Supplement 1. Verbatim MME calculation methods from studies cited in the CDC pain Guideline[1], identified from a previous methods review.[2]

Inches, Centimeters, and Yards: Measurement Variations Inhibit Clinical Interpretation of Morphine Equivalence

Clinical Journal of Pain

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Full documentation available at OpioidData.org

Tennant et al.[3] (1982): mean daily dose reported but methods not specified

Ralphs et al.[4] (1994): The dose of opiates was converted to morphine equivalents using locally developed standard drug conversion tables.

Allan et al.[5] (2005): milligrams of morphine equivalents (MME) not used

Reid et al.[6] (2002): MME not used

Cowan[7] (2005): MME not used

Banta-Green[8] (2009): MME not used

Dunn et al.[9] (2010): We then calculated the average daily morphine equivalent dose dispensed for 90-day exposure windows by adding the morphine equivalents for the prescriptions dispensed during the 90 days and then dividing by 90. For each 90-day exposure window and each person, we calculated the average daily opioid dose dispensed and divided these into 5 categories: none, 1 to 19 mg, 20 to 49 mg, 50 to 99 mg, and 100 mg or more. We included opioid dose as a time-varying covariate, estimated for continuously updated 90-day exposure windows. Participants could be classified as either exposed to opioids (at any of 4 dosage levels) or unexposed on any given day, on the basis of their average daily opioid dose during the previous 90 days, including the event date.

Sullivan et al.[10] (2010): Opioid dose per day supplied was calculated by adding the total morphine equivalents for the three major opioid groups and dividing by the sum of the total days supply (assuming maximum authorized use as calculated by the dispensing pharmacist). If the total days supply exceeded the number of days in the period (180 days), suggesting concurrent use of different opioid types, the daily dose was calculated by dividing the total dose dispensed by 180 days.

Wild et al.[11] (2010): MME not used

Bhonert et al.[12]: Next, each patient's total maximum daily dose for each day of the study observation period was calculated by adding the daily doses of all fills that covered that particular day. The specific daily dose contributed by each fill was determined by dividing the total morphine-equivalent milligrams dispensed in that fill by the number of days supplied. This measurement of dose reflects the maximum daily dose prescribed and not necessarily the actual amount consumed. Morphine-equivalent maximum daily dose was converted into a categorical variable with the values of 0 mg, 1 mg to less than 20 mg, 20 mg to less than 50 mg, 50 mg to less than 100 mg, and 100 mg or more. In addition, a time-varying indicator of whether patients were prescribed a regularly scheduled opioid plus a simultaneous as-needed opioid was coded for each day of the study observation period that a patient had at least 1 opioid prescription using the following 3 mutually exclusive categories: 0, only regularly scheduled opioids; 1, only as-needed opioids; or 2, both a regularly scheduled opioid and as-needed opioid prescriptions.

Gomes et al.[13] (2011a): The dose of opioid was calculated as the number of tablets dispensed multiplied by the strength of the pills (in milligrams) for each prescription. The average daily dose for each of these prescriptions was then calculated as the dose (in milligrams) divided by the number of days' supply for which the prescription was written, converted to morphine equivalents using morphine equivalence ratios used by the Canadian National Opioid Use Guideline Group.

Gomes et al.[14] (2011b): For each individual who received at least one opioid prescription in a given calendar year, we calculated the mean daily dose dispensed (mg) of oral morphine, or equivalent, on the basis of the person's first 90 days of opioid therapy. If the supply of drug dispensed for a prescription in that interval extended beyond 90 days, we excluded the excess. The adjusted total amount of morphine equivalents dispensed over the 90 days was divided by 90 to obtain the mean daily dose for the period.

Naliboff[15] et al. (2011): Opioid medication dosages were taken from the computerized pharmacy record and were converted into morphine equivalents per day in order to have a standardized unit for reporting opioid amounts across different drugs.

Cicero et al.[16] (2012): MME not used

Paulozzi et al.[17] (2012): we calculated the dosage of opioid prescribed in MME per day in three different ways. The single peak dosage was the highest amount per day in any single opioid prescription. The total peak dosage was the highest dosage per day at any time during the exposure period after summing dosages from all overlapping opioid prescriptions. The average dosage was the average daily opioid dosage during the entire study period from all opioid prescriptions combined. For regression analysis, we categorized each measure of daily dosage into 0–40, >40–120, and >120 MME/day.

Mitra et al.[18] (2013): All patch dosages were recalculated to morphine equivalent to an equipotent dose using a widely applied guide "DUROGESIC® [sic]: Simple Dosing Guidelines."

Baumblatt et al.[19] (2014): To calculate the mean daily dosage, all opioid prescriptions were combined and converted to MMEs and divided by 365 days. We categorized mean daily dosage into less than 20, 20 to 40, 41 to 80, 81 to 100, 101 to 200, 201 to 400, and more than 400 MMEs/d and defined high risk as a mean of more than 100 MMEs/d for a year.

Edlund et al.[20] (2014): Average daily dose was measured in morphine equivalents and grouped as none (0 mg), low dose (1–36 mg), medium dose (36–120 mg), and high dose (120+mg).

Zedler et al.[21] (2014): For each opioid prescription dispensed during the baseline period, the product of the number of units dispensed and the opioid strength per unit (milligrams) was divided by the number of days supplied. The resulting opioid daily dose dispensed (milligrams per day) was then multiplied by a conversion factor derived from published sources to estimate the daily dose in morphine equivalents (MED). The maximum prescribed daily MED during the baseline period was calculated for each patient by summing the daily MED for all opioid prescriptions dispensed to the patient during those 6 months. It reflects the maximum prescribed daily dose and not necessarily the actual amount consumed.

Dasgupta et al.[22] (2015): The average daily MME per individual in 2010 was calculated by taking the total milligrams and dividing by the days supply, taking into account overlapping prescriptions.

Jones et al.[23] (2015): MME not used

Liang et al. [24] (2015): To calculate the 2 time-varying opioid therapy measures, all filled Schedule II or III prescriptions for opioid analgesics (excluding injectable formulations) were identified from claims in 6-month intervals starting with the first prescription. The total MED was computed from all opioids dispensed in a 6-month interval multiplied by strength (in milligrams) and then multiplied by a morphine equivalent conversion factor derived from published data, conversion tables on the Internet, and drug information resources. When opioid prescriptions spanned two 6-month intervals,

the total MED was allocated proportionate to the time in each interval. We consulted with a clinical pharmacist to review these calculations. Finally, the total MED was summed for all opioid prescriptions filled in the same interval. We calculated the mean daily MED for filled opioid prescriptions for each 6-month interval by dividing the total MED by total days' supply covered by all these prescriptions. Based on categories used in other studies,
0, 1 to 19, 20 to 49, 50 to 99, and ⩾100 mg. Because other studies have not examined total dose in relation to the risk of drug overdose, we examined quartiles of nonzero total MED. When an overdose event occurred in a 6-month interval, both daily MED and total MED were computed from the 6 months exactly preceding that event.

Miller et al.[25] (2005): To assess and control for the effect of the opioid dose, we con- verted each opioid agent to the morphine-equivalent dose following the method of Von Korff et al. We computed the morphine-equivalent mean daily dose by dividing the total quantity prescribed by days' supply and converted the daily dose thus calculated into a corresponding morphine-equivalent dose. After the conversion, prescriptions in morphine-equivalent mean daily doses were categorized as 1 mg to less than 20 mg, 20 mg to less than 50 mg, 50 mg to less than 100 mg, and 100 mg or greater.

Park et al.[26] (2016): Maximum morphine-equivalent daily opioid dose was modeled as time-varying and recoded into the following categories: 0 mg, 1 to <20 mg/d, 20 to <50 mg/d, 50 to <100 mg/d, and >100.1 mg/d. These dosage categories were chosen to allow for comparison with other published work on unintentional overdose as well recent recommendations that caution against prescribing more than 90 to 100 mg/d. To avoid double-counting dosage, opioid fills that seemed to be continuations of the same treatment plan (ie, were the same opioid formulation and dosage) were assumed to not start until the end of the days' supply of the previous fill. Also consistent with the Bohnert article, for each day that an individual had at least 1 opioid prescription, a 3-level time-varying indicator of opioid fill type was calculated to reflect schedule, with the categories of: only regularly scheduled opioids; only pro re nata (PRN) opioids; or both regularly scheduled opioid and PRN opioid prescriptions.

Gaither et al.[27] (2016): MME not used

Turner et al.[28] (2015): The total MED was computed by summing the MEDs for all opioid prescriptions within a given 6-month interval. The mean daily MED in a 6-month interval was calculated by dividing the total MED by days' supply for all prescriptions in that interval, excluding overlapping days. We examined five categories for the mean daily MED (i.e., 0, 1– 19, 20–49, 50–99, and ≥100 mg), similar to other studies. For the first overdose, the mean daily MED was based on data from exactly 6 months before that event

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Supplement 2. Equations for calculating milligrams of morphine equivalents

Inches, Centimeters, and Yards: Measurement Variations Inhibit Clinical Interpretation of Morphine Equivalence

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Dispensing Data Processing

Outpatient pharmacies are legally required to submit detailed information on dispensed controlled substance prescriptions to state-controlled databases. These data were made available in de-identified format masking the identity of individual patients. In Florida, multiple prescription fills by the same individual are linked using name, date of birth, and other information by the database vendor (Appriss Health, Inc., Louisville, KY); one-way hashed unique patient, prescriber and pharmacy identifiers allow for longitudinal observation. In California, a custom fuzzy string matching and network building algorithm identifies patient matches across prescriptions, using name and either a) the same date of birth and zip code, or b) the same street address and city. Prescriptions dispensed from federal institutional pharmacies, inpatient facilities, and methadone clinics were not systematically included, nor were prescriptions dispensed in other states to Florida or California residents. We analyzed opioid analgesic dispensing records for state residents aged 18 years and older in California (adult population 30,571,507) and Florida (adult population 17,071,450), intended for use from July 1, 2018 to September 30, 2018. Only days supply for use during this period was retained if prescriptions originated before or extended beyond these dates. All solid oral and transdermal formulations of opioid analgesics were included. Liquid injectables were excluded because of widespread scientific disagreement on conversion factors and relatively low volume. We used National Drug Codes to identify opioids and excluded codeine and hydrocodone cough syrups, and buprenorphine-containing products, because the CDC conversion tables claim: "Buprenorphine products are listed in this file but do not have an associated MME conversion factor. Buprenorphine products are partial opioid agonists prescribed for pain and as part of medication assisted treatment for opioid use disorder. Buprenorphine doses are not expected to be associated with overdose risk in the same dose-dependent manner as doses for full agonist opioids."

Equations

Prepared by Alan Kinlaw
Version-controlled UNC institutional repository for equations: https://doi.org/10.17615/zst5-nc25

In demonstrating MME calculations, consider the following clinical scenario:

A patient receives 30mg extended-release oxycodone twice-a-day for around-the-clock pain for 30 days (60 tablets), and one 5mg oxycodone twice a day as needed for breakthrough pain for 7 days (14 tablets). Both prescriptions are dispensed on the first day of a 30-day month, with no subsequent dispensings.
The four definitional variants result in daily MME of: 75.8, 93.5, 31.2, or 105 milligrams per day.

To [illegible] daily MME, notation is as follows:

q_{ij}, quantity (units) dispensed for prescription j for person i
m_{ij}, strength per unit in milligrams for a given prescription j for person i
c_{ij}, equianalgesic potency conversion factor for medication in prescription j for person i
d_{ij}, days supply on a given prescription j for person i
s_{ij}, start (dispensing) date of prescription j for person i
w_i, start date of observation window for person i
l_i, length (in days) of observation window for person i

g_{ik},	date of follow-up day k during observation window for person i

For each prescription j that occurs for each person i, we calculate o_{ij} as the number of days supply that overlap the relevant observation window:

$$\begin{aligned} o_{ij} = {} & \{d_{ij}\}\{I[s_{ij} \geq w_i]\}\{I[(s_{ij} + d_{ij}) \leq (w_i + l_i)]\} + \\ & \{w_i + l_i - s_{ij}\}\{I[s_{ij} \geq w_i]\}\{I[(s_{ij} + d_{ij}) > (w_i + l_i)]\} + \\ & \{s_{ij} + d_{ij} - w_i\}\{I[s_{ij} < w_i]\}\{I[(s_{ij} + d_{ij}) \leq (w_i + l_i)]\} + \\ & \{l_i\}\{I[s_{ij} < w_i]\}\{I[(s_{ij} + d_{ij}) > (w_i + l_i)]\} \end{aligned}$$

Of the four mutually exclusive terms that are summed to calculate o_{ij}, only one can return a non-zero value. This is a result of the indicator functions (e.g., $I[s_{ij} \geq w_i]$), which return a value of 1 if the stated inequality is true, else 0.

Stated in spoken words, the windows are:

o_{ij} = “prescription starts and ends during window” +
“prescription starts during window and ends after window” +
“prescription starts before window and ends during window” +
“prescription starts before window and ends after window” +

Stated in SAS code to calculate o, the windows are:

```
if s ge w and (s+d) le (w+l) then o = d;
else if s ge w and (s+d) gt (w+l) then o = w+l-s;
else if s lt w and (s+d) le (w+l) then o = s+d-w;
else if s lt w and (s+d) gt (w+l) then o = l;
```

Of the four mutually exclusive terms that are summed to calculate o_{ij}, only one can return a non-zero value. This is a result of the indicator functions (e.g., $I[s_{ij} \geq w_i]$), which return a value of 1 if the stated inequality is true, else 0.

To ensure that MME calculations for each prescription were based only on days supply that elapsed within the relevant observation window, we calculated f_{ij}, a scaling factor for that prescription’s relevant days supply:

$$f_{ij} = \frac{o_{ij}}{d_{ij}}$$

The range of f_{ij} is (0,1]. When prescriptions elapse entirely within the observation window, $f_{ij} = 1$. This scaling factor was applied to the traditional MME calculation (quantity) × (strength) × (equianalgesic conversion factor) to calculate a_{ij}, a prescription’s MME occurring within the observation window:

$$a_{ij} = (qmc)_{ij}\frac{o_{ij}}{d_{ij}} = (qmcf)_{ij}$$

The MME calculations for the above example are as follows, for patient i=1. The MME for the first prescription, $a_{i=1,j=1} = (qmcf)_{i=1,j=1}$, which is equal to (60 tablets) × (30mg per tablet) × (1.5 conversion factor from oxycodone to morphine)[17] × (1 scaling factor for relevant days supply), resulting in 2,700 MME. For the second prescription for this patient, $a_{i=1,j=2}$, the MME is equal to (14 tablets) × (5mg per tablet) × (1.5 conversion factor from oxycodone to morphine)[17] × (1 scaling factor for relevant days supply), resulting in 105 MME. Therefore, the total MME across both prescriptions for this patient, $a_{i=1} =$

$\sum_{j=1}^{2} a_{i=1,j} = a_{i=1,j=1} + a_{i=1,j=2}$, results in 2,805 MME. This total MME for the patient is the numerator in the first three definitions of the daily MME, as shown below.

Definition 1 – Total days supply

The numerator is the sum of MMEs across all prescriptions for patient i:

$$\sum_{j=1}^{n} a_{ij} = \sum_{j=1}^{n} (qmcf)_{ij}$$

The denominator is the sum of all days supply across all prescriptions for that patient that overlap the observation period. Therefore, similar to the scaled MME (a_{ij}) that is applied toward the numerator, it is necessary to use o_{ij} values in the denominator for this calculation. Although o_{ij} may be equivalent to d_{ij} (i.e., when the first mutually exclusive term in Equation 1 is triggered), this should not be assumed outright; otherwise there may be irrelevant days supply that count toward the denominator and tend to bias the daily MME value downward. According to Definition 1, we calculate x_i, the daily average MME for patient i, as:

$$x_i = \frac{\sum_{j=1}^{n} a_{ij}}{\sum_{j=1}^{n} o_{ij}} = \frac{\sum_{j=1}^{n} (qmcf)_{ij}}{\sum_{j=1}^{n} o_{ij}} = \frac{\sum_{j=1}^{n} (qmc)_{ij} \left(\frac{o}{d}\right)_{ij}}{\sum_{j=1}^{n} o_{ij}}$$

Note that this approach allows the same day to contribute multiple times to the denominator (i.e., when prescriptions overlap with each other), and it allows the denominator to potentially exceed the number of unique days in the observation window. Applying this definition to the example scenario:

$$x_{i=1} = \frac{\sum_{j=1}^{2} a_{i=1,j}}{\sum_{j=1}^{2} o_{i=1,j}}$$

$$= \frac{(qmcf)_{i=1,j=1} + (qmcf)_{i=1,j=2}}{\begin{array}{c}\{[(d_{i=1,j=1})(1)(1) + (w_{i=1} + l_{i=1} - s_{i=1,j=1})(1)(0) + (s_{i=1,j=1} + d_{i=1,j=1} - w_{i=1})(0)(1) + (l_{i=1})(0)(0)] + \\ [(d_{i=1,j=2})(1)(1) + (w_{i=1} + l_{i=1} - s_{i=1,j=2})(1)(0) + (s_{i=1,j=2} + d_{i=1,j=2} - w_{i=1})(0)(1) + (l_{i=1})(0)(0)]\}\end{array}}$$

$$= \frac{(qmc)_{i=1,j=1} \left(\frac{o}{d}\right)_{i=1,j=1} + (qmc)_{i=1,j=2} \left(\frac{o}{d}\right)_{i=1,j=2}}{(d_{i=1,j=1}) + (d_{i=1,j=2})}$$

$$= \frac{(60)(30)(1.5)\left(\frac{30}{30}\right) + (14)(5)(1.5)\left(\frac{7}{7}\right)}{30 + 7} = \frac{2{,}805\ MME}{37\ days\ supply} = 75.8\ daily\ MME$$

Definition 2 – On-therapy days

During the observation window l_i for patient *i,* we consider each date g_{ik}, where k indexes the day during follow-up such that $k = g - w + 1 = \{1, \dots, l_i\}$. To classify each date g_{ik} as whether the patient had medication supply for each prescription j, we assign a binary indicator, h_{ijk}. For each prescription, $j = 1$ to $j = n$, for each patient i on each day, $k = 1\ to\ k = l_i$, during their observation window*,* this medication supply indicator is:

$$h_{ijk} = I[s_{ij} \le g_{ik} \le (s_{ij} + d_{ij})],$$

which returns a value of 1 if the date on observation day k falls during the patient's exposure to prescription j based on days supply, else 0. For each patient i, each unique day k (or alternatively, each person-date g_{ik}) can then be classified as exposed or unexposed, by assigning it the maximum value of h that was observed across all prescriptions j that may have overlapped that person-date. This person-day binary exposure summary variable is:

$$u_{ik} = \max_{ik}\left(h_{i,j=1,k}, \dots, h_{i,j=n,k}\right),$$

which returns a value of 1 for each patient *i* on each day k if they had at least one available medication based on days supply from any of their prescriptions $j = 1\ to\ j = n$, else 0.

Finally, the denominator for the daily MME for patient i is the sum of all their exposed person-days during the observation window, $\sum_{k=1}^{l} u_{ik}$.

According to Definition 2, we calculate x_i, the daily average MME for patient i, as:

$$x_i = \frac{\sum_{j=1}^{n} a_{ij}}{\sum_{k=1}^{l} u_{ik}} = \frac{\sum_{j=1}^{n} (qmcf)_{ij}}{\sum_{k=1}^{l} u_{ik}} = \frac{\sum_{j=1}^{n} (qmc)_{ij} \left(\frac{o}{d}\right)_{ij}}{\sum_{k=1}^{l} u_{ik}}$$

Contrary to Definition 1, this approach does not allow the same day to contribute multiple times to the denominator (i.e., when prescriptions overlap with each other), and it does not allow the denominator to potentially exceed the number of unique days in the observation window. Applying this definition to the example scenario:

$$x_{i=1} = \frac{\sum_{j=1}^{2} a_{i=1,j}}{\sum_{k=1}^{l} u_{ik}} = \frac{(qmcf)_{i=1,j=1} + (qmcf)_{i=1,j=2}}{\sum_{k=1}^{l} \max_{i=1,k}\left(h_{i=1,j=1,k}, h_{i=1,j=2,k}\right)}$$

$$= \frac{(qmcf)_{i=1,j=1} + (qmcf)_{i=1,j=2}}{\max_{i=1,k=1}\left(h_{i=1,j=1,k=1}, h_{i=1,j=2,k=1}\right) + \cdots + \max_{i=1,k=60}\left(h_{i=1,j=1,k=60}, h_{i=1,j=2,k=60}\right)}$$

$$= \frac{(qmc)_{i=1,j=1} \left(\frac{o}{d}\right)_{i=1,j=1} + (qmc)_{i=1,j=2} \left(\frac{o}{d}\right)_{i=1,j=2}}{\max_{i=1,k=1}\left(h_{i=1,j=1,k=1}, h_{i=1,j=2,k=1}\right) + \cdots + \max_{i=1,k=60}\left(h_{i=1,j=1,k=60}, h_{i=1,j=2,k=60}\right)}$$

$$= \frac{(qmc)_{i=1,j=1} \left(\frac{o}{d}\right)_{i=1,j=1} + (qmc)_{i=1,j=2} \left(\frac{o}{d}\right)_{i=1,j=2}}{u_{i=1,k=1} + u_{i=1,k=2} + \cdots + u_{i=1,k=59} + u_{i=1,k=60}}$$

$$= \frac{(60)(30)(1.5)\left(\frac{30}{30}\right) + (14)(5)(1.5)\left(\frac{7}{7}\right)}{1 + 1 + \cdots + 0 + 0} = \frac{2700 + 105}{1(30) + 0(30)} = \frac{2{,}805\ MME}{30\ days\ supply} = 93.5\ daily\ MME$$

Definition 3 – Fixed observation window

This common definition derives from early studies cited in the CDC Guideline often referencing an even earlier study, and is still used. The US Department of Health and Human Services Office of the Inspector General recommends this method, which is one of the only public sources with explicit description. The numerator is the sum of MMEs across all prescriptions, and the denominator is days elapsed during follow-up, hospital stay, or beneficiary enrollment. Although 90-day observation windows are most common, 180 days and 365 days were also used in studies supporting the Guideline. Applying this definition 2,805 divided by 90 days results in 31.2 milligrams per day.

First, we scale the MME calculation (quantity) × (strength) × (equianalgesic conversion factor) to calculate a_{ij}, a prescription's MME occurring within the observation window:

$$a_{ij} = (qmc)_{ij} \frac{o_{ij}}{d_{ij}} = (qmcf)_{ij}$$

Note that care should be taken to match the length of the observation window, l_i to the desired specification when calculating o_{ij} and subsequently, a_{ij}.

According to Definition 3, we calculate x_i, the daily average MME for patient i, as:

$$x_i = \frac{\sum_{j=1}^{n} a_{ij}}{l_i} = \frac{\sum_{j=1}^{n} (qmc)_{ij} \left(\frac{o}{d}\right)_{ij}}{l_i}$$

Applying this definition to the scenario, where no additional prescriptions are observed in the next 2 months, and using 90-day prespecified observation window (l_i):

$$x_{i=1} = \frac{\sum_{j=1}^{2} a_{i=1,j}}{l_{i=1}} = \frac{(qmcf)_{i=1,j=1} + (qmcf)_{i=1,j=2}}{l_{i=1}}$$

$$= \frac{(qmc)_{i=1,j=1} \left(\frac{o}{d}\right)_{i=1,j=1} + (qmc)_{i=1,j=2} \left(\frac{o}{d}\right)_{i=1,j=2}}{l_{i=1}}$$

$$= \frac{(60)(30)(1.5)\left(\frac{30}{30}\right) + (14)(5)(1.5)\left(\frac{7}{7}\right)}{90} = \frac{2700 + 105}{90} = \frac{2{,}805\ MME}{90\ days\ window} = 31.2\ daily\ MME$$

Definition 4 – Maximum daily dose

Toxicologic framing identifies the highest single day MME exposure, irrespective of days supply or opioid tolerance. This definition appears to underlie the calculator in the CDC Opioid Guideline mobile app. This method was used by studies cited in the Guideline, and may be most relevant for prescriptions in patients who are opioid naïve. However, "maximum" does not include what could be consumed in cases of intentional self-harm. The first prescription is 30mg × 2 (twice-per-day) × 1.5 (conversion factor) for 90 MME, plus the second prescription with 5mg × 2 × 1.5 for 15 MME, resulting in 105 milligrams per day.

For each prescription, $j = 1\ to\ j = n$, for each patient i, we assume that the prescription is apportioned evenly across the prescribed days supply (i.e., no unmeasured dose reductions). We calculate y_{ij}, the average prescription-specific MME per day for that prescription during the observation window, as:

$$y_{ij} = \frac{a_{ij}}{o_{ij}} = \frac{(qmcf)_{ij}}{o_{ij}} = \frac{(qmc)_{ij}\left(\frac{o_{ij}}{d_{ij}}\right)}{o_{ij}} = \frac{(qmc)_{ij}}{d_{ij}}$$

Then, as in Definition 2, each person-day should be classified as exposed or unexposed depending on whether the patient had at least one prescription that overlapped that date based on days supply. For each prescription, $j = 1\ to\ j = n$, for each patient i on each day, $k = 1\ to\ k = l_i$, during their observation window, the average prescription-specific MME per day is:

$$p_{ijk} = (y_{ij})(h_{ijk}) = (y_{ij})\ I\left[s_{ij} \leq g_{ik} \leq \left(s_{ij} + d_{ij}\right)\right],$$

which returns that prescription's contribution to that daily MME if the date on observation day k falls during the patient's exposure to prescription j based on days supply, else 0.

For each patient *i*, each unique day k (or alternatively, each person-date g_{ik}) can then receive a value for total MME across all prescriptions, $j = 1\ to\ j = n$, as:

$$z_{ik} = \sum_{j=1}^{n} p_{ijk}$$

According to Definition 4, we calculate x_i, the maximum daily dose for patient i across all of their observation days, $k = 1\ to\ k = l_i$, as:

$$x_i = \max_{\mathrm{i}}\left(z_{i,k=1}, \dots, z_{i,k=l}\right)$$

Applying this definition to the example scenario, we first calculate the average prescription-specific MME per day for that prescription during the observation window, for each prescription:

$$y_{i=1,j=1} = \frac{(qmc)_{i=1,j=1}}{d_{i=1,j=1}} = \frac{(60)(30)(1.5)}{30} = 90\ MME\ per\ day\ for\ j = 1$$

$$y_{i=1,j=2} = \frac{(qmc)_{i=1,j=2}}{d_{i=1,j=2}} = \frac{(14)(5)(1.5)}{7} = 15\ MME\ per\ day\ for\ j = 2$$

Given that prescription $j = 1$ was issued on day $k = 1$ and it had 30 days supply, and prescription $j = 2$ was issued on day $k = 1$ and it had 7 days supply, we deduce each component of z_{ik}:

$$p_{i=1,j=1,k\ni\{1,2,3,\dots,30\}} = \left(y_{i=1,j=1}\right)\left(h_{i=1,j=1,k\ni\{1,2,3,\dots,30\}}\right) = (90)(1) = 90$$

$$p_{i=1,j=1,k\ni\{31,32,33,\dots,60\}} = \left(y_{i=1,j=1}\right)\left(h_{i=1,j=1,k\ni\{31,32,33,\dots,60\}}\right) = (90)(0) = 0$$

$$p_{i=1,j=2,k\ni\{1,2,3,\dots,7\}} = \left(y_{i=1,j=2}\right)\left(h_{i=1,j=2,k\ni\{1,2,3,\dots,7\}}\right) = (15)(1) = 15$$

$$p_{i=1,j=2,k\ni\{8,9,10,\dots,60\}} = \left(y_{i=1,j=2}\right)\left(h_{i=1,j=2,k\ni\{8,19,10,\dots,60\}}\right) = (15)(0) = 0$$

We can identify three day ranges between $k = 1\ to\ k = 60$ that carry unique values of z_{ik}. The first is days $k = 1\ to\ k = 7$, when days supply for both prescription $j = 1\ and\ j = 2$ are available. The second is days $k = 8\ to\ k = 30$, when days supply for prescription $j = 1$ is available. And the third is days $k = 31\ to\ k = 60$, when no prescriptions have available days supply. These are represented below:

$$z_{i=1,k\ni\{1,2,3,\dots,7\}} = \sum_{j=1}^{2} p_{i=1,j,k\ni\{1,2,3,\dots,7\}} = p_{i=1,j=1,k\ni\{1,2,3,\dots,7\}} + p_{i=1,j=2,k\ni\{1,2,3,\dots,7\}} = 90 + 15 = 105$$

$$z_{i=1,k\ni\{8,9,10,\dots,30\}} = \sum_{j=1}^{2} p_{i=1,j,k\ni\{8,9,10,\dots,30\}} = p_{i=1,j=1,k\ni\{8,9,10,\dots,30\}} + p_{i=1,j=2,k\ni\{8,9,10,\dots,30\}} = 90 + 0 = 90$$

$$z_{i=1,k\ni\{31,32,33,\ldots,60\}} = \sum_{j=1}^{2} p_{i=1,j,k\ni\{31,32,33,\ldots,60\}} = p_{i=1,j=1,k\ni\{31,32,33,\ldots,60\}} + p_{i=1,j=2,k\ni\{31,32,33,\ldots,60\}} = 0$$

$$x_i = \max_{\mathrm{i}}\left(z_{i,k=1}, \ldots, z_{i,k=60}\right) = \max_{\mathrm{i}}(\{105,90,0\}) = 105\ MME\ maximum\ daily\ dose$$

Supplement 3.

Daily MME Meta Analysis

Adapting a method recently developed by FDA to analyze a related opioid methods question, we used meta analytic techniques to test the impact of the four definitions in the real-world. The general set up is to compare opioid use in FL vs. CA across the 4 definitions of daily MME. We previously observed that Florida had higher unadjusted levels of opioid use, presumably an interaction with an older population and the enactment of clinical pain management legislation. We took two approaches, 1) treating daily MME as categorical by comparing the proportion of "high dose" users among opioid recipients, and 2) comparing means of daily MME between the states in a continuous manner, stratified by medicines used for acute versus chronic pain.

In [7]:

```
di "Stata MP"
version
di "Notebook generated on $S_DATE at $S_TIME ET"
```

```
Stata MP

version 16.0

Notebook generated on 26 May 2021 at 11:20:41 ET
```

Comparing "High Dose" patients in CA and FL

Input dataset from table of high dose patients (>90 daily MME) among adult outpatient opioid recipients identified using the PDMP of each state.

In [2]:

```
di "===== Proportion of high dose patients FL vs CA greater than 90 daily MME ====="
di "D1. Sum of days supply"
    csi  87295 87078   1398296  2343792
di "D2. On-therapy days"
    csi 136995 140822  1348596   2290048
di "D3. Defined observation window"
    csi 97346 86407  1388245   2344463
di "D4. Maximum daily dose"
    csi 211429 249471  1274162   2181399
```

```
===== Proportion of high dose patients FL vs CA greater than 90 daily MME =====

Definition 1


                 |   Exposed   Unexposed  |      Total
-----------------+------------------------+------------
           Cases |     87295       87078  |     174373
        Noncases |   1398296     2343792  |    3742088
-----------------+------------------------+------------
           Total |   1485591     2430870  |    3916461
                 |                        |
            Risk |  .0587611    .0358217  |   .0445231
                 |                        |
                 |      Point estimate    |    [95% Conf. Interval]
                 |------------------------+------------------------
 Risk difference |         .0229394       |    .0224949    .0233839
      Risk ratio |         1.640376       |    1.625414    1.655475
 Attr. frac. ex. |         .3903837       |    .3847723    .3959439
 Attr. frac. pop |         .1954347       |
                 +-------------------------------------------------
                               chi2(1) = 11405.78  Pr>chi2 = 0.0000

Definition 2


                 |   Exposed   Unexposed  |      Total
-----------------+------------------------+------------
           Cases |    136995      140822  |     277817
        Noncases |   1348596     2290048  |    3638644
-----------------+------------------------+------------
           Total |   1485591     2430870  |    3916461
                 |                        |
            Risk |  .0922158    .0579307  |   .0709357
                 |                        |
                 |      Point estimate    |    [95% Conf. Interval]
                 |------------------------+------------------------
 Risk difference |         .0342851       |    .0337349    .0348353
      Risk ratio |          1.59183       |    1.580486    1.603256
 Attr. frac. ex. |         .3717922       |    .3672831    .3762692
 Attr. frac. pop |         .1833353       |
                 +-------------------------------------------------
                               chi2(1) = 16446.29  Pr>chi2 = 0.0000

Definition 3


                 |   Exposed   Unexposed  |      Total
-----------------+------------------------+------------
           Cases |     97346       86407  |     183753
        Noncases |   1388245     2344463  |    3732708
-----------------+------------------------+------------
           Total |   1485591     2430870  |    3916461
                 |                        |
            Risk |  .0655268    .0355457  |   .0469181
                 |                        |
                 |      Point estimate    |    [95% Conf. Interval]
                 |------------------------+------------------------
 Risk difference |         .0299811       |    .0295201    .0304421
      Risk ratio |         1.843451       |    1.827062    1.859988
 Attr. frac. ex. |         .4575392       |    .4526731    .4623621
 Attr. frac. pop |         .2423885       |
                 +-------------------------------------------------
                               chi2(1) = 18534.92  Pr>chi2 = 0.0000

Definition 4


                 |   Exposed   Unexposed  |      Total
-----------------+------------------------+------------
           Cases |    211429      249471  |     460900
        Noncases |   1274162     2181399  |    3455561
-----------------+------------------------+------------
           Total |   1485591     2430870  |    3916461
                 |                        |
            Risk |  .1423198    .1026262  |   .1176828
                 |                        |
                 |      Point estimate    |    [95% Conf. Interval]
                 |------------------------+------------------------
 Risk difference |         .0396936       |    .0390145    .0403727
      Risk ratio |         1.386778       |    1.379279    1.394318
 Attr. frac. ex. |         .2789041       |    .2749835    .2828035
 Attr. frac. pop |         .1279419       |
                 +-------------------------------------------------
                               chi2(1) = 13991.68  Pr>chi2 = 0.0000
```

Scrape "Risk ratio" and CIs into new input dataset. Create log-transformed variables to meet normal distribution assumption of meta analytic statistics.

In [3]:

```
clear all
qui: input definition irr ll ul str31 label
1  1.640376      1.625414    1.655475     "D1. Sum of days supply"
2   1.59183     1.580486    1.603256    "D2. Accounting for overlap days"
3   1.843451    1.827062    1.859988   "D3. Defined observation window"
4  1.386778      1.379279    1.394318   "D4. Maximum daily dose"
end

gen lnirr=ln(irr)
gen lnll=ln(ll)
gen lnul=ln(ul)

qui: meta set lnirr lnll lnul, studylabel(label)
```

```
. gen lnirr=ln(irr)

. gen lnll=ln(ll)

. gen lnul=ln(ul)

. qui: meta set lnirr lnll lnul, studylabel(label)
```

Run meta analysis command using fixed effects model. Since there is no sampling variation, fixed effects is the preferred *a priori* specification.

In [4]:

```
meta summarize, fixed eform
```

```
  Effect-size label:  Effect Size
        Effect size:  lnirr
          Std. Err.:  _meta_se
        Study label:  label

Meta-analysis summary                               Number of studies =      4
Fixed-effects model                                 Heterogeneity:
Method: Inverse-variance                                      I2 (%) =   99.91
                                                                  H2 = 1085.83

--------------------------------------------------------------------------------
                       Study |        exp(ES)    [95% Conf. Interval]  % Weight
-----------------------------+--------------------------------------------------
      D1. Sum of days supply |          1.640       1.625       1.655     15.27
D2. Accounting for overlap~s |          1.592       1.580       1.603     25.06
D3. Defined observation wi~w |          1.843       1.827       1.860     16.07
      D4. Maximum daily dose |          1.387       1.379       1.394     43.60
-----------------------------+--------------------------------------------------
                  exp(theta) |          1.542       1.536       1.547
--------------------------------------------------------------------------------
Test of theta = 0: z = 237.00                          Prob > |z| = 0.0000
Test of homogeneity: Q = chi2(3) = 3257.49               Prob > Q = 0.0000
```

For the sake of completeness, random effects models are also run, using the Sidik-Jonkman `random(sj)` estimator because tau is expected to be large Veroniki et al., with DerSimonian–Laird `random(dl)` as well separately for comparison, but fixed effects (above) is the more technically correct model specification.

In [5]:

```
meta summarize, random(sj) eform
```

```
  Effect-size label:  Effect Size
        Effect size:  lnirr
          Std. Err.:  _meta_se
        Study label:  label

Meta-analysis summary                               Number of studies =      4
Random-effects model                                Heterogeneity:
Method: Sidik-Jonkman                                           tau2 =  0.0137
                                                              I2 (%) =   99.90
                                                                  H2 =  954.41

--------------------------------------------------------------------------------
                       Study |        exp(ES)    [95% Conf. Interval]  % Weight
-----------------------------+--------------------------------------------------
      D1. Sum of days supply |          1.640       1.625       1.655     24.99
D2. Accounting for overlap~s |          1.592       1.580       1.603     25.00
D3. Defined observation wi~w |          1.843       1.827       1.860     24.99
      D4. Maximum daily dose |          1.387       1.379       1.394     25.02
-----------------------------+--------------------------------------------------
                  exp(theta) |          1.607       1.433       1.803
--------------------------------------------------------------------------------
Test of theta = 0: z = 8.11                            Prob > |z| = 0.0000
Test of homogeneity: Q = chi2(3) = 3257.49               Prob > Q = 0.0000
```

In [6]:

```
meta summarize, random(dl) eform
```

```
  Effect-size label:  Effect Size
        Effect size:  lnirr
          Std. Err.:  _meta_se
        Study label:  label

Meta-analysis summary                               Number of studies =      4
Random-effects model                                Heterogeneity:
Method: DerSimonian-Laird                                       tau2 =  0.0156
                                                              I2 (%) =   99.91
                                                                  H2 = 1085.83

--------------------------------------------------------------------------------
                       Study |        exp(ES)    [95% Conf. Interval]  % Weight
-----------------------------+--------------------------------------------------
      D1. Sum of days supply |          1.640       1.625       1.655     24.99
D2. Accounting for overlap~s |          1.592       1.580       1.603     25.00
D3. Defined observation wi~w |          1.843       1.827       1.860     24.99
      D4. Maximum daily dose |          1.387       1.379       1.394     25.01
-----------------------------+--------------------------------------------------
                  exp(theta) |          1.607       1.422       1.816
--------------------------------------------------------------------------------
Test of theta = 0: z = 7.61                            Prob > |z| = 0.0000
Test of homogeneity: Q = chi2(3) = 3257.49               Prob > Q = 0.0000
```

Results are similar, but SJ is preferred based on simulations in Veroniki et al. The fixed effects model over emphasizes precision (e.g., confuses it for more information) in D4 due to the higher number of high dose patients. Since there is no sampling variation

Interpretation

The proportion of "high dose" patients was consitently higher in Florida across all variants. However, the magnitude of the difference varied greatly: 84.3% (95% CI: 82.7%, 86.0%) for Definition 3 (defined observation window); 64.0% (95% CI: 62.5%, 65.5%) for Definition 1 (sum of days supply); 59.2% (95% CI: 58.0%, 60.3%) for Definition 2 (accounting for overlap days); and 38.7% (95% CI: 37.9%, 39.4%) for Definition 4 (maximum daily dose). Metrics confirmed very high heterogenity between the definitions, with I2 greater than 99% and H2 of 1086, supported by tests of hetereogenity chi2 of 3257 on 3 degrees of freedom (p<0.0001), and overall effect z=237, with 1 degree of freedom and p<0.0001.

Meta Analysis of Means by Type of Opioid

In this meta analysis we examine the impact of definitional variation on acute vs. chronic pain patients, measured by opioid formulation type. We stratified the sample into three sub-groups: 1) patients receiving on only immediate-release or short-acting opioids labeled for acute pain (hereafter immediate-release; 2) patients receiving only extended-release or long-acting opioids generally labeled for chronic pain (hereafter extended-release); and 3) patients receiving both immediate-release and extended-release opioids contemporaneously within the 3 month observation period (e.g., chronic pain patients receiving opioids for breakthrough pain or during taper).

Continuing with the approach in the previous meta analysis, we calculated mean differences in daily MME between Florida and California, treating each of the 4 daily MME definitions as separate studies run on the same sample (e.g., fixed effects).

Immediate-release only

In [6]:

```
clear
input definition n_fl m_fl sd_fl n_ca m_ca sd_ca
1 1338828 34.0531498 28.4797412 2273028 30.3156249 222.6063485
2 1338828 35.0964146 30.180772 2273028 31.5819604 223.0198312
3 1338828 12.5794512 25.2892396 2273028 10.3398905 42.5422362
4 1338828 44.7478467 48.3917948 2273028 39.6430507 280.3601706
end

qui: meta esize n_fl m_fl sd_fl n_ca m_ca sd_ca, esize(mdiff)
meta summarize, fixed
```

```
     definit~n       n_fl       m_fl      sd_fl       n_ca       m_ca      sd_ca


  Effect-size label:  Mean Diff.
        Effect size:  _meta_es
          Std. Err.:  _meta_se

Meta-analysis summary                     Number of studies =      4
Fixed-effects model                       Heterogeneity:
Method: Inverse-variance                            I2 (%) =   98.63
                                                        H2 =   72.98

--------------------------------------------------------------------
           Study |     Mean Diff.    [95% Conf. Interval]  % Weight
-----------------+--------------------------------------------------
         Study 1 |          3.738       3.359       4.116      3.92
         Study 2 |          3.514       3.135       3.894      3.90
         Study 3 |          2.240       2.160       2.319     89.72
         Study 4 |          5.105       4.626       5.584      2.45
-----------------+--------------------------------------------------
           theta |          2.418       2.343       2.493
--------------------------------------------------------------------
Test of theta = 0: z = 63.18                     Prob > |z| = 0.0000
Test of homogeneity: Q = chi2(3) = 218.94          Prob > Q = 0.0000
```

Extended-release only

In [7]:

```
clear
input definition n_fl m_fl sd_fl n_ca m_ca sd_ca
1 26039 86.9071545 87.9504585 40038 90.2232825 100.0878302
2 26039 96.9302372 102.8249551 40038 103.7573329 134.372793
3 26039 66.8367252 81.142005 40038 72.753132 104.6161615
4 26039 143.0437107 159.4875273 40038 153.6802569 205.2125971
end

qui: meta esize n_fl m_fl sd_fl n_ca m_ca sd_ca, esize(mdiff)
meta summarize, fixed
```

```
     definit~n       n_fl       m_fl      sd_fl       n_ca       m_ca      sd_ca


  Effect-size label:  Mean Diff.
        Effect size:  _meta_es
          Std. Err.:  _meta_se

Meta-analysis summary                     Number of studies =      4
Fixed-effects model                       Heterogeneity:
Method: Inverse-variance                            I2 (%) =   86.38
                                                        H2 =    7.34

--------------------------------------------------------------------
           Study |     Mean Diff.    [95% Conf. Interval]  % Weight
-----------------+--------------------------------------------------
         Study 1 |         -3.316      -4.806      -1.826     35.11
         Study 2 |         -6.827      -8.745      -4.909     21.19
         Study 3 |         -5.916      -7.415      -4.418     34.70
         Study 4 |        -10.637     -13.578      -7.695      9.01
-----------------+--------------------------------------------------
           theta |         -5.622      -6.504      -4.739
--------------------------------------------------------------------
Test of theta = 0: z = -12.48                    Prob > |z| = 0.0000
Test of homogeneity: Q = chi2(3) = 22.03           Prob > Q = 0.0001
```

Both Extended-release and Immediate-release

In [8]:

```
clear
input definition n_fl m_fl sd_fl n_ca m_ca sd_ca
1 120724 82.95423 59.1676551 117804 74.1906194 64.4024217
2 120724 160.1525421 131.6299812 117804 143.9839494 151.4652358
3 120724 133.0969773 125.945819 117804 122.7372442 148.5490438
4 120724 267.949697 238.0130378 117804 250.7462218 282.0999741
end

qui: meta esize n_fl m_fl sd_fl n_ca m_ca sd_ca, esize(mdiff)
meta summarize, fixed
```

```
     definit~n       n_fl       m_fl      sd_fl       n_ca       m_ca      sd_ca


  Effect-size label:  Mean Diff.
        Effect size:  _meta_es
          Std. Err.:  _meta_se

Meta-analysis summary                     Number of studies =      4
Fixed-effects model                       Heterogeneity:
Method: Inverse-variance                            I2 (%) =   98.34
                                                        H2 =   60.27

--------------------------------------------------------------------
           Study |     Mean Diff.    [95% Conf. Interval]  % Weight
-----------------+--------------------------------------------------
         Study 1 |          8.764       8.267       9.260     69.06
         Study 2 |         16.169      15.031      17.307     13.13
         Study 3 |         10.360       9.255      11.464     13.94
         Study 4 |         17.203      15.111      19.296      3.88
-----------------+--------------------------------------------------
           theta |         10.286       9.873      10.698
--------------------------------------------------------------------
Test of theta = 0: z = 48.90                     Prob > |z| = 0.0000
Test of homogeneity: Q = chi2(3) = 180.81          Prob > Q = 0.0000
```

Interpretation

- ER only group had *lower* mean daily MME in Florida than California?!
- Heterogeneity by I^2 was high for all 3 definitions
- Heterogeneity was lowest for ER-only group by both I^2 and X^2
- For ER+IR group, the definitional variants would have resulted in us concluding that the average dose was 8.8 (8.3, 9.3) milligrams to 17.2 (15.1, 19.3) milligrams higher in Florida.