of prenatally diagnosed congenital microcephaly

Appendix 2

Gestational Age Assessment Guide

Definitions of terms used:

Intrauterine insemination (IUI) – A procedure in which a fine catheter is inserted through the cervix into the uterus to deposit a sperm sample directly into the uterus, to achieve fertilization and pregnancy.

Embryo transfer – The procedure in which one or more embryos are placed in the uterus or fallopian tube.

Ultrasound (U/S):

- 1st trimester (≤ 13 6/7 weeks).

- 2nd trimester scan (14 0/7–27 6/7 weeks).

- 3rd trimester (28 0/7 + weeks).

LMP (last menstrual period) – GA is calculated from the first day of the mother's LMP. If LMP and U/S do not correlate, default to U/S GA assessment.

***Certain LMP**: (LMP date + 280 days): Use LMP if within 7 days at ≤ 14 weeks; within 14 days at ≤26 weeks; within 21 days beyond 26 weeks.

***Uncertain LMP – first trimester** (≤13 6/7 weeks by LMP): Use the approximate date of the last menstrual period (LMP) if corroborated by physical exam, or a first trimester ultrasound. If there is a discrepancy of >7 days between the LMP and the first trimester ultrasound, the ultrasound-established dates will take preference over LMP for gestational age dating.

***Uncertain LMP – second trimester** (14 0/7–27 6/7 weeks by LMP): Use the approximate date of the LMP if corroborated by physical exam including fundal height, or a second trimester ultrasound. If there is a discrepancy of >10 days between the LMP and the second trimester ultrasound, the ultrasound-established dates will take preference over LMP for GA dating.

***Uncertain LMP – third trimester** >28 weeks – third trimester ultrasound.

***No LMP date:** If menstrual dates are unknown, the ultrasound established dates will be used for gestational age dating or 2nd trimester fundal height and/or newborn physical examination.

Pregnancy symptoms– nausea, fatigue, tender swollen breasts, frequent urination.

Antenatal Physical Examination– pelvic bimanual examination confirming enlarged uterus.

Newborn Physical Examination– New Ballard Score – physical and neurological assessment.

Fundal Height (FH) in cms

Birth Weight (BW) in grams

GA Levels of Certainty (Check all that are present)

Level 1

□ 1. Certain LMP* or intrauterine insemination (IUI) date or embryo transfer (ET) date with confirmatory 1st trimester scan (< 13 6/7 weeks).

OR

□ 2. 1st trimester scan (< 13 6/7 weeks).

Level 2A

□ 1. Certain LMP* with 2nd trimester scan (14 0/7 weeks to 27 6/7 weeks). If LMP and U/S do not correlate, default to U/S GA assessment.

OR

□ 2. Certain LMP* with 1st trimester physical examination.

Level 2B

□ Uncertain LMP with 2nd trimester scan (14 0/7 weeks to 27 6/7 weeks).

Level 3A

□ 1. Certain LMP with 3rd trimester scan – 28 0/7 weeks +.

OR

□ 2. Certain LMP with confirmatory 2nd trimester FH.

OR

□ 3. Certain LMP with birth weight.

OR

□ 4. Uncertain LMP with 1st trimester physical examination.

Level 3B

□ 1. Uncertain LMP with FH.

OR

□ 2. Uncertain LMP with newborn physical assessment.

OR

□ 3. Uncertain LMP with Birth weight.