*Background*: The NIH HEAL CDE program requires clinical pain studies to collect data on prescribed/dispensed opioid use for pain management in trials involving human subjects. Prescribed/dispensed opioid use will be reported as daily morphine milligram equivalents (MMEs), which is a metric to estimate analgesic profile and/or overdose potential of the prescribed opioid medications. **Daily MMEs should NOT be used in evaluating opioid medications for the treatment of opioid use disorder.**

There are four definitions to calculate daily MMEs: (1) Total Day Supply (nonoverlapping prescription days); (2) Therapy Days (overlapping prescription days); (3) Fixed Observation Windows; (4) Maximum Daily Dose (Dasgupta et al., 2021). The standardization of calculating daily MMEs is not established in clinical or research settings, and each definition has utility based on the primary research goal. Hence, data collection on these four definitions within HEAL-funded studies presents a unique opportunity to build an evidence base on best practices in calculating daily MMEs and work towards standardizing daily MME reporting.

The collection of these data is intended for **research purposes** only. These data will not be shared with prescription drug monitory programs (PDMPs) or health care professionals overseeing opioid use for pain management for participants enrolled in the study. The data collection effort is **NOT intended for any clinical decision-making** by clinicians while prescribing opioids. The MME conversion factors in this tool DO NOT constitute any clinical guidance for prescribing or recommendations for converting patients from one form of opioid analgesic to another. These calculations are for the conversion of opioid medication TO morphine equivalents, and are not intended to be used in the reverse direction.

*Instructions*: Daily MMEs will be collected at two separate time points per participant. It is recommended that individual studies within a HEAL-funded program harmonize on these data collection time points, and harmonize on the sampling frame (e.g., past week, past month, etc.). Please enter the information requested in the following form about the most recent opioids prescribed to study participants. The MME tool will automatically calculate the MME for each opioid medication, and then calculate the total and daily MME across all the opioid medications based on four definitions. Opioid medication, dose, prescription duration, and the four daily MME definition values must be included as part of your submission to the HEAL Data Ecosystem. This intensive data collection effort will create a valuable data resource to enable comparisons across opioid analgesic medications (and different routes of administration), between time points, and across HEAL funded studies.

**This tool should be completed by research staff, and not by participants.**

Is the participant taking an opioid medication for pain management? \_ 1. Yes \_ 0. No

*If the answer is no, the rest of this document is not applicable.*

Select all opioid medication(s) that apply.

\_ 1. Buprenorphine (e.g., Suboxone, Butrans, Bunavail)

\_ 2. Butorphanol (e.g., Stadol, Dolorex)

\_ 3. Codeine

\_ 4. Dihydrocodeine (e.g., Panlor-DC, Trezix)

\_ 5. Fentanyl (e.g., Abstral, Subsys, Duragesic)

\_ 6. Hydrocodone (e.g., Lortab, Vicodin)

\_ 7. Hydromorphone (e.g., Dilaudid)

\_ 8. Levorphanol tartrate

\_ 9. Meperidine (e.g., Demerol)

\_ 10. Methadone (e.g., Dolophine, Methadose)

\_ 11. Morphine (e.g., Avinza, Duramorph)

\_ 12. Opium

\_ 13. Oxycodone (e.g., OxyContin, Percodan)

\_ 14. Oxymorphone (e.g., Opana)

\_ 15. Pentazocine (e.g., Talwin)

\_ 16. Tapentadol (e.g., Nucynta)

\_ 17. Tramadol (e.g., Ultram)

Next, enter information about the opioid medications.

*If opioid medication = 1,* ***Buprenorphine***

Buprenorphine Disclaimer: There is a range of buprenorphine products that include formulations with FDA approval for pain and formulations that have FDA approval for opioid use disorder, which are prescribed off label for pain management. The CDC currently recommends that buprenorphine should not be counted in total MME or MME/Day calculations because buprenorphine has partial agonist properties at opioid receptors that confer a ceiling effect on respiratory depression (Dowell et al., 2022). There are several national prescribing guidelines, however, that endorse the use of buprenorphine as an analgesic for chronic pain management. For participants who have been prescribed buprenorphine for pain management (**and not OUD**), this tool will create daily MME values based on the four definitions with and without buprenorphine daily MMEs. The MME values, inclusive and exclusive of buprenorphine products, will only be used for research purposes.

Please note buprenorphine to morphine conversions are approximate (not defined by direct clinical studies of analgesic equivalence). Conversion factors are from CDC 2016.

Which format(s) of buprenorphine is/are taken? *Select all that apply*

\_ 1. Sublingual film/tablet (mg) (e.g., Suboxone, Subutex, Zubsolv)

\_ 2. Transdermal patch (mcg/hr) (e.g., Butrans)

\_ 3. Buccal film (mcg) (e.g., Bunavail, Belbuca)

*[continued on next page]*

*If buprenorphine form is 1, sublingual*

Buprenorphine sublingual dose (mg)? \_\_\_\_\_

Number of buprenorphine sublingual doses per day? \_\_\_\_\_

Duration of buprenorphine sublingual prescription (in days)? \_\_\_\_\_

Buprenorphine sublingual calculated MME \_\_\_\_\_

 *Conversion factor = 40
 Calculated MME = 40 \* dose \* number of doses per day \* duration*

*If buprenorphine form is 2, transdermal*

Buprenorphine transdermal dose (mcg/hr)? \_\_\_\_\_

Number of days each buprenorphine transdermal patch is worn? \_\_\_\_\_

 *Patch is typically replaced every 7 days*

Duration of buprenorphine transdermal prescription (in days)? \_\_\_\_\_

 *Total days encompassed by the prescription
 e.g. 4 patches at 7 days per patch, duration would be 28 (days)*

Buprenorphine transdermal calculated 24 hour MME \_\_\_\_\_

 *Conversion factor for one day = 2.2
 Calculated 24 hour MME = 2.2 \* dose*

Buprenorphine transdermal calculated MME \_\_\_\_\_

 *[Buprenorphine transdermal calculated 24 hour MME] \* duration*

*If buprenorphine form is 3, buccal*

Buprenorphine buccal dose (mcg)? \_\_\_\_\_

Number of buprenorphine buccal doses per day? \_\_\_\_\_

Duration of buprenorphine buccal prescription (in days)? \_\_\_\_\_

Buprenorphine buccal calculated MME \_\_\_\_\_

 *Conversion factor = 0.03
 Calculated MME = 0.03 \* dose \* number of doses per day \* duration*

*If opioid medication = 2,* ***Butorphanol***

Butorphanol dose (mg)? \_\_\_\_\_

Number of butorphanol doses per day? \_\_\_\_\_

Duration of butorphanol prescription (in days)? \_\_\_\_\_

Butorphanol calculated MME \_\_\_\_\_

 *Conversion factor = 7
 Calculated MME = 7 \* dose \* number of doses per day \* duration*

*If opioid medication = 3,* ***Codeine***

Codeine dose (mg)? \_\_\_\_\_

Number of codeine doses per day? \_\_\_\_\_

Duration of codeine prescription (in days)? \_\_\_\_\_

Codeine calculated MME \_\_\_\_\_

 *Conversion factor = 0.15
 Calculated MME = 0.15 \* dose \* number of doses per day \* duration*

*If opioid medication = 4,* ***Dihydrocodeine***

Dihydrocodeine dose (mg)? \_\_\_\_\_

Number of dihydrocodeine doses per day? \_\_\_\_\_

Duration of dihydrocodeine prescription (in days)? \_\_\_\_\_

Dihydrocodeine calculated MME \_\_\_\_\_

 *Conversion factor = 0.25
 Calculated MME = 0.25 \* dose \* number of doses per day \* duration*

*If opioid medication = 5,* ***Fentanyl***

Which format(s) of fentanyl is/are taken?

\_ 1. buccal or SL tablets or lozenge/troche (mcg) (e.g., Fentora, Abstral, Actiq)

\_ 2. film or oral spray (mcg) (e.g., Onsolis or Subsys)

\_ 3. nasal spray (mcg) (e.g., Lazanda)

\_ 4. patch (mcg/hr) (e.g., Duragesic)

*If fentanyl form is 1, buccal/SL*

Fentanyl buccal or SL tablets or lozenge/troche dose (mcg)? \_\_\_\_\_

Number of fentanyl buccal or SL tablets or lozenge/troche doses per day? \_\_\_\_\_

Duration of fentanyl buccal or SL tablets or lozenge/troche prescription (in days)? \_\_\_\_\_

Fentanyl buccal tablet, SL tablet, or lozenge/troche calculated MME \_\_\_\_\_

 *Conversion factor = 0.13
 Calculated MME = 0.13 \* dose \* number of doses per day \* duration*

*If fentanyl form is 2, film/oral spray*

Fentanyl film or oral spray dose (mcg)? \_\_\_\_\_

Number of fentanyl film or oral spray doses per day? \_\_\_\_\_

Duration of fentanyl film or oral spray prescription (in days)? \_\_\_\_\_

Fentanyl film or oral spray calculated MME \_\_\_\_\_

  *Conversion factor = 0.18
 Calculated MME = 0.18 \* dose \* number of doses per day \* duration*

*If fentanyl form is 3, nasal spray*

Fentanyl nasal spray dose (mcg)? \_\_\_\_\_

Number of fentanyl nasal spray doses per day? \_\_\_\_\_

Duration of fentanyl nasal spray prescription (in days)? \_\_\_\_\_

Fentanyl nasal spray calculated MME \_\_\_\_\_

  *Conversion factor = 0.16
 Calculated MME = 0.16 \* dose \* number of doses per day \* duration*

*If fentanyl form is 4, patch*

Fentanyl transdermal patch dose (mcg/hr)? \_\_\_\_\_

Number of days each fentanyl transdermal patch is worn? \_\_\_\_\_

*e.g., if patch is replaced every 3 days, enter 3*

Duration of fentanyl transdermal patch prescription (in days)? \_\_\_\_\_

 *e.g., 10 patches at 3 days per patch = 30 days*

Fentanyl transdermal patch calculated 24 hour MME \_\_\_\_\_

 *Conversion factor for one day = 2.4
 Calculated 24 hour MME = 2.4 \* dose*

Fentanyl transdermal patch calculated MME \_\_\_\_\_

*Total MME (24 hour MME \* duration)*

 *[Fentanyl transdermal patch calculated 24 hour MME] \* duration*

*[continued on next page]*

*If opioid medication = 6,* ***Hydrocodone***

 *Conversion factor = 1*

Which formulation(s) of hydrocodone is being taken? *Select all that apply*

\_ 1. Short acting or unspecified

\_ 2. Long acting/extended release

*If formulation is 1, short acting*

Hydrocodone short acting dose (mg)? \_\_\_\_\_

Number of hydrocodone short acting doses per day? \_\_\_\_\_

Duration of hydrocodone short acting prescription (in days)? \_\_\_\_\_

*If formulation is 2, long acting*

Hydrocodone long acting dose (mg)? \_\_\_\_\_

Number of hydrocodone long acting doses per day? \_\_\_\_\_

Duration of hydrocodone long acting prescription (in days)? \_\_\_\_\_

Hydrocodone calculated MME \_\_\_\_\_

 *Calculate the MME for short acting and long acting formulations and then add together*

*Sum (add) the MME for short acting (1 \* dose \* number of doses in 24h \* duration) and
 long acting (1 \* dose \* number of doses in 24h \* duration) formulations*

*Hydrocodone calculated MME = sum(( [mme\_hydrocod\_conv] \* [mme\_hydrocod\_dose] \* [mme\_hydrocod\_24h] \* [mme\_hydrocod\_rxdur]), ([mme\_hydrocod\_conv] \* [mme\_hydrocod\_la\_dose] \* [mme\_hydrocod\_la\_24h] \* [mme\_hydrocod\_la\_rxdur]) )*

*If opioid medication = 7,* ***Hydromorphone***

 *Conversion factor = 5*

Which formulation(s) of hydromorphone is being taken? *Select all that apply*

\_ 1. Short acting or unspecified

\_ 2. Long acting/extended release

*If formulation is 1, short acting*

Hydromorphone short acting dose (mg)? \_\_\_\_\_

Number of hydromorphone short acting doses per day? \_\_\_\_\_

Duration of hydromorphone short acting prescription (in days)? \_\_\_\_\_

*If formulation is 2, long acting*

Hydromorphone long acting dose (mg)? \_\_\_\_\_

Number of hydromorphone long acting doses per day? \_\_\_\_\_

Duration of hydromorphone long acting prescription (in days)? \_\_\_\_\_

Hydromorphone calculated MME \_\_\_\_\_ *Calculate the MME for short acting and long acting formulations and then add together*

 *Sum (add) the MME for short acting (1 \* dose \* number of doses in 24h \* duration) and
 long acting (1 \* dose \* number of doses in 24h \* duration) formulations*

*Hydromorphone calculated MME = sum(( [mme\_hydromor\_conv] \* [mme\_hydromor\_dose] \* [mme\_hydromor\_24h] \* [mme\_hydromor\_rxdur]), ([mme\_hydromor\_conv] \* [mme\_hydromor\_la\_dose] \* [mme\_hydromor\_la\_24h] \* [mme\_hydromor\_la\_rxdur]) )*

*If opioid medication = 8,* ***Levorphanol******tartrate***

Levorphanol tartrate dose (mg)? \_\_\_\_\_

Number of levorphanol tartrate doses per day? \_\_\_\_\_

Duration of levorphanol tartrate prescription (in days)? \_\_\_\_\_

Levorphanol tartrate calculated MME \_\_\_\_\_

 *Conversion factor = 11
 Calculated MME = 11 \* dose \* number of doses per day \* duration*

*If opioid medication = 9,* ***Meperidine******hydrochloride***

Meperidine hydrochloride dose (mg)? \_\_\_\_\_

Number of meperidine hydrochloride doses per day? \_\_\_\_\_

Duration of meperidine hydrochloride prescription (in days)? \_\_\_\_\_

Meperidine hydrochloride calculated MME \_\_\_\_\_

 *Conversion factor = 0.1
 Calculated MME = 0.1 \* dose \* number of doses per day \* duration*

*If opioid medication = 10,* ***Methadone***

Methadone dose (mg)? \_\_\_\_\_

Number of methadone doses per day? \_\_\_\_\_

Duration of methadone prescription (in days)? \_\_\_\_\_

Methadone calculated MME \_\_\_\_\_

 *Conversion factor = 4.7
 Calculated MME = 4.7 \* dose \* number of doses per day \* duration*

*If opioid medication = 11,* ***Morphine***

 *Conversion factor = 1*

Which formulation(s) of morphine is being taken? *Select all that apply*

\_ 1. Short acting or unspecified

\_ 2. Long acting/extended release

*If formulation is 1, short acting*

Morphine short acting dose (mg)? \_\_\_\_\_

Number of Morphine short acting doses per day? \_\_\_\_\_

Duration of Morphine short acting prescription (in days)? \_\_\_\_\_

*If formulation is 2, long acting*

Morphine long acting dose (mg)? \_\_\_\_\_

Number of Morphine long acting doses per day? \_\_\_\_\_

Duration of Morphine long acting prescription (in days)? \_\_\_\_\_

Morphine calculated MME \_\_\_\_\_

*Calculate the MME for short acting and long acting formulations and then add together*

 *Sum (add) the MME for short acting (1 \* dose \* number of doses in 24h \* duration) and
 long acting (1 \* dose \* number of doses in 24h \* duration) formulations*

*Morphine calculated MME = sum(( [mme\_morphine\_conv] \* [mme\_morphine\_dose] \* [mme\_morphine\_24h] \* [mme\_morphine\_rxdur]), ([mme\_morphine\_conv] \* [mme\_morphine\_la\_dose] \* [mme\_morphine\_la\_24h] \* [mme\_morphine\_la\_rxdur]) )*

*If opioid medication = 12,* ***Opium***

Opium dose (mg)? \_\_\_\_\_

Number of Opium doses per day? \_\_\_\_\_

Duration of Opium prescription (in days)? \_\_\_\_\_

Opium calculated MME \_\_\_\_\_

 *Conversion factor = 1
 Calculated MME = 1 \* dose \* number of doses per day \* duration*

*If opioid medication = 13,* ***Oxycodone***

 *Conversion factor = 1.5*

Which formulation(s) of oxycodone is being taken? *Select all that apply*

\_ 1. Short acting or unspecified

\_ 2. Long acting/extended release

*If formulation is 1, short acting*

Oxycodone short acting dose (mg)? \_\_\_\_\_

Number of Oxycodone short acting doses per day? \_\_\_\_\_

Duration of Oxycodone short acting prescription (in days)? \_\_\_\_\_

*If formulation is 2, long acting*

Oxycodone long acting dose (mg)? \_\_\_\_\_

Number of Oxycodone long acting doses per day? \_\_\_\_\_

Duration of Oxycodone long acting prescription (in days)? \_\_\_\_\_

Oxycodone calculated MME \_\_\_\_\_

 *Calculate the MME for short acting and long acting formulations and then add together*

 *Sum (add) the MME for short acting (1.5 \* dose \* number of doses in 24h \* duration) and
 long acting (1.5 \* dose \* number of doses in 24h \* duration) formulations*

*Oxycodone calculated MME = sum(([mme\_oxycod\_conv] \* [mme\_oxycod\_dose] \* [mme\_oxycod\_24h] \* [mme\_oxycod\_rxdur]),([mme\_oxycod\_conv] \* [mme\_oxycod\_la\_dose] \* [mme\_oxycod\_la\_24h] \* [mme\_oxycod\_la\_rxdur]))*

*If opioid medication = 14,* ***Oxymorphone***

 *Conversion factor = 3*

Which formulation(s) of oxymorphone is being taken? *Select all that apply*

\_ 1. Short acting or unspecified

\_ 2. Long acting/extended release

*If formulation is 1, short acting*

Oxymorphone short acting dose (mg)? \_\_\_\_\_

Number of Oxymorphone short acting doses per day? \_\_\_\_\_

Duration of Oxymorphone short acting prescription (in days)? \_\_\_\_\_

*If formulation is 2, long acting*

Oxymorphone long acting dose (mg)? \_\_\_\_\_

Number of Oxymorphone long acting doses per day? \_\_\_\_\_

Duration of Oxymorphone long acting prescription (in days)? \_\_\_\_\_

Oxymorphone calculated MME \_\_\_\_\_

*Calculate the MME for short acting and long acting formulations and then add together*

 *Sum (add) the MME for short acting (3 \* dose \* number of doses in 24h \* duration) and
 long acting (3 \* dose \* number of doses in 24h \* duration) formulations*

*Oxymorphone calculated MME = sum(([mme\_oxycod\_conv] \* [mme\_oxycod\_dose] \* [mme\_oxycod\_24h] \* [mme\_oxycod\_rxdur]),([mme\_oxycod\_conv] \* [mme\_oxycod\_la\_dose] \* [mme\_oxycod\_la\_24h] \* [mme\_oxycod\_la\_rxdur]))*

*If opioid medication = 15,* ***Pentazocine***

Pentazocine dose (mg)? \_\_\_\_\_

Number of Pentazocine doses per day? \_\_\_\_\_

Duration of Pentazocine prescription (in days)? \_\_\_\_\_

Pentazocine calculated MME \_\_\_\_\_

 *Conversion factor = 0.37
 Calculated MME = 0.37 \* dose \* number of doses per day \* duration*

*If opioid medication = 16,* ***Tapentadol***

 *Conversion factor = 0.3*

Which formulation(s) of Tapentadol is being taken? *Select all that apply*

\_ 1. Short acting or unspecified

\_ 2. Long acting/extended release

*If formulation is 1, short acting*

Tapentadol short acting dose (mg)? \_\_\_\_\_

Number of Tapentadol short acting doses per day? \_\_\_\_\_

Duration of Tapentadol short acting prescription (in days)? \_\_\_\_\_

*Calculated MME for* Tapentadol *short acting = 0.3 \* dose \* number of doses per day \* duration*

 *If short acting was not selected, calculated MME for short acting = 0*

*If formulation is 2, long acting*

Tapentadol long acting dose (mg)? \_\_\_\_\_

Number of Tapentadol long acting doses per day? \_\_\_\_\_

Duration of Tapentadol long acting prescription (in days)? \_\_\_\_\_

*Calculated MME for* Tapentadol *long acting = 0.3 \* dose \* number of doses per day \* duration*

 *If long acting was not selected, calculated MME for long acting = 0*

Tapentadol calculated MME \_\_\_\_\_

*Calculate the MME for short acting and long acting and then add together*

 Tapentadol *calculated MME =*

 *calculated MME for short acting + calculated MME for long acting*

*If opioid medication = 17,* ***Tramadol***

 *Conversion factor = 0.2*

Which formulation(s) of Tramadol is being taken?

\_ 1. Short acting or unspecified

\_ 2. Long acting/extended release

*If formulation is 1, short acting*

Tramadol short acting dose (mg)? \_\_\_\_\_

Number of Tramadol short acting doses per day? \_\_\_\_\_

Duration of Tramadol short acting prescription (in days)? \_\_\_\_\_

*Calculated MME for* Tramadol *short acting = 0.2 \* dose \* number of doses per day \* duration*

 *If short acting was not selected, calculated MME for short acting = 0*

*If formulation is 2, long acting*

Tramadol long acting dose (mg)? \_\_\_\_\_

Number of Tramadol long acting doses per day? \_\_\_\_\_

Duration of Tramadol long acting prescription (in days)? \_\_\_\_\_

*Calculated MME for* Tramadol *long acting = 0.2 \* dose \* number of doses per day \* duration*

 *If long acting was not selected, calculated MME for long acting = 0*

Tramadol calculated MME \_\_\_\_\_

*Calculate the MME for short acting and long acting and then add together*

 *Tramadol* *calculated MME =*

 *calculated MME for short acting + calculated MME for long acting*

**Therapy days and Observation Windows**

**EXCLUDING** buprenorphine

Calculated Values

**Total MME across prescriptions** \_\_\_\_\_

Sum of MME across all prescriptions*, except for buprenorphine*

*Note: Total opioid exposure (numerator for MME/Day calculations)*

**Total Days Supply** \_\_\_\_\_

Sum of prescription duration days, *except for buprenorphine*

*Denominator for MME/Day Definition 1.*

Entered Values

**On-therapy Days** \_\_\_\_\_

Please ENTER the sum of prescription duration days,
excluding buprenorphine days, with each calendar day counted only ONCE.

If only one prescription or no overlapping days this will be same as the total days supply.

*Denominator for MME/Day Definition 2.*

**Fixed Observation Window** \_\_\_\_\_

ENTER the number of days. This is a study-defined interval.

Examples: 7 days, 30 days, 60 days, 90 days.

*Denominator for MME/Day Definition 3.*

**Opioid MME/Day Calculations**

EXCLUDING buprenorphine

**MME/Day Definition 1. Total Days Supply** \_\_\_\_\_

(excluding buprenorphine)

Total MME across prescriptions/Total Days Supply

**MME/Day Definition 2. On-therapy Days** *\_\_\_\_\_*

(excluding buprenorphine)

Total MME /On-therapy Days

**MME/Day Definition 3. Fixed Observation Window** \_\_\_\_\_

(excluding buprenorphine)

Total MME /Fixed Observation Window

**MME/Day Definition 4. Maximum Daily Dose** \_\_\_\_\_

Highest single-day MME exposure

This is the sum of 24 hour MME

*Complete these calculations if Buprenorphine was selected as one of the opioid medications.*

**Therapy days and Observation Windows**

WITH Buprenorphine

Calculated Values

**Total MME across prescriptions - with buprenorphine \_\_\_\_\_**

*Total opioid exposure (numerator for MME/Day calculations)*

**Total Days Supply - with buprenorphine \_\_\_\_\_**

*Denominator for MME/Day Definition 1*

Entered Values

**On-therapy Days - with buprenorphine \_\_\_\_\_**

Please ENTER the sum of prescription duration days, with each calendar day counted only ONCE.

If only one prescription or no overlapping days this will be same as the total days supply.

*Denominator for MME/Day Definition 2*

**Fixed Observation Window \_\_\_\_\_**

ENTER the number of days. This is a study-defined interval.

Examples: 7 days, 30 days, 60 days, 90 days.

*Denominator for MME/Day Definition 3.*

**Opioid MME/Day Definition Calculations**

WITH buprenorphine

**MME/Day Definition 1. Total Days Supply - with buprenorphine** \_\_\_\_\_

Total MME /Total Days Supply

**MME/Day Definition 2. On-therapy Days** **- with buprenorphine** \_\_\_\_\_

Total MME /On-therapy Days

**MME/Day Definition 3. Fixed Observation Window - with buprenorphine** \_\_\_\_\_

Total MME /Fixed Observation Window

**MME/Day Definition 4. Maximum Daily Dose - with buprenorphine**  \_\_\_\_\_

Highest single-day MME exposure

This is the sum of the 24 hour MME

**Notes: Additional Information about MME/Day Definitions**

24h MME for Drug X:
Morphine milliequivalent calculation for Drug X for a single day, calculated as (dose) \* (number of doses per day) \* (conversion factor)

MME for Drug X:
Total Morphine milliequivalent calculation for Drug X,  calculated as (dose) \* (number of doses per day) \* (conversion factor) \* (prescription duration in days)

Total MME:
The MME for Drug X, summed across all prescriptions. This is the numerator for MME/Day definitions 1, 2, and 3.

MME/Day:
An aggregate measure, calculating the Total MME divided by a specified time window (a number of days). The MME/Day definitions specify the number of days.

*Time Windows*

Total Days Supply:
The sum of the entered prescription duration (days) for each medication (Med 1 duration + med 2 duration...). This is the denominator for MME/Day definition 1.

On-therapy Days:
The sum of prescription duration (days) for each medication, but with each calendar day counted only ONCE. If there is only one prescription, or if there is no calendar overlap (no days on which more than one prescription is active), this will be the same as the total days supply. If there are overlapping prescriptions, this is the number of unique calendar days. This is the denominator for MME/Day definition 2.

Fixed Observation Window:
A study-defined window of time. Typical choices are 7 day, 14 day, 30 day, 90 day. This is the denominator for MME/Day definition 3.

Maximum Daily Dose (single day):

Typically, the one day with highest opioid exposure is entered, and the sum of 24 hour MME across the drugs that apply to this day is calculated. Highest MME in one day is definition 4.

*MME/Day* *Definitions*

MME/Day Definition 1. Total Days Supply.
Total MME / Total Days Supply

* Note that the same calendar day may contribute multiple times, if overlapping prescriptions.
* Reason to select this definition: The least complicated calculation; appears best suited when immediate-release opioids are prescribed for short discrete times.
* Identified challenge with this definition: It consistently underestimated MME per day when overlapping prescriptions were present or when immediate-release and extended release opioids were prescribed concurrently.

MME/Day Definition 2. On-therapy Days.
Total MME / On-therapy Days

* Note that this definition uses unique calendar days (each calendar day is only counted once)
* Reason to select this definition: Provides a smoothed measure useful in studies of dose-dependent adverse effects, including opioid-induced constipation or overdose in patients with opioid tolerance or who have been stable on opioids.
* Identified challenge with this definition: The metric is time-varying and affords the greatest flexibility to define medication gap periods and leftover/unused medications to improve pharmacoepidemiologic studies.

MME/Day Definition 3. Fixed Observation Window.
Total MME / Fixed observation window.

* If this definition is selected, PIs must report on the duration of the fixed window.
* Reason to select this definition: Most suitable for studies with a known or suspected duration of risk during which adverse events are expected to occur, such as incidence of opioid use disorder. This definition may be useful when prescriptions are filled at irregular time intervals on a as needed basis (pro re nata, prn).
* Identified challenge with this definition: The definition consistently had the lowest milligrams per day for immediate-release opioids. It is the most robust to misspecification, amenable to transformations, and has the least noise when constructing continuous functions. However, since it assumes uniform exposure/risk within a window, there is less scope for time-varying adjustment.
* This is the definition recommended by the Department of Health and Human Services Office of the Inspector General.

MME/Day Definition 4. Maximum Daily Dose.
Sum of 24h MME for the day with highest opioid exposure.

* Report the highest single-day exposure.
* Reason to select this definition: A toxicological perspective may be appropriate for patients with no opioid tolerance and in the presence of comorbidities for respiratory depression. It appears to be best suited for immediate dose-dependent toxic effects, such as respiratory depression.
* Identified challenged with this definition: This definition may have limited use if it includes opioids where fatal toxicity does not involve respiratory depression (e.g., tramadol) or have atypical mu-opioid receptor agonism (e.g., tapentadol, buprenorphine).
* The definition assumes uniform risk of adverse outcomes regardless of time on-therapy. More so than the others, this definition is prone to influence from early refills, unused medication, and how the 90 MME threshold is operationalized.
* This definition underlies the algorithm embedded in the CDC Opioid Guideline mobile app. There may be difficulty reconciling findings with studies using the other definitions because it returns a MME per day that is significantly higher.

MME calculations are for research purposes only and are not meant to be used for clinical surveillance purposes.

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