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An Approach to Evaluate the Effects of Concomitant Prescribing of Opioids and Benzodiazepines on Veteran Deaths and Suicides

Committee on Developing a Protocol to Evaluate
the Concomitant Prescribing of Opioids and Benzodiazepine
Medications and Veteran Deaths and Suicides

Board on Health Care Services

Health and Medicine Division

A Consensus Study Report of

The National Academies of
SCIENCES • ENGINEERING • MEDICINE

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COMMITTEE ON DEVELOPING A PROTOCOL TO EVALUATE THE CONCOMITANT PRESCRIBING OF OPIOIDS AND BENZODIAZEPINE MEDICATIONS AND VETERAN DEATHS AND SUICIDES

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Reviewers

This Consensus Study Report was reviewed in draft form by persons chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the National Academies of Sciences, Engineering, and Medicine in making each published report as sound as possible and to ensure that it meets institutional standards of quality, objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process.

We thank the following for their review of this report:

CHAD M. BRUMMETT, University of Michigan Medical School
BETH DARNALL, Stanford University School of Medicine
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SUSAN SHORTREED, Kaiser Permanente Washington Health Research Institute
JASVINDER A. SINGH, The University of Alabama at Birmingham and Birmingham Veterans Affairs Medical Center

Although the reviewers listed above provided many constructive comments and suggestions, they were not asked to endorse the conclusions or

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recommendations of this report, nor did they see the final draft before its release. The review of the report was overseen by **RODERICK J. LITTLE,** University of Michigan, and **LINDA C. DEGUTIS,** Henry M. Jackson Foundation. They were responsible for making certain that an independent examination of this report was carried out in accordance with the standards of the National Academies and that all review comments were carefully considered. Responsibility for the final content rests entirely with the authoring committee and the National Academies.

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Acronyms and Abbreviations

AFD	Adult Functioning and Disability supplement
CDC	Centers for Disease Control and Prevention
CDW	Corporate Data Warehouse
DoD	Department of Defense
GABA	gamma-aminobutyric acid
GAD	Generalized Anxiety Disorder scale
IP	inverse probability
MME	morphine milligram equivalent
NDI	National Death Index
NHIS	National Health Interview Survey
NIDA	National Institute on Drug Abuse
NSAID	nonsteroidal anti-inflammatory drug
OEF	Operation Enduring Freedom
OIF	Operation Iraqi Freedom
OND	Operation New Dawn
OSI	Opioid Safety Initiative

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PTSD	posttraumatic stress disorder
RCT	randomized controlled trial
SUD	substance use disorder
TBI	traumatic brain injury
VA	Department of Veterans Affairs
VHA	Veterans Health Administration

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Summary

Opioid analgesics are commonly prescribed to treat chronic and acute pain. Marked increases in prescribing of opioids for acute and chronic pain occurred in the United States from the later 1990s to approximately 2012. Those increases, prompted by efforts to improve pain management, resulted in unanticipated morbidity and mortality in the United States, both in the civilian and the Department of Veterans Affairs/Department of Defense (VA/DoD) treatment environments. The population rate of opioid prescribing for pain has been declining since 2012, yet it remains at much higher levels than it was before 2000. Furthermore, multiple studies have demonstrated that a higher daily dosage of prescribed opioids is associated with a higher risk of death from overdose.

Whereas opioids are primarily prescribed for pain, benzodiazepines are prescription sedatives that are typically prescribed for anxiety or insomnia. Studies show that benzodiazepine prescribing also increased significantly from the later 1990s to approximately 2012 and has remained at high levels, despite evidence of severe adverse effects associated with chronic use. The concomitant use of opioids and benzodiazepines is also associated with increased rates of unintentional overdose and death and with higher rates of suicide.

Responding to the concern about opioid and benzodiazepine use in the veteran population, the VA requested that the National Academies of Sciences, Engineering, and Medicine "develop a protocol/study design to evaluate the relationship between concomitant opioid and benzodiazepine medication practices at the VA, for treating mental health and combat-related trauma, which potentially led to veteran's deaths and suicides."

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BACKGROUND

Due to the effects of active duty and combat-related injuries, among other potential predisposing factors, the VA population has higher rates of chronic pain, traumatic brain injury, posttraumatic stress disorder, depression, substance use disorder, and accompanying mental health problems than civilians. Those co-occurring conditions increase the risk for suicidal ideation and suicide, and chronic opioid and benzodiazepine treatment is relatively common.[1] Even so, current studies do not indicate that VA medical providers were prescribing opioids at higher doses or frequencies than civilian providers, and rates of opioid prescribing by VA providers have decreased in concert with the rates of civilian providers over the past few years. Of note, the VA and DoD published their *Clinical Practice Guidelines for Opioid Therapy for Chronic Pain* in 2010, updated in 2015, to disseminate recommendations for safer prescribing. The guideline highlights the most important risk factors associated with adverse events in chronic opioid treatment and provides guidance on appropriate dosing and duration of opioid treatment. Moreover, in response to increasing concerns about the risks of chronic opioid treatment, the VA implemented the Opioid Safety Initiative in 2013, which includes best-practice prescribing education for medical providers, overdose education and naloxone[2] training for patients, and a clinical-decision-support tool for hospital leaders to track prescribing. That initiative was associated with a decreased prescribing of chronic opioid treatment during the ensuing 5-year period, 2013–2018.

Current studies do not clearly indicate to what extent opioid and benzodiazepine co-prescribing in the VA during that period contributed to severe adverse consequences, including opioid overdose deaths. Nevertheless, congressional leaders remained concerned about possible overprescribing of opioids and benzodiazepines to veterans during the years 2010–2017. Thus, the Committee on Developing a Protocol to Evaluate the Concomitant Prescribing of Opioids and Benzodiazepine Medications and Veteran Deaths and Suicides was charged by the VA to "develop a protocol/study design to evaluate the relationship between concomitant opioid and benzodiazepine medication practices at the VA, for treating mental health and combat-related trauma, which potentially led to veteran's deaths and suicides." In responding to its task, the committee proposes observational studies using VA and Centers for Disease Control and Prevention (CDC)

[1] Benzodiazepine users tend to report a longer history of opioid use and prior detoxifications; use higher doses of opioids; higher frequency of injection drug use, needle sharing, and co-occurring use of alcohol and cocaine; and greater criminal activity.

[2] Naloxone is a medication approved by the Food and Drug Administration (FDA) to prevent overdose by opioids such as heroin, morphine, and oxycodone.

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data to emulate hypothetical randomized trials, should the VA decide to conduct those studies.

DEFINING THE RESEARCH QUESTION

The committee interpreted its task to focus on the following overarching research question: What were the effects of opioid initiation and tapering (i.e., dosage reduction or discontinuation) strategies in the presence of benzodiazepines in veterans on all-cause mortality and suicide mortality from 2010 to 2017?[3] The committee's focus on that specific research question was a result of its interpretation of the intent of the Statement of Task and the committee's review of the literature.

First, the committee determined that initiation and tapering represent two critical decision points in opioid treatment. A decision to initiate opioids is of necessity made for any person who eventually progresses to long-term opioid therapy. Tapering is the second decision point of focus identified by the committee. Given the focus of the Statement of Task on adverse consequences, tapering is highly relevant for two main reasons: (1) the avoidance of known adverse consequences of long-term opioid therapy, such as increased mortality, is often a motivation for the decision to taper opioid dosage rather than continuing treatment, and (2) some clinicians and patients have raised concerns that, rather than reducing the risk for harm, tapering a patient who is tolerant to opioids may contribute to adverse consequences, particularly suicide. The committee concluded that a study of the effect of opioid tapering on all-cause mortality and suicide would reduce clinical uncertainty and would be timely in the context of current opioid policy and practice decisions.

Second, the Statement of Task specifically focused on "concomitant opioid and benzodiazepine" prescribing. After reviewing the literature, the committee concluded that patients receiving both medications are at particularly high risk for adverse outcomes relative to patients on opioids alone, and there was very limited evidence regarding opioid prescribing strategies specifically for patients receiving benzodiazepines. Thus, although the effects of opioid initiation and tapering on patient outcomes are important areas of inquiry, the focus on patients prescribed benzodiazepines is more responsive to the Statement of Task and also addresses a particularly important sub-group of patients.

Finally, the Statement of Task specifically focused on the outcomes of "deaths and suicides." The committee believed that a focus on all-cause

[3] The Consolidated Appropriations Act, 2018, Number: 115-141, Session: 115th Congress (Second Session), from which the committee's Statement of Task was written, specified an interest in the time period of "fiscal years 2010 to 2017."

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mortality appropriately reflected the fundamental importance to clinical decisions of evidence of increased or decreased risk of death from any cause. Furthermore, mortality from any cause was the outcome most likely to be complete within VA data resources, given the ability of VA patients to get care outside the VA. Additionally, the inclusion of suicide as an outcome separate from all-cause mortality was relevant to the concerns of patients, clinicians, and other stakeholders about suicide among veterans generally as well as among veterans with pain specifically.

The committee notes that the Statement of Task could be interpreted in other ways, such as the tapering of benzodiazepines for patients prescribed both opioids and benzodiazepines. Should the VA or others be interested in conducting related studies, those studies can be modeled on the committee's approach.

THE TARGET TRIAL FRAMEWORK

Randomized trials are the preferred method for estimating the causal effects of treatment strategies on clinical outcomes. The primary advantage of a randomized trial is that the randomization assures a high likelihood that confounding variables are balanced across treatment groups. However, prospective randomized trials in which patients are enrolled and randomized into treatment groups are often infeasible for a variety of reasons, such as ethics and resource limitations, and the results from such trials may have limited generalizability to routine clinical settings. For that reason, studies using observational data are often appropriate for evaluating the connections between treatments and outcomes.

To develop the study strategy using observational data, the committee suggests the use of a "target trial" methodology, which involves describing a hypothetical randomized trial that is emulated (i.e., closely approximated) by an observational study. Specifying a target trial before emulating that trial using observational data can help mitigate some of the limitations of observational studies, for instance, by identifying and describing how to measure confounders. An observational study is most useful when any important confounding variables can be identified, measured, and therefore controlled for by using study design (matching or exclusion) or statistical analysis (stratification or mathematical modeling). In Chapter 2 the committee describes the rationale, advantages, and limitations of the target trial methodology and presents the target trials that the committee believes would best respond to the charge. Chapter 3 details considerations of how those target trials would be emulated using existing data from the VA and CDC. It should be noted that while the committee is familiar with those databases, it did not consider specifics such as which VA databases could be most useful.

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For clarity, in this report the committee uses the term "target trial" to refer to the hypothetical randomized trial that would directly address the research question, "protocol" to include all components of the design (e.g., patient enrollment, treatment strategies, outcome) and analysis of the target trial, and "observational analysis" to refer to the data analysis proposed to emulate the target trial using existing observational data.

TARGET TRIAL PROTOCOL AND OBSERVATIONAL EMULATION

The committee developed protocols for two different hypothetical target trials, each of which would quantify effects on suicide and other causes of death. The first trial focuses on the initiation of opioids in the presence of benzodiazepines and the second on the tapering of opioids in the presence of benzodiazepines. Both studies were developed for patients receiving chronic benzodiazepine treatment. The committee then designed protocols and analytic strategies for those trials, recognizing that many other studies could also be of interest. The object of the trials is to determine preferred approaches for opioid initiation or reduction strategies for patients participating in the trials.

Figure S-1 illustrates the opioid initiation and tapering target trials proposed by the committee. The committee describes seven components in the protocol of the target trials: eligibility criteria, treatment strategies, treatment assignment, start and end of follow-up, outcomes, causal contrasts, and the statistical analysis plan.

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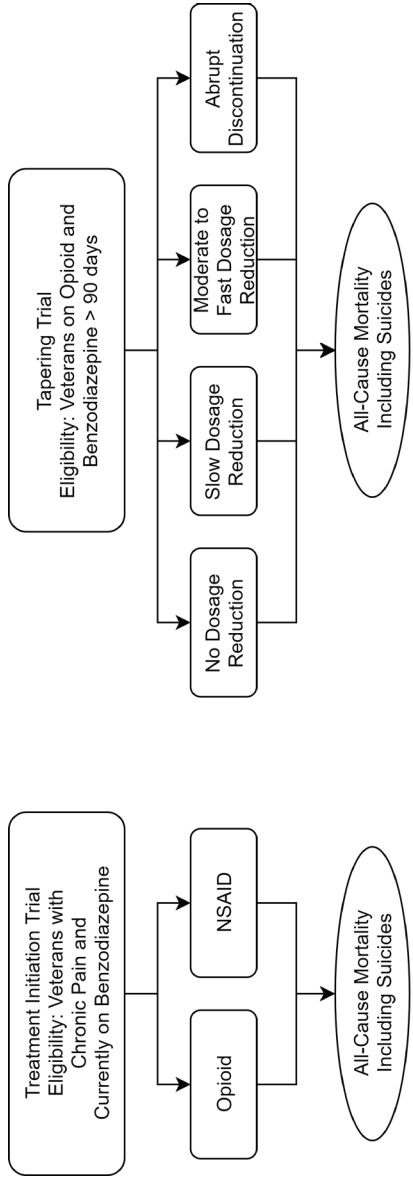

FIGURE S-1 Opioid treatment initiation and tapering target trial schematic.
NOTE: NSAID = nonsteroidal anti-inflammatory drug.

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In Table S-1, the committee illustrates a suggested set of initial choices for the required specification of the target trials. The choices listed in this table should be considered preliminary because the specification of the target trial components is an iterative process, with insights from pilot analyses of the available observational data resulting in changes to the definitions and choices that can be incorporated into a feasible and valid analysis plan.

TABLE S-1 Proposed Specifications for Initiation and Tapering Target Trials

Protocol Component	Initiation Target Trial	Tapering Target Trial
Eligibility criteria	Chronic pain diagnosis[a] No prescriptions for opioids or non-aspirin NSAIDS in the last 90 days Long-term benzodiazepine therapy (defined based on pilot data) Exclude: Individuals with serious illness[b] Individuals prescribed opioids used for treatment of opioid use disorder Individuals with surgery or acute painful injury within the past 90 days[c]	Long-term opioid therapy defined as 3+ opioid fills ≥21 days apart in a ≥84-day period for ≥84-day supply Average opioid MME[d]/day is ≥30 over the prior 84 days[e] Long-term benzodiazepine therapy (defined based on pilot data) Exclude: Individuals with serious illness Individuals prescribed opioids for the treatment of opioid use disorder Individuals with surgery or acute painful injury within the 90 days prior to baseline
Treatment strategies	(a) Initiation of treatment with an opioid and continuation for 1 year, unless not tolerated by the participant (b) Initiation of treatment with a non-aspirin NSAID and continuation for 1 year, unless not tolerated by the participant	(a) No dosage reduction: ≤5% average decrease per month for 3 months (b) Slow dosage reduction[f]: >5% but ≤10% average decrease per month for 3 months (c) Moderate to fast dosage reduction: >10% average decrease per month for 3 months (d) Complete discontinuation within 3 months from baseline Participants who cannot tolerate their assigned dosage change will be excused from following their assigned strategy. Percentage of taper is relative to opioid dose at baseline and is calculated over the next 3 months. After that period, dosage is left to the physician's discretion.

continued

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TABLE S-1 Continued

Protocol Component	Initiation Target Trial	Tapering Target Trial
Treatment assignment	Individual randomization, stratified on baseline dose	
Start and end of follow-up	Start of follow-up (baseline): start of treatment for chronic pain, defined as being dispensed one or more prescriptions of an opioid or NSAID for at least a 30-day supply over a 30-day period (this could be across multiple prescriptions), and also having a chronic pain diagnosis End of follow-up: the earliest of 18 months,[g] death, or administrative end of follow-up (end of the study)	Start of follow-up (baseline): time of assignment to a treatment strategy End of follow-up: the earliest of 6 months,[b] death, or administrative end of follow-up (end of the study)
Outcomes	(a) All-cause mortality (b) Death from suicide (Same for initiation and tapering trials)	
Causal contrast	(a) Intention-to-treat effect (b) Per-protocol effect (Same for initiation and tapering trials)	
Statistical analysis	Intention-to-treat analysis: check for balance on key variables, e.g., mental health diagnoses and substance use disorders. Per-protocol analysis: patients will be censored at the time they deviate from their assigned strategy. To adjust for the potential selection bias induced by censoring, inverse probability weighting will be used. The weights will be a function of the baseline and post-baseline (time-varying) confounders. Both analyses may require further adjustment for selection bias due to loss to follow-up. Pre-specified sub-groups to be examined for potential effect modification include, e.g., pain severity, history of overdose, history of suicide attempt, non-suicide death (for the suicide death analysis).	

[a] The intention of this definition is to exclude opioids and nonsteroidal anti-inflammatory drugs (NSAIDs) prescribed for acute pain. However, researchers should consider that there might be a large proportion of veterans prescribed opioids for whom there is not a chronic pain diagnosis.

[b] Serious illness is defined as a health condition that carries a high risk of mortality and negatively affects a person's daily functioning. The committee recommends operationaliz-

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TABLE S-1 Continued

ing this as any of the following conditions: cancer, chronic obstructive pulmonary disease, congestive heart failure, dementia, or severe neurologic disorder (e.g., amyotrophic lateral sclerosis, multiple sclerosis).

[c] 90 days was chosen to minimize likelihood of opioids being prescribed for acute rather than chronic pain conditions. However, the committee acknowledges that the choice of 90 as opposed to 30 or 60 is arbitrary.

[d] MME = morphine milligram equivalent.

[e] This threshold was used because labeling for OxyContin extended release defines "opioid tolerant" as consuming 30 MME/day. Researchers might consider a lower dose threshold if the purpose is to include anyone who could be considered for a taper.

[f] Speed of tapering: there is a lack of primary literature on the optimal rate of tapering speed (i.e., rate of dosage decrease per week/month). Within the context of concomitant opioid and benzodiazepine use and likely psychiatric comorbidity, a more conservative approach would be prudent.

[g] The committee believes that the 18-month timeline balanced the desire for a longer length of follow-up than prior initiation studies with the fact that there would be a greater degree of non-adherence from the assigned treatment group with the longer lengths of follow-up.

[h] The committee believes that the 6-month timeline balanced a desire for a longer length of follow-up with potential for non-adherence and a concern that suicide is a relatively short-term outcome in tapering studies.

Figure S-2 illustrates the proposed observational studies that would emulate those target trials using existing VA and CDC data.

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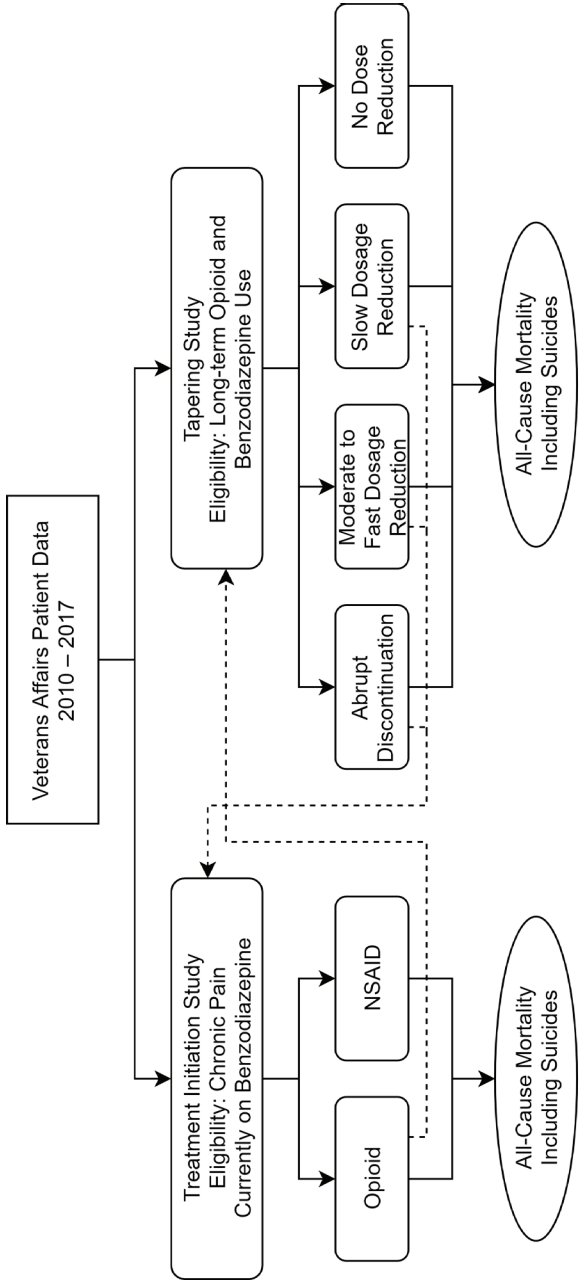

Study populations are not exclusive. A patient initiated with opioid may eventually enter a tapering group. A patient whose opioids are tapered may eventually enter the intiation study.

FIGURE S-2 Opioid treatment initiation and tapering study schematic.
NOTE: NSAID = nonsteroidal anti-inflammatory drug.

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Tables S-2 and S-3 reiterate the specifications of the target initiation and tapering target trials from Table S-1 in the "target trial" column and suggest emulation procedures using available observational data. Tables S-2 and S-3 describe an initial emulation strategy that has not been evaluated and would likely require modification after an initial review of the available data. Additional considerations for emulating the target trials using observational data and potential limitations are detailed in Chapter 3.

TABLE S-2 Opioid Initiation Target Trial Emulation

Study Component	Target Trial	Emulation Using Observational Data
Eligibility criteria	Chronic pain diagnosis No prescriptions for opioids or non-aspirin NSAIDS in the last 90 days Long-term benzodiazepine therapy (defined based on pilot data) Exclude: Individuals with serious illness[a] Individuals prescribed opioids used for treatment of opioid use disorder Individuals with surgery or acute painful injury within the past 90 days[b]	Data to determine the use of analgesics during the last 90 days and the use of benzodiazepines will come from pharmacy fills and will require information specifically on fill dates, dose, and supply duration. Data for the diagnoses of chronic pain, serious illnesses, surgeries, or acute painful injuries will come from the medical visit records. Opioid use for opioid use disorder treatment will be measured through a combination of pharmacy fills (for buprenorphine) and clinic codes for opioid treatment programs.
Treatment strategies	(a) Initiation of treatment with an opioid and continuation for 1 year, unless not tolerated by the participant (b) Initiation of treatment with a non-aspirin NSAID and continuation for 1 year, unless not tolerated by the participant	Patients will be assigned to the strategies consistent with their pharmacy fill data, based on initiation at baseline with an opioid or NSAID. Adherence to the strategy is defined by continued fills during the year after baseline. An example of non-adherence would be if a patient could not tolerate over-sedation from opioid use and discontinued as a result.

continued

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TABLE S-2 Continued

Study Component	Target Trial	Emulation Using Observational Data
Treatment assignment	Individual randomization	Assumed to be random conditional on baseline confounders, including, but not limited to —Medical illnesses —Mental health diagnoses —Pain intensity —Substance use disorder (SUD) diagnoses —History of overdose with prescribed opioid —Medication history —Age Diagnoses associated with clinical visits in VA medical records will be used to define these variables.
Start and end of follow-up	Start of follow-up (baseline): time of assignment to a treatment strategy End of follow-up: the earliest of 18 months, death, or the administrative end of follow-up (end of the study)	Start of follow-up (baseline): time of assignment to a treatment strategy. End of follow-up: the earliest of 18 months, the date of death based on National Death Index records, or the administrative end of follow-up.
Outcomes	(a) All-cause mortality (b) Death from suicide	Deaths ascertained from National Death Index data, with all-cause mortality measured as a death record with a date of death and suicide deaths as those records with underlying cause of death recorded as ICD-10 codes X60–X84, Y87.0, *U03.[c]
Causal contrast	(a) Intention-to-treat effect (b) Per-protocol effect	Observational analog of the intention-to-treat effect: this effect may be close to null and therefore relatively uninformative because adherence to the assigned treatment strategies is expected to be low in the observational data. Observational analog of the per-protocol effect.

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TABLE S-2 Continued

Study Component	Target Trial	Emulation Using Observational Data
Statistical analysis	Intention-to-treat analysis: check for balance on key variables, e.g., mental health diagnoses and SUDs. Per-protocol analysis: patients will be censored at the time they deviate from their assigned strategy. To adjust for the potential selection bias induced by censoring, inverse probability weighting will be used. The weights will be a function of the baseline and post-baseline (time-varying) confounders. Both analyses may require further adjustment for selection bias due to loss to follow-up. Pre-specified sub-groups to be examined for potential effect modification include, e.g., patients with pain severity, history of overdose, or a history of suicide attempt.	Intention-to-treat analysis: same as in target trial, except that an individual may have multiple eligibility points, and adjustment for baseline confounders is required. Per-protocol analysis: same, except that a single subject may have multiple eligibility points. All variables will be obtained from medical records, including clinic visit information, diagnoses, and pharmacy records.

[a] Serious illness is defined as a health condition that carries a high risk of mortality and negatively affects a person's daily functioning. The committee recommends operationalizing this as any of the following conditions: cancer, chronic obstructive pulmonary disease, congestive heart failure, dementia, or severe neurologic disorder (e.g., amyotrophic lateral sclerosis, multiple sclerosis).

[b] 90 days was chosen to minimize the likelihood of opioids being prescribed for acute rather than chronic pain conditions. However, the committee acknowledges that the choice of 90 as opposed to 30 or 60 is arbitrary.

[c] The researchers who perform the study should determine whether this definition is sufficiently accurate for their purposes.

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TABLE S-3 Opioid Tapering Target Trial Emulation

Study Component	Target Trial	Emulation Using Observational Data
Eligibility criteria	Long-term opioid therapy defined as 3+ opioid fills ≥21 days apart in a ≥84-day period for ≥84-day supply Average opioid MME[a]/day is ≥30 over the prior 84 days[b] Long-term benzodiazepine therapy (defined based on pilot data) Exclude: Individuals with serious illness[c] Individuals prescribed opioids for the treatment of opioid use disorder Individuals with surgery or acute painful injury within the 90 days prior to baseline	Data to determine opioid use will come from pharmacy fills and will require information specifically on fill dates, dose, and supply duration. Data for diagnoses qualifying as serious illnesses will come from the medical visit records. Opioid use for opioid use disorder treatment will be measured through a combination of pharmacy fills (for buprenorphine) and clinic codes for opioid treatment programs.
Treatment strategies	(a) No dosage reduction: ≤5% average decrease per month for 3 months (b) Slow dosage reduction[d]: >5% but ≤10% average decrease per month for 3 months (c) Moderate to fast dosage reduction: >10% average decrease per month for 3 months (d) Complete discontinuation within 3 months from baseline Participants who cannot tolerate their assigned dosage change will be excused from following their assigned strategy. Percentage of taper is relative to opioid dose at baseline and is calculated over the next 3 months. After that period, dosage is left to the physician's discretion.	The treatment strategy to which a participant is assigned is determined by the average change in opioid dose during the 3-month period after baseline. This will minimize the impact of changes that are due to non-clinical reasons, as those changes should be followed by a correction (e.g., early prescription fill due to patient vacation, followed by a late fill). Tapering treatment strategies are defined the same as in the target trial. An example of non-adherence would be if a patient's pain worsened and functioning declined and the patient returned to the original dosage after starting a taper.

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TABLE S-3 Continued

Study Component	Target Trial	Emulation Using Observational Data
Treatment assignment	Individual randomization	Assumed to be random conditional on the baseline confounders, including —Medical illnesses —Mental health diagnoses —Substance use disorder (SUD) diagnoses —History of overdose with prescribed opioid —Age Diagnoses associated with clinical visits in VA medical records will be used to define these variables.
Start and end of follow-up	Start of follow-up (baseline): time of assignment to a treatment strategy End of follow-up: the earliest of 6 months, death, or the administrative end of follow-up (end of the study)	Start of follow-up (baseline): time of assignment to a treatment strategy. End of follow-up: the earliest of 6 months, the date of death based on National Death Index records, or the administrative end of follow-up.
Outcomes	(a) All-cause mortality (b) Death from suicide	Deaths will be ascertained from National Death Index data, with all-cause mortality measured as a death record with a date of death and suicide deaths as those records with underlying cause of death recorded as ICD-10 codes X60–X84, Y87.0, *U03.[e]
Causal contrast	(a) Intention-to-treat effect (b) Per-protocol effect	Observational analog of the intention-to-treat effect: this effect may be close to null and therefore relatively uninformative because adherence to the assigned treatment strategies is expected to be low in the observational data. Observational analog of the per-protocol effect.

continued

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TABLE S-3 Continued

Study Component	Target Trial	Emulation Using Observational Data
Statistical analysis	Intention-to-treat analysis: check for balance on key variables, e.g., mental health diagnoses and SUDs. Per-protocol analysis: patients will be censored at the time they deviate from their assigned strategy. To adjust for the potential selection bias induced by censoring, inverse probability weighting will be used. The weights will be a function of the baseline and post-baseline (time-varying) confounders. Both analyses may require further adjustment for selection bias due to loss to follow-up. Pre-specified sub-groups to be examined for potential effect modification include, e.g., patients with pain severity, history of overdose, or a history of suicide attempt.	Intention-to-treat analysis: N/A Per-protocol analysis: same as in target trial, except that a single subject may contribute two clones. All variables will be obtained from medical records, including clinic visit information, diagnoses, and pharmacy records.

[a] MME = morphine milligram equivalent.

[b] This threshold was used because labeling for OxyContin extended release defines opioid tolerant as consuming 30 MME/day. Researchers might consider a lower dose threshold if the purpose is to include anyone who could be considered for a taper.

[c] Serious illness is defined as a health condition that carries a high risk of mortality and negatively affects a person's daily functioning. The committee recommends operationalizing this as any of the following conditions: cancer, chronic obstructive pulmonary disease, congestive heart failure, dementia, or severe neurologic disorder (e.g., amyotrophic lateral sclerosis, multiple sclerosis).

[d] Speed of tapering: there is no generally accepted rate of tapering speed (i.e., rate of dosage decrease per week/month)—options would need to be explored using pilot data. The tapering speeds proposed for this trial should not be considered medical guidance.

[e] The researchers who perform the study should determine whether this definition is sufficiently accurate for their purposes.

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The committee identified several challenges in their protocol development. The first was that prescribing practices and standards of care evolved in important ways from 2010 to 2017 and continue to evolve in response to increasing concerns about high-risk prescribing practices. A second challenge relates to the complexity of the patients who are prescribed both opioids and benzodiazepines, such as veterans with combat-related trauma or with co-occurring conditions. Thus, a consideration in developing a protocol for such an evaluation is that it will be important to identify prescribing practices that will lead to further reductions in inappropriate prescribing in a more challenging patient population for which existing approaches have not adequately addressed the problem. Furthermore, safe tapering protocols are necessary for reducing opioid and benzodiazepine use.

CLOSING COMMENTS

The committee emphasizes that the examples of study protocols in this report are only two possible target trials, chosen because they directly address the Statement of Task, are the minimum number of studies needed to address the Statement of Task, and address gaps in the literature. Adjustments to the protocols would likely be necessary after a preliminary examination of the observational data and a determination of how best to approach the studies and analyze the data. Many other studies would also be of interest beyond the outcomes of mortality and suicide in the population of veterans treated with opioids and benzodiazepines. For example, standardized self-report measures of pain, social and emotional functioning, depression, anxiety, and co-prescription of other central nervous system depressant medications could be examined to determine their effects on patient functioning over time. An examination of the clinical and functional outcomes of veterans who have been prescribed only opioids or only benzodiazepines would also be informative.

The VA medical record contains a wealth of clinical information that could be analyzed to determine the potential benefits, as well as risks, to patients with a wide variety of characteristics who were prescribed opioids and benzodiazepines. The committee views the proposed studies and any related investigations as an excellent opportunity to use the rich VA clinical databases to clarify the connections between important clinical conditions, changes in opioid and benzodiazepine prescribing practices over the years 2010–2017, and outcomes. Significant changes in prescribing practice occurred over that time period, so comparisons of outcomes of different treatment strategies could yield important insights into the best treatment practices. For example, because of concerns about high-dose opioid treatment, many practitioners in the United States have dramatically curtailed opioid prescribing in recent years in response to the increasing rates of

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opioid use disorder, yet that leaves many patients struggling to cope with chronic pain problems for which they had previously relied on opioid medication. The proposed observational studies might reveal important insights into health care providers' pain treatment practices, which could inform the use of opioid treatment as part of chronic pain management in the future.

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Introduction

The Department of Veterans Affairs (VA)[1] requested that an ad hoc committee of the National Academies of Sciences, Engineering, and Medicine be assembled to "develop a protocol/study design to evaluate the relationship between concomitant opioid and benzodiazepine medication practices at the VA, for treating mental health and combat-related trauma, which potentially led to veteran's deaths and suicides." Thus, a committee was formed to address that task. The committee considered both the characteristics of randomized controlled trials (RCTs) that could address the Statement of Task directly—but would now be infeasible to conduct—and analysis strategies that leveraged existing observational data to emulate those (target) trials. The committee's target trial protocols lay out the purpose and details of each trial (e.g., eligibility criteria, treatment strategies, outcomes, analysis plan), while the proposed observational designs specify how to emulate the target trials using existing VA clinical databases.

This first chapter will provide a brief background on the use of opioids and benzodiazepines for treating pain and anxiety in the general population, followed by a discussion of their use in the veteran population. The chapter is not meant to provide in-depth information on the neurobiology and pharmacology of those drugs, nor is it meant to provide a discussion of all possible uses of opioids and benzodiazepines; however, the committee has included a very brief section on the neurobiology and principles of

[1] The Department of Veterans Affairs is composed of the Veterans Health Administration (VHA), the Veterans Benefits Administration, and the National Cemetery Administration. This report's focus is the VHA.

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addiction and tolerance. Finally, this chapter also provides a description of the committee's approach to its task and the organization of the report.

NEUROBIOLOGY AND PRINCIPLES OF ADDICTION AND TOLERANCE

Substances like opioids and benzodiazepines dysregulate brain systems that are involved with motivation, reward, decision making, and memory. Opioids act in multiple ways in the body, including altering body temperature, causing sedation, depressing respiration, decreasing gastrointestinal transit, and producing euphoria or dysphoria. Those effects are primarily mediated through three opioid receptor subtypes: mu, kappa, and delta (Jones et al., 2012).

The rewarding effects of opioids (e.g., morphine and heroin) are primarily caused by their agonism of the mu opioid receptor. The mu receptor is also responsible for analgesia and respiratory depression. Chronic opioid use is associated with the development of tolerance, which develops at different rates in different people. Opioid overdose can result in respiratory depression and death (Turton and Lingford-Hughes, 2016). Continual opioid use results in tolerance, while abrupt cessation results in the process of withdrawal.

The neurotransmitter[2] gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the brain. GABA-A receptors are the site of action for several neuroactive drugs, including benzodiazepines, barbiturates, picrotoxin, and muscimol. Alcohol also binds to GABA-A receptors (Turton and Lingford-Hughes, 2016).

Benzodiazepines act to enhance the effects of GABA; their binding sites are part of the GABA-A receptor complex, and they act to open the chloride channel by GABA and result in inhibition, which in turn results in anxiolysis[3] and sedation. As noted in McClure et al. (2017), the cumulative and synergistic effects from combining benzodiazepines and opioids result in depressing the central nervous system's medullary controls for respiration, with the benzodiazepines working through the GABA receptors and opioids through mu (m) and delta (d) receptors.[4] Furthermore, for patients

[2] Neurotransmitters are chemicals that are released at the end of a nerve fiber in response to the arrival of a nerve impulse and that, by diffusing across the synapse or junction, cause the transfer of the impulse to another nerve fiber, a muscle fiber, or some other structure (Maiese, 2019).

[3] Anxiolysis is caused by certain drugs and is used to help relieve anxiety during certain medical or surgical procedures. This is also called minimal sedation. See https://www.cancer.gov/publications/dictionaries/cancer-terms/def/anxiolysis (accessed August 2, 2019).

[4] For further information regarding the neurobiology and pharmacology of opioids and benzodiazepines, see, for example, Evans and Cahill (2016) and Turton and Lingford-Hughes (2016).

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and others with substance use disorder (SUD), combining opioid and benzodiazepine drugs increases the subjective peak strength of drug effects and sedation (Lintzeris et al., 2007). In 2010 greater than 30 percent of opioid-related deaths in the United States also involved benzodiazepines (Jones et al., 2013). Among U.S. military veterans who were prescribed opioids and who subsequently died of a drug overdose, approximately half of the overdoses involved concurrent prescriptions for benzodiazepines (Park et al., 2015). In 2016 the Centers for Disease Control and Prevention (CDC) issued guidelines for prescribing opioids for chronic pain. The guidelines note that evidence for the long-term efficacy of opioids for chronic pain is limited and that long-term use is associated with serious risks, such as opioid use disorder and overdose (Dowell et al., 2016).

DEFINITIONS OF PAIN

Pain falls broadly into three main categories: acute pain, chronic non-cancer-related pain, and cancer-related pain.[5] *Acute pain* is a normal response to tissue damage and typically resolves itself once the injured tissue heals or soon after; it is pain experienced after trauma or surgery. *Chronic, non-cancer-related pain* is commonly defined as pain that persists for longer than the expected time frame for healing or pain associated with progressive, nonmalignant disease (Ashburn and Staats, 1999). In clinical and research reports, chronic pain is often operationally defined as pain that has persisted for at least 3 months (Rosenblum et al., 2008). Similarly, Tompkins et al. (2017) define chronic pain as pain that has lasted beyond the normal healing time for a given injury, operationalized as pain lasting more than 3 months, and they note that chronic pain is divided further, for treatment purposes, according to whether or not it is associated with cancer. *Cancer-related pain* refers to pain resulting from primary tumor growth, metastatic disease, or the toxic effects of cancer treatments.

In 1996 the American Pain Society introduced the phrase "pain as the fifth vital sign," which emphasized that pain assessment is as important as the assessment of the standard four vital signs[6] and that clinicians need to take action when patients report pain. The Veterans Health Administration (the VHA) recognized the value of such an approach and included pain as the fifth vital sign in its national pain management strategy. The Joint

[5] With regard to cancer pain, in the 1970s and 1980s palliative care specialists recognized that opioids brought relief to terminal cancer patients, and several studies were published that suggested that patients rarely developed opioid use disorder when opioids were prescribed for cancer pain. Concurrently, the World Health Organization was developing cancer pain treatment guidelines that included pain treatment as a universal right.

[6] The four vital signs are body temperature, blood pressure, pulse (heart rate), and breathing/respiratory rate.

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Commission on Accreditation of Healthcare Organizations[7] mandated pain assessment and treatment in 2001 as a requirement of receiving federal health care dollars. The Federation of State Medical Boards stated that physicians would not receive excessive regulatory scrutiny for prescribing opioids, and the Drug Enforcement Administration agreed to follow a balanced policy in examining prescriber's practices and to reduce the oversight of physicians that had high rates of opioid prescribing (Tompkins et al., 2017). Additionally, a few research studies, published during the 1990s and 2000, resulted in diminished concern among providers and patients, as they suggested that patients rarely developed addiction to opioids when they were prescribed for pain (see Tompkins et al., 2017). The combination of these factors led to an increasing reliance on prescription opioids for pain management.

Prevalence of Chronic Pain

In an effort to estimate the prevalence of chronic pain and high-impact chronic pain[8] in the United States, CDC analyzed data from the 2016 National Health Interview Survey (NHIS). According to that analysis, an estimated 20.4 percent (50.0 million) of U.S. adults had chronic pain, and 8.0 percent of U.S. adults (19.6 million) had high-impact chronic pain. Chronic pain is a major cause of decreased quality of life and disability and is often challenging to treat effectively (Chou et al., 2014).

OPIOID USE TO TREAT PAIN

Opioid analgesics[9] are commonly prescribed to treat chronic and acute pain and are available legally by prescription. In the mid-1990s, as noted above, professional societies argued that there was an epidemic of untreated pain, and wider use of opioid medications was encouraged (Evans et al., 2019). In 1996 Purdue Pharmaceuticals introduced OxyContin (oxycodone extended release). The Food and Drug Administration approved the drug labeling, which claimed that iatrogenic addiction was very rare and that the drug's delayed absorption was believed to reduce abuse liability. That

[7] The Joint Commission on Accreditation of Healthcare Organizations is a nonprofit organization based in the United States that accredits more than 20,000 health care organizations and programs in the country.

[8] High-impact chronic pain is pain that has lasted 3 months or longer and is accompanied by at least one major activity restriction, such as being unable to work outside the home, go to school, or do household chores (Pitcher, 2018).

[9] Opioids include drugs such as hydrocodone (e.g., Vicodin), morphine (e.g., Duramorph, MS Contin), oxycodone (e.g., OxyContin, Percocet), hydromorphone (e.g., Dilaudid), and fentanyl (e.g., Duragesic).

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action resulted in an increase in the number of OxyContin prescriptions from 670,000 in 1997 to about 6.2 million in 2002, when the label was changed to drop the misleading language (Tompkins et al., 2017). However, beginning in the 1990s, as the frequency of opioid prescribing and the volume of opioids dispensed increased in the United States, the number of overdoses and deaths from prescription opioids also increased. From 1999 to 2017 about 218,000 people died in the United States from overdoses related to prescription opioids (CDC, 2019a). In 2017 there were 70,237 fatal drug overdoses in the United States and prescription opioids were involved in 17,029 (24.2 percent) of them (CDC, 2019b). Furthermore, adults aged 25–54 had higher rates of drug overdose deaths in 2017 than those aged 55 and over.

In 2016 CDC issued new guidelines[10] for prescribing opioids for treating chronic pain in the United States. The guidelines address when to initiate or continue opioids for chronic pain; opioid selection, dosage, duration, follow-up, and discontinuation; and assessing the risk and addressing the harms of opioid use (Dowell et al., 2016). A study by Zhu et al. (2019) found that between July 2012 and December 2017 many providers stopped initiating opioid therapy, but a sub-group of providers continued to write high-risk initial opioid prescriptions.[11]

Treating Cancer Pain with Opioids

It should be noted that there has been some controversy surrounding the appropriateness of use of opioids for cancer pain, and guidelines recommend against using them along with benzodiazepines. With regard to cancer surgery, studies have emerged that highlight chronic opioid use. For example, Lee et al. (2017) found new and persistent use of opioids in cancer patients following curative-intent surgery. The study identified a total of 68,463 patients who had different types of cancer surgery with the intent of cure between 2010 and 2014. The primary outcomes examined were new and persistent opioid use (i.e., continued filling of opioid prescriptions for 90–180 days post-surgery in opioid-naïve patients). The risk of new persistent opioid use was 10.4 percent 1 year after surgery; furthermore, those patients continued filling prescriptions with daily doses similar to chronic opioid users (i.e., equivalent to six tablets per day of 5 mg of hydrocodone). A more recent study by Brescia et al. (2019) found new and persistent use

[10] CDC developed the guidelines using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework, and CDC notes that recommendations are made on the basis of a systematic review of the scientific evidence while considering benefits and harms, values and preferences, and resource allocation.

[11] High-risk prescriptions are those that are in doses or durations above those recommended by CDC.

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of opioids following lung resection surgery conducted between 2010 and 2014. New and persistent use was defined by the authors as continued opioid prescription refills between 90 and 180 days following surgery. Data from that study were evaluated, and 14 percent of the 3,026 patients identified as "opioid-naïve" continued to fill opioid prescriptions after 90 days.

OPIOID USE AND SUICIDE

A study by Ilgen et al. (2016) that used a case-cohort design found evidence linking chronic non-cancer pain to an increased risk of suicide. Evidence of such a link has been consistently found in studies using varying methods of assessing pain, the population examined, and the primary outcome (suicide attempt, suicide death). The association between pain and suicide is partially attenuated once one controls for other psychiatric disorders, such as depression, but, even so, it remains significant.

The study's authors note that the treatment of pain is controversial with regard to suicide risk, as under-treatment could place individuals with pain at risk for suicide. However, the use of prescription opioids also could increase the risk of suicide in some cases because of the lethality of opioids and the opioids' potential negative effects on mental health in certain individuals. It is noteworthy that there is evidence in the literature of an association between the use of opioids and an increased risk of suicide (Sarchiapone et al., 2011).

A 2019 review by Bohnert and Ilgen examined the associations among opioid use, overdose, and suicide in the United States. The authors found that there are several key factors beyond opioid use that are related to suicide and overdose. Most mental health conditions are linked to an increased risk of suicide and unintentional overdose, including both illicit drug and medication-related overdoses, but the type of link differed according to the specific mental health condition. SUDs had a stronger association with unintentional overdoses, while other mental health conditions were generally linked more strongly with intentional overdose. The use of other medications and drugs in combination with opioids—for example, the concurrent use of recreational drugs, such as alcohol and cocaine, with opioids—can increase the risk of death as well. Additionally, some of the demographic characteristics associated with suicide and overdose in the United States are also associated with veteran status, such as male sex and white race.

PRESCRIBING OPIOIDS

Although the overall opioid prescribing rate in the United States has been declining since 2012, the amount of opioids in morphine milligram

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equivalents (MMEs)[12] prescribed is still about three times higher than it was in 1999 (CDC, 2018). Additionally, the pattern of drugs involved in drug overdose deaths has changed in recent years (Hedegaard et al., 2018a). The age-adjusted rate of drug overdose deaths involving synthetic opioids other than methadone (e.g., fentanyl, fentanyl analogs, and tramadol) increased by 45 percent between 2016 and 2017, from 6.2 to 9.0 per 100,000 (Hedegaard et al., 2018b). The rates of drug overdose deaths involving heroin (4.9 per 100,000), natural and semisynthetic opioids (4.4), and methadone (1.0) were the same in 2016 and 2017. There was also a shift from prescribed opioids to illegally obtained opioids (heroin and illegally manufactured fentanyl) as the predominant cause of opioid overdose deaths (Hedegaard et al., 2018b).

Patterns of Opioid Prescribing

A study by Schieber et al. (2019) examined trends and geographic patterns in opioid prescribing between January 1, 2006, and December 31, 2017. The authors abstracted data from outpatient prescribing records[13] to obtain estimates of the number of opioid prescriptions dispensed from approximately 59,400 retail, non-hospital pharmacies, which dispense 93 percent of all retail prescriptions in the United States. Findings from this cross-sectional study of approximately 223.7 million retail opioid prescriptions, which were filled between 2006 and 2017, indicated that the amount of opioids prescribed annually increased up to 2010, then decreased, with a net reduction of 13 percent occurring between 2016 and 2017. Other findings noted in the study are that one in three opioids was prescribed for 30 days or more, increasing 3 percent annually (with a two- to three-fold variation among states). High-dose prescriptions decreased by 53 percent, but half of those were filled as extended-release and long-acting formulations. The authors note that the risk of opioid use disorder, overdose, and death from prescription opioids increases as dosage, duration, and use of extended-release and long-acting formulations increase.

BENZODIAZEPINES

Whereas opioids are primarily prescribed for pain, benzodiazepines are prescription sedatives that are typically prescribed for anxiety or insomnia,

[12] MME is a way to calculate the total amount of opioids that takes into account the differences in opioid drug type and strength.

[13] Records were abstracted from the IQVIA Xponent database. See https://www.iqvia.com/locations/united-states/commercial-operations/essential-information/prescription-information (accessed August 2, 2019).

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and they include such drugs as diazepam (Valium), alprazolam (Xanax), and clonazepam (Klonopin) (Olfson et al., 2015). Benzodiazepines are medications that cause mild to severe depression of the nervous system and are also used for sedation during surgery. Benzodiazepines can lead to SUD; furthermore, long-term use can lead to tolerance and the need for higher doses (Fluyau et al., 2018). In a recent study examining benzodiazepine prescribing patterns in the United States, Agarwal and Landon (2019) found that the outpatient use of benzodiazepines had increased substantially—from 3.8 percent to 7.4 percent of ambulatory care visits between 2003 and 2015; concomitant prescribing with other sedating medications had also increased. Furthermore, between 2002 and 2014 the number of opioid recipients who were also dispensed benzodiazepines increased from 7 to 10 percent (a relative percent increase of almost 43 percent), with more than half of the concomitant users receiving both prescriptions from the same prescribers, typically family medicine or internal medicine providers (Hwang et al., 2016). A 2015 study by Olfson et al. examined the benzodiazepine prescribing practices in the United States and focused on patient age and duration of use. Findings indicate that roughly 1 in 20 adults filled a benzodiazepine prescription during the course of 1 year and that the use is substantially higher in women than men and increases with age. Furthermore, among benzodiazepine users there was an age-related increase in long-term use, which may pose added risks of fractures, cognitive decline, and benzodiazepine dependence in older adults. Despite a benzodiazepine-related risk of falls, fractures, and motor vehicle crashes among older people and guidelines that have suggested that older adults avoid the use of benzodiazepine (AGS, 2019), Olfson and colleagues (2015) found that the use of benzodiazepine was approximately three times more prevalent in older than in younger adults.

CONCOMITANT USE OF OPIOIDS AND BENZODIAZEPINES

Concomitant use of opioids and any other central nervous system depressants, including commonly prescribed doses of benzodiazepines, can have significant adverse effects. Those adverse effects are often not fully appreciated by prescribers or by patients taking the medications. This section highlights a few recent studies that examine the concomitant prescribing of opioid and benzodiazepines in the general population and its potential risks, such as overdose and fatalities.

According to the National Institute on Drug Abuse (NIDA), greater than 30 percent of overdoses involving opioids also involve benzodiazepines (NIDA, 2018). Combining both drugs can be unsafe because both drugs sedate users and suppress breathing—often the cause of overdose fatality.

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In 2015, 23 percent of people who died of an opioid overdose also tested positive for benzodiazepines. According to NIDA, in a study of more than 300,000 continuously insured patients receiving opioid prescriptions between 2001 and 2013, the percentage of persons also prescribed benzodiazepines rose from 9 percent in 2001 to 17 percent in 2013. The study showed that people concurrently using both drugs are at higher risk of visiting the emergency department or of being admitted to a hospital for a drug-related emergency (NIDA, 2018).

Overdoses and fatalities are of particular concern when opioids and benzodiazepines are prescribed concurrently. A study by Hirschtritt et al. (2018) examined annual trends in outpatient visits, which included prescriptions for opioids, benzodiazepines, and their combination among adults. Data from the 1993–2014 National Ambulatory Medical Care Survey among non-elderly (i.e., ages 18–64) adults were used to examine the probability of an ambulatory care visit including a prescription for an opioid, benzodiazepine, or both. From 1993 to 2014, benzodiazepine-with-opioid visits increased from 9.8 to 62.5 (odds ratio [OR] = 9.23, 95% confidence interval [CI] = 5.45–15.65) per 10,000 visits. The authors identified a significant increase in the outpatient co-prescription of opioids and benzodiazepines, notably among adults aged 50–64 years during primary care visits.

In a prospective, outpatient-based study of adult patients prescribed high-dose opioids, those concurrently being prescribed benzodiazepines were nearly 10 times more likely to die from overdose than those who were not (Dasgupta et al., 2016). Sun et al. (2017) found that privately insured, non-elderly adults who received prescriptions for both opioids and benzodiazepines were more likely to visit the emergency department or have an inpatient admission for opioid overdose than those prescribed opioids alone. Furthermore, in the emergency department setting between 2004 and 2011, the percentage of opioid overdose deaths among adults that also involved benzodiazepine use increased steadily from 18 to 31 percent (Jones and McAninch, 2015). Using 2013–2014 Medicare Part D data, Hernandez and colleagues (2018) found that in the first 90 days of concurrent opioid and benzodiazepine use, the risk of opioid-related overdose was five times greater than among those using only opioids. However, after 180 days the risk of overdose was no higher among those taking opioids and benzodiazepine concurrently than among those using opioids only. Another study (Yarborough et al., 2018) examining the correlates of benzodiazepine use and adverse outcomes among patients with chronic pain who were prescribed long-term opioid therapy found that dual use was associated with increased odds of falls and emergency department visits.

A study by Schepis et al. (2018) examined data from adults 50 years old and older who participated in the 2015–2016 National Survey on Drug

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Use and Health[14] for the purpose of evaluating a link between prescription opioid or benzodiazepine misuse and suicidal ideation. After controlling for many correlates, the authors found that past use without misuse of prescription opioids or benzodiazepines was not associated with past-year suicidal ideation in older adults.

According to the National Vital Statistics Reports (Hedegaard et al., 2018a), for the top 10 drugs involved in drug overdose deaths in 2016, the proportion of deaths involving both the referent drug and at least one other concomitant drug ranged from 50 percent for methamphetamine to 96 percent for the benzodiazepines alprazolam or diazepam. Approximately 70 percent of drug overdose deaths involving fentanyl or heroin—the top two drugs involved in drug overdose deaths in 2016—involved at least one other specific drug, and drug combinations often involved drugs of different drug classes. For example, the opioid oxycodone and the benzodiazepine alprazolam were mentioned concomitantly in more than 1,500 deaths. In some instances, the most frequently mentioned concomitant drug was in the same drug class as the referent drug (e.g., the opioids fentanyl and heroin were both mentioned in approximately 5,900 deaths). In 2016 unintentional drug overdose deaths most frequently mentioned fentanyl, heroin, and cocaine, while suicides by drug overdose more frequently mentioned oxycodone, diphenhydramine, hydrocodone, and alprazolam. In addition, benzodiazepine users tended to report a longer history of opioid use and prior detoxifications; to use higher doses of opioids; to have a higher frequency of injection drug use, needle sharing, co-occurring use of alcohol and cocaine; and to report greater criminal activity (Darke et al., 2010; Rooney, 1999; Ross and Darke, 2000; Stein et al., 2017). Clearly, concurrent prescribing of opioids and benzodiazepines conveys a significant risk that until recently was underappreciated by patients and health care providers.

OPIOID AND BENZODIAZEPINE USE IN THE DEPARTMENT OF VETERANS AFFAIRS

The committee was tasked with designing a study to examine the association between concomitant prescribing of opioids and benzodiazepines and veterans' deaths and suicides. This section of the chapter provides information on the VA patient population and briefly discusses mental health disorders and pain in veterans and how they are treated in the VA.

[14] The National Survey on Drug Use and Health provides national and state-level data on the use of tobacco, alcohol, illicit drugs (including the non-medical use of prescription drugs), and mental health in the United States. It is a survey of self-reported substance use and mental health. It began in 1971 and is conducted every year in all 50 states and the District of Columbia.

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The focus is on Iraq and Afghanistan war veterans because they have been well studied and recent research has provided a wealth of information about them. This section is not an in-depth look at mental health issues at the VA (NASEM, 2018), nor does it provide a detailed look at VA's prescribing practices. The section also briefly describes the Clinical Practice Guideline for Opioid Therapy for Chronic Pain from the VA and the Department of Defense (DoD) as context for VA treatment practices and the VA's Opioid Safety Initiative.

The VA Population

According to the VA population model estimates, there are approximately 624,000 World War II veterans, 1.5 million veterans from the Korean Conflict, 6.6 million Vietnam era veterans, and 7.2 million Gulf War veterans from Operation Enduring Freedom (OEF), Operation Iraqi Freedom (OIF), and Operation New Dawn (OND) (VA, 2019). The demographic profile of veterans is expected to change in the next few decades. Currently, 91 percent are men and 9 percent are women, according to the VA's 2016 population model estimates. Projections also indicate that the veteran population will become slightly younger by 2045, with 33 percent of veterans younger than 50 (compared with 27 percent in 2016), despite the overall aging of the U.S. population. The number of veterans ages 50–69 is expected to shrink from 39 percent to 33 percent, while the number of those 70 and older is predicted to be around one-third of the total (34 percent) by 2045.

Similar to trends in the overall U.S. population, the U.S. veteran population is predicted to become more racially and ethnically diverse. Between 2016 and 2045, the number of veterans who are non-Hispanic white is expected to drop from 77 percent to 64 percent; the number of veterans who are Hispanic is expected to nearly double from 7 percent to 13 percent; and the number of African American veterans is expected to increase from 12 percent to 16 percent (VA, 2019).

Mental Health and Pain in the VA Population

Many veterans returning from the wars in Iraq and Afghanistan[15] have physical combat injuries, some of which had caused chronic pain or traumatic brain injury (TBI), or both, and are often associated with co-occurring SUDs and other mental health disorders such as posttraumatic stress disorder (PTSD), major depressive disorder, anxiety disorders, and

[15] Often referred to jointly as OEF/OIF/OND for Operation Enduring Freedom, Operation Iraqi Freedom, and Operation New Dawn.

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accompanying serious mental health symptoms such as suicidal ideation (IOM, 2013; NASEM, 2018; Tanielian and Jaycox, 2008). Those co-occurring conditions create significant challenges for prescribing effective and well-tolerated treatments. Furthermore, there are high rates of SUD among veterans, especially those with mental health disorders. The highest rates of SUD comorbidities occur in veterans who have bipolar disorder and schizophrenia and in Vietnam veterans (Petrakis et al., 2011). SUDs in veterans continue to rise despite attempts by the VA to reduce them. SUDs are associated with negative correlates, including medical problems and other psychiatric disorders (e.g., depression and anxiety), interpersonal and vocational impairment, and increased rates of suicide attempts (Teeters et al., 2017).

Mental Health

As early as 2004 it was estimated that more than one-fourth of troops returning from OEF and OIF suffered from mental health disorders (Hoge et al., 2004). Later estimates suggested that one-fifth of the troops reported symptoms of PTSD or depression and that about the same fraction had experienced a probable TBI during deployment (Tanielian and Jaycox, 2008). RAND reports that a full one-third of returning OEF and OIF service members reported symptoms of mental health or cognitive problems (Hosek, 2011; Tanielian and Jaycox, 2008). Furthermore, 18.5 percent of a representative sample of returning service members met the diagnostic criteria for PTSD or depression, 19.5 percent reported a probable TBI during deployment, and 7 percent met the criteria for both a mental health problem and a probable TBI (Tanielian and Jaycox, 2008). In addition, the prevalence of SUD among OEF/OIF/OND veterans is greater than among the general population (Larson et al., 2012). A high incidence of suicide has been reported in veterans, and an average of 20 veterans die by suicide each day. In 2018 the VA identified suicide prevention as its highest priority (GAO, 2018).

Suicidal ideation also has been reported as a potential concerning outcome of the experiences common to veterans. A study of veterans recently returning from deployment reported a 12.5 percent prevalence of suicidal ideation in the previous 2 weeks. The authors found positive associations of suicidal ideation with depression and PTSD and negative associations with the availability of social support (Bossarte et al., 2012). In a more recent study, Arenson et al. (2018) examined the association of suicidal ideation with comorbid PTSD and depression and examined the role of military and psychosocial covariates. Seven hundred forty-six veterans were evaluated

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for PTSD and depression and suicidal ideation using the CAPS[16] and the PHQ-9,[17] respectively. Forty-nine percent of veterans with co-occurring PTSD and depression reported suicidal ideation, a higher rate than those with depression alone (34 percent), PTSD alone (11 percent), or neither (2 percent). In fully adjusted models anger, hostility, anxiety, and alcohol use did not explain the elevated risk of suicidal ideation in the co-occurring group (Arenson et al., 2018). The authors note that, inasmuch as suicidal ideation is a known risk factor for suicide attempts and completed suicides, veterans with co-occurring PTSD and depression represent a vulnerable group that might need more intensive monitoring and treatment in order to reduce suicide risk.

Pain

Although one in three Americans has chronic non-cancer pain (NASEM, 2017), the proportion of veterans who report chronic pain (often related with military service) is higher. For example, in a survey of OEF and OIF veterans, 44 percent reported moderate to severe pain (Toblin et al., 2014).

The prevalence of pain in U.S. veterans was studied by Nahin (2017). The study author compared veterans with non-veterans of similar age and sex. Data from the 2010–2014 NHIS[18] Sample Adult Core and the NHIS Adult Functioning and Disability supplement (AFD) were analyzed. The NHIS asks questions to determine veteran status. The first question is, "Are you currently serving in the armed forces?" If the respondent answers "yes," he or she is coded as active military and is excluded from further questions. If the individual responds "no," he or she is then asked about ever having served on active duty, and those individuals responding "yes" to this question are coded as veterans, while those responding "no" are coded as non-veterans.

Combining data from 5 consecutive years of the NHIS resulted in a population sample of 6,647 veterans and 61,049 non-veterans. Thus, approximately 67,700 adults completed the AFD, and participants with severe pain were identified using a validated pain severity coding system embedded in the NHIS AFD. More veterans (65.6 percent) than non-veterans (56.4 percent) reported having had pain in the previous 3 months. The rate of severe pain was almost 50 percent higher in veterans (9.1 percent) than in non-veterans (6.3 percent). Of the 5-year NHIS AFD sample, 9.7 percent were identified as U.S. military veterans. Veterans were older than non-veterans

[16] CAPS = Clinician-Administered PTSD Scale for DSM-5.

[17] PHQ-9 = Patient Health Questionnaire–depression module.

[18] The NHIS collects data on a broad range of health topics through personal household interviews.

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and more likely to be male. Veterans were also more likely to report having any pain in the prior 3 months than non-veterans (65.6 percent versus 56.4 percent). Nahin noted that the prevalence of severe pain was more common in veterans, particularly in veterans who served in recent conflicts, than in members of the general population (Nahin, 2017).

Another study on pain in veterans examined the combat exposure–pain relationship, with associated mediators and gender as a moderator. More than 2,000 veterans at the VA San Diego Healthcare System completed paper or electronic self-report measures of pain intensity and somatic pain. Analyses examined the associations of pain with combat exposure and PTSD, depression, and resilience as mediators of the combat exposure–pain association. The authors, controlling for age, found that veterans with combat exposure had significantly higher pain intensity and somatic pain. Further PTSD and depression scores significantly mediated the combat exposure–pain relationship. Gender was also found to moderate the combat exposure–pain intensity association through depression scores (Buttner et al., 2017). Thus, combat exposure is associated with pain intensity and somatic pain, with greater levels of PTSD and depression mediating the combat exposure–pain link and gender moderating the depression-mediated combat exposure–pain association.

Treatment of Chronic Pain in the VA

Treatment of chronic pain is complex, and the VA is focusing on veteran-centric approaches that can be tailored to individual veterans' needs.[19] This section highlights a few studies that focus on chronic pain treatment in the VA.

The prevalence of opioid prescriptions among veterans increased from 18.9 percent to 33.4 percent in fiscal years 2004 to 2012, and the groups with the highest prevalence of opioid use were women and young adults (i.e., 18–34 years old) (Mosher et al., 2015). Furthermore, within 3 months of returning from Afghanistan, 44 percent of the military veterans reported chronic pain, and 15 percent reported using opioids (Toblin et al., 2011, 2014). Chronic pain has also been associated with poorer physical function, independent of comorbid mental health problems, in OEF and OIF veterans.

A study by Bohnert et al. (2011) examined the association of maximum prescribed daily opioid dosage and dosing schedule (as needed, regularly scheduled, or both) with the risk of opioid overdose death among patients with cancer, chronic pain, acute pain, and SUDs. The authors examined

[19] Laurence Meyer's statement to the Senate Committee on Appropriations Subcommittee on Military Construction, Veterans Affairs, and Related Agencies, November 15, 2017.

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VHA data from 2004 through 2008 for all unintentional prescription opioid overdose decedents (n = 750) and from a randomly selected cohort of patients (n = 154,684) who used medical services in 2004 or 2005 and received opioid pain therapy. That analysis demonstrated that, among patients receiving opioid pain medication, higher doses of opioids were associated with an increased risk of opioid overdose deaths.

Edlund et al. (2014) analyzed VHA administrative and pharmacy data from 2009 to 2011 in an effort to characterize the dosing and duration of opioid therapy for chronic non-cancer pain. The authors calculated the distribution of individual mean daily opioid doses, individual total days covered with opioids in 1 year, and individual total opioid dose in 1 year. They found that the median daily dose was 21 MMEs, but about 4.5 percent of individuals had a mean daily dose that was higher than 120 MMEs. The median days covered in 1 year was 115 to 120 for those receiving opioids. Fifty-seven percent had at least 90 days covered with opioids per year. Major depression and PTSD were positively associated with receiving high doses of opioids, but non-opioid SUDs were not. Among VHA patients with chronic non-cancer pain, opioid therapy was often prescribed, but for most patients the average daily dose was modest. Doses and duration of therapy were unchanged from 2009 to 2011.

Lisi et al. (2018) performed a cross-sectional analysis of VA administrative data to examine the sociodemographic and clinical characteristics associated with opioid use among veterans of OEF/OIF/OND. The analysis included only veterans who had at least one visit to a chiropractic clinic between 2004 and 2014 and at least one filled prescription for opioids within a window of 90 days before to 90 days after the index chiropractic clinic visit. More than 14,000 veterans with at least one chiropractic visit were identified, and 4,396 (31.3 percent) had received one or more opioid prescriptions.[20] Moderate to severe pain, PTSD, depression, and current smoking were associated with a higher likelihood of receiving an opioid prescription. However, the percentage of veterans receiving opioid prescriptions was lower in each of the three 30-day time frames assessed after the index chiropractic visit than before. The authors did not attempt to assess causation or otherwise explain that observation.

Gellad et al. (2018) found that veterans receiving medications from the VA and Medicare (sometimes concurrently) were at an increased risk of high-dose opioid exposure. Specifically, among veterans dually enrolled in

[20] Opioid medications included formulations from the CN101 VA drug class such as butorphanol, codeine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, morphine, nalbuphine, opium, oxycodone, oxymorphone, pentazocine, propoxyphene, and tapentadol. Buprenorphine and methadone were excluded because they are predominantly used to treat opioid use disorder.

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the VA and Medicare Part D, filing prescriptions from two different health care providers was associated with more than two to three times the risk of high-dose opioid exposure. The authors examined records of veterans enrolled in the VA and Medicare Part D who filled at least two opioid prescriptions in 2013. The outcomes examined were the proportion of patients with a Pharmacy Quality Alliance measure of opioid–benzodiazepine overlap (≥2 filled prescriptions for benzodiazepines with ≥30 days of overlap with opioids) and the proportion of patients with high-dose opioid–benzodiazepine overlap (≥30 days of overlap with a daily opioid dose >120 MMEs). Augmented inverse probability weighting regression was used to compare those measures by prescription drug source: the VA only, Medicare only, or the VA and Medicare. Of 368,891 eligible veterans, 18.3 percent received prescriptions from the VA only, 30.3 percent from Medicare only, and 51.4 percent from both the VA and Medicare. The proportion with Pharmacy Quality Alliance opioid–benzodiazepine overlap was larger among the veterans who had received prescriptions from two prescribers than in the VA-only group (23.1 percent versus 17.3 percent) and in the Medicare-only group (23.1 percent versus 16.5 percent). The proportion with high-dose overlap was also larger among the group who received prescriptions from two prescribers than in the VA-only group (4.7 percent versus 2.3 percent) and the Medicare-only group (4.7 percent versus 2.9 percent). Thus, among a national cohort of veterans dually enrolled in the VA and Medicare, receiving prescriptions from both sources was associated with a greater risk of receiving potentially unsafe overlapping prescriptions for opioids and benzodiazepines. However, as noted by the authors, the study had several weaknesses, including the data being from 2012, an inability to capture medications purchased without insurance, and the potential presence of unmeasured confounding.

Finally, a recent study found that more than half of VA medical enrollees are also covered by Medicare. Those veterans can choose where they get their prescriptions, which may lead to unsafe opioid use. Moyo et al. (2019) conducted a nested case-control study designed to evaluate the association between dual-system opioid prescribing and death from prescription opioid overdose. The cases and controls were identified from all veterans enrolled in both the VA and Medicare Part D. The 215 case patients who died of prescription opioid overdose in 2012 or 2013 were matched with 833 living control patients on the basis of date of death (i.e., the index date), using sex, race/ethnicity, disability, enrollment in Medicaid or low-income subsidies, managed care enrollment, region and rurality of residence, and a medication-based measure of comorbid conditions. The authors categorized the "exposure," or the source of the opioid prescription within 6 months of the index date, as the VA only, Part D only, or the VA and Part D. The outcome measured was unintentional or undetermined-intent death from

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prescription opioid overdose, identified from the National Death Index (NDI). The study found that, overall, 60 case patients (28 percent) and 117 control patients (14 percent) had received dual opioid prescriptions and that dual users had significantly higher odds of death from prescription opioid overdose than those who received opioids from the VA only or Part D only.

Commenting on the findings of the Moyo et al. (2019) study, Meyer and Clancy (2019) said in an accompanying editorial that the VA is taking steps to address its significant opioid problem, such as exploring and using non-pharmacological alternatives for pain management and expanding access to different treatment methods such as physical therapy, yoga, and acupuncture. Meyer and Clancy reported that the VA has documented decreases in opioid prescribing as well as in the number of patients prescribed opioids and benzodiazepines in combination.

The VA/DoD Clinical Practice Guidelines

In light of the epidemic of opioid misuse and opioid use disorder, including among veterans, the VA and DoD published *Clinical Practice Guidelines for Management of Opioid Therapy for Chronic Pain* in 2010 and updated those guidelines in 2015 to assist health care providers (VA/DoD, 2017). The VA/DoD guidelines were developed specifically for service members, veterans, their families, and the communities to which they returned. The guidelines incorporate the characteristics and needs of those populations regarding specific risk factors (e.g., suicide, SUDs, and other co-occurring medical and mental health conditions).

The VA/DoD's stated goal for the guidelines "is to improve the patient's health and well-being by providing evidence-based guidance to providers who are taking care of patients on or being considered for LOT [long-term opioid therapy]" (VA/DoD, 2017, p. 5). The VA identifies the most important risk factors for the development of opioid-related adverse events in its population as being the duration and dose of opioid analgesic use, and it presents numerous additional factors that increase the risk of adverse outcomes that should be considered prior to or continuing opioid therapy (VA/DoD Clinical Practice Guidelines for Opioid Therapy for Chronic Pain, 2017).

The VA Opioid Safety Initiative

In 2013 the Opioid Safety Initiative (OSI) was launched by the VA in an effort to help ensure that veterans were prescribed opioids in a safe manner. Since that time (the fourth quarter of fiscal year 2013 to the first quarter of fiscal year 2018), the percentage of patients dispensed an opioid has

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decreased from about 17 percent to about 10 percent, or by about 267,000 veterans (GAO, 2018). According to the VA, the requirements of the OSI were communicated to all veterans integrated service networks to ensure that opioids were used in a safe and effective manner. The implementation of the OSI included the provision of a clinical "dashboard," based on the electronic health record data, that is used to identify patients who might be high risk for adverse outcomes with opioid use and identify providers whose prescribing practices might not reflect the best evidence for improving patient care. The OSI includes specific indicators, such as the number of unique pharmacy patients dispensed an opioid and the unique patients on long-term opioid therapy.

According to the VA, the goals of the OSI are related to increased education, monitoring, safe and effective prescribing and management methods, tool development, collaboration, and use of alternative pain treatment. Furthermore, the VA notes that as part of the OSI,

> the VA launched the Opioid Overdose Education and Naloxone Distribution program, which was implemented as a risk mitigation strategy aimed at reducing deaths from opioid overdose. The program components included education and training regarding the following topics: opioid overdose prevention, recognition, and rescue response; risk mitigation strategies; and issuing naloxone kits, which can be used as an antidote to opioid overdose. Other initiatives are aimed at improving the safe use of opioids, including the OSI Toolkit and the patient guide *Taking Opioids Responsibly for Your Safety and the Safety of Others: Patient Information Guide on Long-term Opioid Therapy for Chronic Pain*. The OSI Toolkit was developed to provide clinicians with materials to inform clinical decision-making regarding opioid therapy and safe opioid prescribing. (VA, 2017)

STATEMENT OF TASK

In 2018 the U.S. Congress appropriated $500,000 to study outcomes in veterans prescribed both opioids and benzodiazepines. The Consolidated Appropriations Act of 2018[21] included the following language:

> "*Overmedication*.—As indicated in the Senate report, and in addition to the funding levels highlighted for opioid abuse above, the agreement provides $500,000 for the National Academies of Sciences, Engineering, and Medicine to conduct an assessment of the potential overmedication

[21] Public Law 141, 115th Congress (March 23, 2018).

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of veterans during fiscal years 2010 to 2017 that led to suicides, deaths, mental disorders, and combat-related traumas."

"*Overprescription Prevention Report*.—The Committee is discouraged by multiple GAO reports retaining VHA on the "high-risk" list and the unfathomable increase in polydrug use and narcotics prescriptions by VA related to pain management and mental health treatment. Specifically, combinations of opioid and Benzodiazepines have proven fatal when taken concurrently, with research demonstrating this phenomenon for nearly 40 years. The Committee provides $500,000 to enter into an agreement with the National Academies of Sciences, Engineering, and Medicine to conduct an assessment to research, collect, and analyze the potential overmedication of veterans during fiscal years 2010–2017 that led to veterans deaths, veterans suicides, treatment of mental disorders, pain management practices, mental health staffing levels, and combat related trauma."

The VA contacted the National Academies to address the language in the Consolidated Appropriations Act. To address the intent of the congressional language and given the appropriated resources, the VA and the National Academies agreed on the following Statement of Task (see Box 1-1).

The VA and the National Academies understood that to actually conduct such a study (i.e., as specified by congressional language), a protocol and study design would need to be proposed. Thus, this report can be considered as a first step in addressing the congressional language.

APPROACH TO THE TASK AND ORGANIZATION OF THE REPORT

The National Academies appointed an eight-person committee with expertise in pharmacoepidemiology, RCTs, pain management, addiction, and psychiatry to address the task. The committee held three in-person

BOX 1-1
Statement of Task

An ad hoc committee under the auspices of the National Academies of Sciences, Engineering, and Medicine will develop a protocol/study design to evaluate the relationship between concomitant opioid and benzodiazepine medication practices at the Department of Veterans Affairs, for treating mental health and combat-related trauma, which potentially led to veterans' deaths and suicides.

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meetings and one phone meeting over a 6-month period. In an effort to better understand the task and the intent of the congressional language, the committee met, at its first meeting, with VA leadership responsible for opioid and benzodiazepine prescribing policy in addition to those involved in research and data collection and oversight. Following that meeting the committee interpreted the congressional language and committee charge as a desire on the part of the Congress to study the concomitant prescribing of opioids and benzodiazepines in veterans when used to treat mental disorders and pain and in the context of high levels of combat-related trauma, including PTSD, as well as the potential impact of those medications on veterans' deaths and suicides. Given that understanding of the task and with a consideration of the existing literature on this topic, the committee focused on the following research question: What were the effects of (1) opioid initiation and (2) tapering (i.e., discontinuing or reducing opioid dosage) strategies in the presence of benzodiazepines in veterans on all-cause mortality and suicide mortality from 2010 to 2017?

Thus, in addressing its task, the committee proposes target trial protocols and corresponding observational studies to answer the research question. The committee agreed that, ideally, one or more RCTs would be conducted to answer questions about the comparative effectiveness or safety of opioids and benzodiazepines. However, RCTs are frequently impractical in this situation (Armstrong, 2012). The committee also agreed that observational data could be analyzed to approximate an RCT when conducting an RCT was not possible or practical. Causal inference from large observational databases can be viewed as an attempt to emulate a randomized experiment in order to answer the question of interest (Hernán and Robins, 2016). The committee describes observational data analysis strategies to emulate two target trials—one for the initiation of opioids in the presence of benzodiazepines and one for the tapering of opioids in the presence of benzodiazepines.

In Chapter 2 the committee describes protocols for target trials for opioid initiation and tapering to respond to the charge. In Chapter 3 the committee proposes strategies and analytic plans for implementing observational studies to emulate the target trials using existing VA data. The committee notes that the proposed studies are not the only way to respond to the Statement of Task. Should the VA or others be interested in conducting related studies, such as the tapering of benzodiazepines for patients prescribed both opioids and benzodiazepines, those studies can be modeled on the committee's approach.

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2

Specifying the Target Trial

A useful procedure to precisely articulate a causal question is to describe a "target trial," that is, a hypothetical randomized trial that would answer the question of interest if resource constraints or ethical issues did not preclude conducting it. The process of defining a target trial aids both in the definition of research questions and in the evaluation of various observational data sources and analysis strategies. To address the research question, the target trial is then emulated using available data sources.

The committee proposes two target trials that address the questions raised in the Statement of Task and then proposes a procedure to emulate those trials using existing Department of Veterans Affairs (VA) data. This chapter describes the research question the committee chose to address based on the Statement of Task and lays out the target trial framework. Chapter 3 follows by setting forth procedures for the use of observational data to emulate the target trials described in this chapter. For clarity, the committee uses the term "target trial" to refer to the hypothetical randomized trial that would directly address the research question; "protocol" to include all components of the design (e.g., patient enrollment, treatment strategies, outcome) and analysis of the target trial; and "observational analysis" to refer to the data analysis proposed to emulate the target trial using existing observational data.

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DEFINING THE QUESTION

The committee interpreted its task to focus on the following research question: What were the effects of opioid initiation and tapering[1] strategies in the presence of benzodiazepines in veterans on all-cause mortality and suicide mortality from 2010 to 2017?[2] The committee's focus on this specific research question was a result of its interpretation of its task and the committee's review of prior literature.

First, the committee determined that initiation and tapering represent two critical decision points in opioid treatment. A decision to initiate opioids is of necessity made for all people who eventually progress to long-term opioid therapy. Opioids can be initiated in multiple ways, including (1) patients with chronic pain are given an initial opioid prescription with the intent of treating them with long-term opioid therapy; (2) patients who have surgery, whether for a chronic pain condition or an unrelated condition, are given opioids post-operatively, and some of them stay on opioids long-term; and (3) patients are started on opioids for an injury or other non-surgical acute pain problem (e.g., acute low back pain, trauma), and some of them stay on opioids long-term. For simplicity of exposition, the committee decided to focus on the first group. However, all three groups contribute to the larger body of individuals who begin long-term opioid therapy and could be the focus of separate—and equally important—studies.

Tapering—broadly defined as any reduction in daily opioid dosage for a patient who is on long-term opioid therapy—is the second decision point of focus identified by the committee. Given the focus of the Statement of Task on adverse consequences, tapering is highly relevant for two main reasons: (1) the desire to avoid the known adverse consequences of long-term opioid therapy, such as increased mortality, is often a motivation for the decision to taper opioid dosage rather than continuing treatment, and (2) some clinicians and patients have raised concerns that, rather than reducing the risk for harm, tapering patients who are tolerant to opioids may contribute to adverse consequences, particularly suicide (discussed later in this chapter under "Potential Harms of Treatment"). The committee concluded that a study of the effect of opioid tapering on all-cause mortality and suicide would reduce clinical uncertainty and would be timely in the context of current opioid policy and practice decisions.

Second, the Statement of Task specifically focuses on "concomitant opioid and benzodiazepine" prescribing. After reviewing prior studies (see

[1] Tapering is defined as opioid dosage reduction or discontinuation (Frank et al., 2017).

[2] The Consolidated Appropriations Act of 2018, Public Law 115-141, 115th Congress (Second Session), from which the committee's Statement of Task was written, specified an interest in the time period of "fiscal years 2010 to 2017" (see Chapter 1).

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Chapter 1), the committee concluded that patients receiving both medications are at a significantly higher risk for adverse outcomes than patients on opioids alone and that there was very limited evidence regarding opioid prescribing strategies specifically for patients receiving benzodiazepines. Thus, although the effects of opioid initiation and tapering on patient outcomes are important areas of inquiry, the focus on patients on benzodiazepines is more responsive to the Statement of Task and also addresses a particularly important sub-group of patients.

Finally, the Statement of Task specifically focuses on the outcomes of "deaths and suicides." The committee believed that a focus on all-cause mortality appropriately reflects the fundamental importance to clinical decisions of evidence of increased or decreased risk of death from any cause. Additionally, the inclusion of suicide as an outcome separate from all-cause mortality is relevant to the concerns that patients, clinicians, and other stakeholders have about suicide among veterans generally as well as, specifically, among veterans with pain. The committee also discussed a number of other adverse outcomes as well as potential benefits of treatment that could be considered as secondary outcomes, depending on availability of data sources. Pain level, functional status, and quality of life are particularly important outcomes to assess in combination with the potential harms of treatment. However, the committee did not consider those outcomes as strictly relevant to the Statement of Task.

THE TARGET TRIAL FRAMEWORK

The committee chose to employ a "target trial" methodology; that is, it created a hypothetical randomized trial and described how it can be emulated (i.e., closely approximated) by an observational study to address the research question. A randomized trial is the preferred method for addressing causal questions about the comparative effectiveness and safety of medical treatments. For every such question, one can imagine a randomized trial that, if large enough and completed successfully, might answer that question. That hypothetical trial is referred to as the *target trial*. In practice, the target trial might be costly, infeasible, unethical, or simply too time consuming and thus not be practical to carry out. Thus, researchers must rely on available observational data (Hernán and Robins, 2016).

Researchers often perform observational analyses of health care databases when the target trial is not a viable option for answering the causal question of interest (Strom et al., 2012). Causal inference from observational databases can be viewed as an attempt to emulate the target trial. If the emulation is successful, then each analysis of the observational data is expected to yield the same effect estimates as the corresponding analysis

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specified in the target trial, had it been successfully conducted. To guide decisions about which of several competing analytic strategies to use, causal analyses of observational data need to be evaluated with respect to how well they emulate the analyses that would occur within the corresponding target trial. Besides providing a structured process for the evaluation and criticism of observational studies, the target trial framework helps avoid common methodologic pitfalls of causal inference from observational data (Sterne et al., 2016).

An important thing to note is that observational data can only be used to emulate pragmatic target trials, that is, trials that compare treatment strategies currently in use and under the usual conditions in which they are applied in the real world (e.g., no placebo control, no blinding, no intensive monitoring). The necessarily pragmatic nature of the emulated target trial is not a limitation when the goal is comparing the effects of realistic treatment strategies in individuals who participate in decisions about their own health care.

This chapter outlines sample protocols for target trials that would quantify the effects of the initiation and discontinuation of opioids in the presence of benzodiazepines on all-cause mortality and suicide and that could be emulated using observational data collected by the VA. Such target trials could, in theory, be conducted, though it is debatable whether the standard of clinical equipoise[3] is met for the research questions of interest. Additionally, recent trials indicate that many patients are unwilling to have their access to opioid medications subject to randomization. For example, 41 percent of VA opioid-naïve patients with a chronic pain diagnosis declined to participate in a randomized trial comparing stepped opioid and opioid-sparing protocols (Krebs et al., 2018). Not only does this mean that such randomized controlled trials would be difficult, if not impossible, to conduct and would take many years to provide answers, but also the degree of self-selection might limit their generalizability to the broader population of VA patients with chronic pain. Furthermore, such studies would need to have very large samples because the outcomes of interest (death and suicide) are rare. Therefore, observational studies have a particularly critical role—and, indeed, even possible advantages—in terms of generalizability.

The proposed research strategy has two basic steps: (1) asking the causal question, and (2) answering the causal question. Step 1 is aided by specifying the protocol of the target trial, and Step 2 is done by either conducting the target trial when possible or by emulating as closely as possible the target trial using observational data. Note that the data requirements

[3] *Clinical equipoise*, a concept taken from medical ethics, asserts that there should exist no decisive evidence that one of the treatment assignment groups is more effective or more safe than another (Cook and Sheets, 2011; London, 2017).

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and data analysis procedures for Step 2 follow naturally from the explicit causal questions articulated in Step 1. The committee begins by describing Step 1.

The protocol of the target trial, like that of any other randomized trial, includes seven components: eligibility criteria, treatment strategies, treatment assignment, start and end of follow-up, outcomes, causal contrasts, and the statistical analysis plan (Hernán and Robins, 2016). Definitions of the baseline (or the start of the follow-up) and time-varying covariates, potential confounders, and the variables defining key sub-groups need to be included, as appropriate, within the seven components of the protocol. Therefore, the specification of the target trial needs to include the complete specification of each of these components (see Table 2-1).

TABLE 2-1 Key Components of the Target Trial Protocol

Protocol Component	Description	Notes
Eligibility criteria	How the patient population is recruited into the trial.	All inclusion and exclusion criteria are based on characteristics ascertained exclusively at baseline.
Treatment strategies	Each of the clinical interventions that are to be compared.	The description needs to include the initial treatment as well as protocol-approved reasons for discontinuation or switching.
Treatment assignment	How participants will be assigned to each treatment strategy at baseline.	The assignment is randomized, possibly conditional on baseline prognostic factors. Patients will be aware of the treatment strategy to which they were assigned.
Start and end of follow-up	Define when the follow-up period starts and ends for each participant.	For each eligible individual, follow-up starts at baseline (the time of treatment assignment) and ends at death, outcome, loss to follow-up, or administrative end of follow-up.
Outcomes	Outcomes of interest and how to ascertain them.	If possible, include negative controls, i.e., outcomes that are known to be unaffected by the studied treatments.
Causal contrast	What comparative effects of the treatment strategies will be estimated.	The intention-to-treat effect (the comparative effect of being assigned to the treatment strategies at baseline) or per-protocol effect (the comparative effect of receiving the treatment as specified in the protocol).

continued

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TABLE 2-1 Continued

Protocol Component	Description	Notes
Statistical analysis	How to estimate the intention-to-treat effect or per-protocol effect via intention-to-treat and per-protocol analyses that appropriately adjust for pre- and post-baseline prognostic factors associated with adherence and loss to follow-up.	Investigators should specify and measure the covariates potentially related to treatment choice, adherence, and outcomes at baseline and during the follow-up. Other variables that may need to be specified include those that define key sub-groups.

SOURCE: Hernán and Robins, 2016.

Because there are many clinical questions about the effects of opioids and benzodiazepines that remain unanswered, multiple target trials might be proposed. As described above, this document focuses on two target trials, with each one comparing multiple clinical strategies in different patient populations. Specifically, one target trial examines the initiation of treatment for patients with chronic pain already taking benzodiazepines, and the other one examines strategies for the tapering of opioids in patients with chronic pain who are currently being treated with both benzodiazepines and opioids. Researchers may want to propose alternative target trials or variations of the committee's proposed trials, for example, trials with different eligibility criteria or treatment strategies. Therefore, this document should not be viewed as a rigid description of the target trials that must be emulated before all other options, but rather as guidance on how to structure the specification of a target trial that precisely characterizes the research question. However, the committee believes the two example target trials are the minimum needed to address the key questions pertinent to the Statement of Task. Chapter 3 will focus on the adequacy of the available observational data to emulate the target trial and the data analyses required to carry out the emulation.

It is rare that one is able to emulate the ideal trial that would be of greatest interest. Rather, the available observational data will usually impose a number of constraints concerning the eligibility criteria, treatment strategies, available sample size (especially in sub-groups), and other components of the target trial protocol. Therefore, the specification of the design of the target trial and the associated analyses will typically be an iterative process in which investigators will learn which particular target trials may be reasonably emulated by the available observational data.

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ADDRESSING THE RESEARCH QUESTION VIA A TARGET TRIAL THAT CAN BE EMULATED USING AVAILABLE OBSERVATIONAL DATA

The research question, "What were the effects of opioid initiation and tapering strategies, in the presence of benzodiazepines, in veterans, on all-cause mortality and suicide mortality from 2010 to 2017?" results in two distinct populations for study, namely: (1) veterans who enter the study on benzodiazepines but are not yet receiving opioids and suffering from pain-related conditions for which opioids were, during the study period, considered reasonable treatment options; and (2) veterans who enter the study actively treated with both benzodiazepines and opioids and for whom a reduction in their dosage of opioids was a treatment option. Thus, the committee proposes two trials, a *treatment initiation trial* and a *tapering trial,* with the first intended to identify optimal treatment initiation strategies for patients with pain who are taking benzodiazepines but are not actively being treated with opioids, and with the second intended to identify optimal approaches for reducing opioid dosages for patients already being treated with both opioids and benzodiazepines. It is important to note that the term "treatment" is used here to include a wide range of pharmacologic and non-pharmacological options.

The committee acknowledges that benzodiazepine initiation and tapering are also important and clinically relevant topics. However, given that the Centers for Disease Control and Prevention (CDC) guidelines recommend that "it might be safer and more practical to taper opioids first" (Dowell et al., 2016, p. 15), the committee chose to focus its proposed trials on the initiation and tapering of opioids and note that the committee's model can be used as a template for other target trials and emulations, such as the initiation and tapering of benzodiazepines in the presence of opioids.

The committee applied the target trial protocol framework (see Table 2-1) to guide the design of the observational analyses proposed in Chapter 3. Table 2-2 describes considerations and options for the design components for each of the two target trials. The committee thought that a trial with the sample size necessary to study suicide and all-cause mortality (or the corresponding observational analyses) would be very likely to rely on administrative data sources rather than on intensive patient assessments. Thus, in designing the protocol for the target trials, the committee thought about the feasibility of emulating those trials using existing data. Nonetheless, Table 2-2 reflects a range of considerations for researchers to consult for finalizing the target trials and corresponding observational study designs that are not limited to options that could be based on available VA data. It is likely that limited availability and quality of observational data will result in a modification of the initial target trial specifications.

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TABLE 2-2 Protocol Considerations for Treatment Initiation and Tapering Target Trials

	Treatment Initiation Trial	Tapering Trial
Eligibility criteria	Considerations: • Qualifying chronic pain diagnoses • Minimum dose and treatment days supply of baseline benzodiazepine use • Length of period without any analgesics prior to initiation • Exclusion criteria, e.g., serious illness, acute pain treatment indications, contraindications for specific analgesic types, etc.	Considerations: • Long-term opioid therapy definition, e.g., minimum length of treatment • Presence of opioid tolerance • Level of baseline benzodiazepine use • Exclusion criteria, e.g., serious illness, opioids used for treatment of opioid use disorders, etc.
Treatment strategies	Pain treatment modalities to consider: • Opioids • Other pharmacologic treatments: o NSAID o Anticonvulsants o Antidepressants o Topical therapies o Medical marijuana • Non-pharmacologic treatments: o Behavioral therapies (e.g., cognitive behavioral therapy) o Physical therapy o Other	Possible opioid dosage strategies to consider: • No change • Complete discontinuation • Speed of tapering • Switch to buprenorphine Non-opioid pain treatments that could be included as additional strategies (e.g., using a factorial design): • Other pharmacological treatments; same list as Initiation Trial • Non-pharmacological treatments; same list as initiation trial
Treatment assignment	Randomization level can be: • Patients • Clinicians • Health care facilities Randomization can be conditional on risk factors. Assignment can be blinded or un-blinded. (Same for initiation and tapering trials)	
Start and end of follow-up	Considerations for censoring: • Select length of follow-up; trade-off between longer time to measure outcomes and greater degree of non-adherence to treatment strategy • Lag time for availability of administrative records • Impact of patients' stopping use of VA care on measures of non-mortality outcomes and potential time-varying confounders (Same for initiation and tapering trials)	

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TABLE 2-2 Continued

	Treatment Initiation Trial	Tapering Trial
Outcomes	All-cause mortality Suicide deaths Injury deaths Circulatory deaths • Respiratory • Cardiovascular Overdose • Intentional • Unintentional Falls and fractures Function and quality of life Health care utilization Mood symptoms • Depression • Anxiety • Fatigue • Insomnia Disability Pain level Anxiety level (Same for initiation and tapering trials)	
Causal contrast	Intention-to-treat effect Per-protocol effect (Same for initiation and tapering trials)	
Statistical analysis	Population sub-groups that could be examined for potential effect modification: • Premorbid conditions o Medical o Mental health o Substance use disorders (SUDs) • Perception that a patient has a SUD or exhibits opioid misuse behaviors • Prescription for central nervous system depressant drugs (e.g., gabapentinoids, muscle relaxants, hypnotics) • Specific pain diagnoses • Pain severity • History of overdose or suicide attempt (Same for initiation and tapering trials)	

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The committee proposes first to characterize prescribing patterns along with the use of non-pharmacological treatment strategies and to use this information to guide the specification of the particular treatment strategies that would be compared in the target trials. As will be described in Chapter 3, the observational data can then be used to emulate a target trial that compares these existing treatment patterns in order to determine the relative mortality risk and whether risk varies across sub-groups defined by baseline characteristics.

While Table 2-2 provides the general considerations and a variety of options for each of the components of the target trials, a greater level of specificity in definition and in the selection of options is required to inform the translation of each target trial component into a trial emulation or observational data analysis strategy. In Table 2-3 the committee illustrates a suggested set of initial choices for the required specification of the target trials. The choices listed in this table should be considered preliminary because the specification of the target trial components is an iterative process, with insights from pilot analyses of the available observational data resulting in changes to the definitions and choices that can be incorporated into a feasible and valid analysis plan. Figure 2-1 illustrates the two trials described in Table 2-3.

TABLE 2-3 Proposed Specifications for Initiation and Tapering Target Trials

Protocol Component	Initiation Target Trial	Tapering Target Trial
Eligibility criteria	Chronic pain diagnosis[a] No prescriptions for opioids or non-aspirin NSAIDS in the past 90 days Long-term benzodiazepine therapy (defined based on pilot data) Exclude: Individuals with serious illness[b] Individuals prescribed opioids used for treatment of opioid use disorder Individuals with surgery or acute painful injury within the past 90 days[c]	Long-term opioid therapy defined as 3+ opioid fills ≥21 days apart in a ≥84-day period for ≥84-day supply (Larochelle et al., 2016) Average opioid MME[d]/day is ≥30 over the prior 84 days[e] Long-term benzodiazepine therapy (defined based on pilot data) Exclude: Individuals with serious illness Individuals prescribed opioids for the treatment of opioid use disorder Individuals with surgery or acute painful injury within the 90 days prior to baseline

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TABLE 2-3 Continued

Protocol Component	Initiation Target Trial	Tapering Target Trial
Treatment strategies	(a) Initiation of treatment with an opioid and continuation for 1 year, unless not tolerated by the participant (b) Initiation of treatment with a non-aspirin NSAID and continuation for 1 year, unless not tolerated by the participant	(a) No dosage reduction: ≤5% average decrease per month for 3 months (b) Slow dosage reduction[f]: >5% but ≤10% average decrease per month for 3 months (c) Moderate to fast dosage reduction: >10% average decrease per month for 3 months (d) Complete discontinuation within 3 months from baseline Participants who cannot tolerate their assigned dosage change will be excused from following their assigned strategy. Percentage of taper is relative to opioid dose at baseline and is calculated over the next 3 months. After that period, dosage is left to the physician's discretion.
Treatment assignment	Individual randomization, stratified on baseline dose	
Start and end of follow-up	Start of follow-up (baseline): start of treatment for chronic pain, defined as being dispensed one or more prescriptions of an opioid or NSAID for at least a 30-day supply over a 30-day period (this could be across multiple prescriptions), and also having a chronic pain diagnosis. End of follow-up: the earliest of 18 months,[g] death, or administrative end of follow-up (end of the study).	Start of follow-up (baseline): time of assignment to a treatment strategy. End of follow-up: the earliest of 6 months,[b] death, or administrative end-of-follow-up (end of the study).
Outcomes	(a) All-cause mortality (b) Death from suicide (Same for initiation and tapering trials)	
Causal contrast	(a) Intention-to-treat effect (b) Per-protocol effect (Same for initiation and tapering trials)	

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TABLE 2-3 Continued

Protocol Component	Initiation Target Trial	Tapering Target Trial
Statistical analysis	Intention-to-treat analysis: check for balance on key variables, e.g., mental health diagnoses and substance use disorders. Per-protocol analysis: patients will be censored at the time they deviate from their assigned strategy. To adjust for the potential selection bias induced by censoring, inverse probability weighting will be used. The weights will be a function of the baseline and post-baseline (time-varying) confounders. Both analyses may require further adjustment for selection bias due to loss to follow-up. Pre-specified sub-groups to be examined for potential effect modification include, e.g., pain severity, history of overdose, history of suicide attempt, non-suicide death (for the suicide death analysis).	

[a] The intention of this definition is to exclude opioids and NSAIDs prescribed for acute pain. However, researchers should consider that there might be a large proportion of veterans prescribed opioids for whom there is not a chronic pain diagnosis (Edelman et al., 2013).

[b] Serious illness is defined by Kelley and Bollens-Lund (2018) as a health condition that carries a high risk of mortality and negatively affects a person's daily functioning. The committee recommends operationalizing this as any of the following conditions: cancer, chronic obstructive pulmonary disease, congestive heart failure, dementia, or severe neurologic disorder (e.g., amyotrophic lateral sclerosis, multiple sclerosis).

[c] 90 days was chosen to minimize likelihood of opioids being prescribed for acute rather than chronic pain conditions. However, the committee acknowledges that the choice of 90 as opposed to 30 or 60 is arbitrary.

[d] MME = morphine milligram equivalent.

[e] This threshold was used because labeling for OxyContin extended release defines "opioid tolerant" as consuming 30 MME/day. Researchers might consider a lower dose threshold if the purpose is to include anyone who could be considered for a taper.

[f] Speed of tapering: there is a lack of primary literature on the optimal rate of tapering speed (i.e., rate of dosage decrease per week/month). Within the context of concomitant opioid and benzodiazepine use and likely psychiatric comorbidity, a more conservative approach would be prudent.

[g] The committee felt that the 18-month timeline balanced the desire for a longer length of follow-up than prior initiation studies with the fact that there would be a greater degree of non-adherence from the assigned treatment group for longer lengths of follow-up.

[h] The committee felt that the 6-month timeline balanced a desire for a longer length of follow-up with potential for non-adherence and a concern that suicide as a relatively short-term outcome in tapering studies.

The sections that follow describe and provide a rationale for the choices made in Table 2-3 and Figure 2-1.

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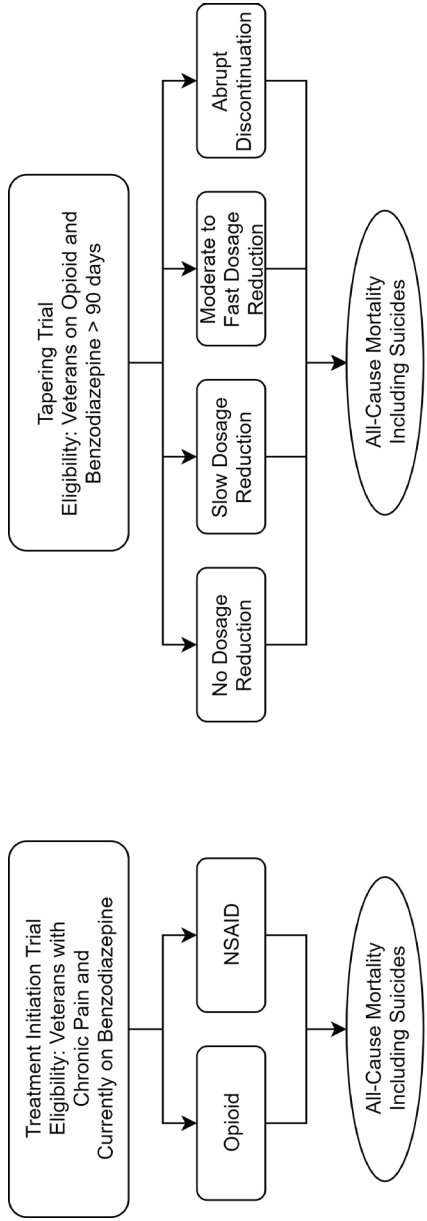

FIGURE 2-1 Opioid treatment initiation and tapering target trial schematic.
NOTE: NSAID = nonsteroidal anti-inflammatory drug.

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ELIGIBILITY CRITERIA

Eligibility criteria determine which patients can be enrolled into a trial. The eligibility criteria for each of the example target trials are intended to define a patient population for which a comparison of the outcomes associated with alternative management strategies would be informative with respect to the research question. Additionally, the treatment strategies to be compared must be realistic options for patients meeting the eligibility criteria. For example, for a comparison of outcomes under different approaches for managing patients with long-term opioid and benzodiazepine use, the eligibility criteria should define a population with such long-term use who would reasonably or historically have been eligible for treatment with different maintenance or tapering strategies (e.g., excluding patients requiring palliative care or hospice). To define a population in a manner as similar as possible to that used in a true randomized trial, all eligibility criteria must be defined at "time zero" of follow-up, that is, at the time of treatment assignment.

While enrollment criteria used in traditional explanatory trials—as opposed to pragmatic trials—are generally intended to define a relatively homogeneous patient population that is likely to demonstrate little variability in response to treatment, pragmatic trials tend to use fewer restrictive enrollment criteria (Sox and Lewis, 2016). Such a population is expected to have clinically distinct sub-groups that may differ in their underlying prognoses or event rates and in their responses to alternative treatment strategies. Here, with the use of a pragmatic strategy the enrollment criteria are purposely broad, with the intent of identifying a wide range of patients who may have been, or may be in the future, treated with opioids, benzodiazepines, or both. This strategy also maximizes the number of patients to whom the results will be applicable.

For the purposes of assigning patients to clinically relevant sub-groups for statistical risk adjustment or for the implementation of planned statistical analyses intended to emulate those defined by the target trial protocol, it will be necessary to measure a wide variety of characteristics or covariates, both at baseline and during the period of follow-up. These characteristics or covariates may be particular to a given patient, to the practitioner or the VA practice setting, to geography, or to other factors that potentially affect treatment selection and outcomes.

Treatment Initiation Target Trial

For the treatment initiation trial, the committee defined the eligible patient population to be patients with a chronic pain diagnosis currently

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being prescribed benzodiazepines but not opioids. The goal was to define a population for which different patterns in the initiation of opioid treatment—including no initiation—in the presence of long-term benzodiazepine use would be relevant treatment options during 2010–2017. Specifically, eligible patients must have had a chronic pain diagnosis and have had a period of 90 or more days since they had last taken opioids, based on pharmacy fill data. Furthermore, the patients must have demonstrated the long-term and stable use of benzodiazepines during that same 90-day time period. Long-term and stable use was required because the question most relevant to the Statement of Task regarded opioid use that is concomitant with benzodiazepine use, and concurrent changes in benzodiazepine use would obscure the effects of opioids on adverse outcomes. The definition of long-term and stable use of benzodiazepines is somewhat inconsistent in existing literature and therefore would need to be determined based on reasonable cut-points from pilot VA data.

Tapering Target Trial

For the treatment tapering trial, the committee defined the eligible population as those VA patients prescribed both opioids and benzodiazepines on a long-term basis, excluding patients in whom attempts at opioid tapering are unlikely or contraindicated, such as patients with terminal medical conditions requiring palliative care or hospice. It should be noted that the taper would be voluntary, and frequent patient monitoring for psychiatric comorbidities during the taper would be critical.

TREATMENT STRATEGIES

Opioids and benzodiazepines have distinct indications for use. Long-term opioid therapy is primarily used to treat chronic pain.[4] It is important to note that long-term opioid therapy always begins as an initial prescription, likely intended to cover 1 month or less (rather than an initial prescription for long-term therapy). That initial prescription may be to treat acute pain that eventually becomes chronic or to treat pain that is already chronic. In either case, opioids may be continued long-term.

Benzodiazepines carry indications for panic disorder, generalized anxiety disorder, insomnia, detoxification from alcohol, and general complaints of anxiety accompanying other psychiatric conditions such as depression, posttraumatic stress disorder (PTSD), and adjustment disorders (Ciraulo and Nace, 2000; Katzman et al., 2014; Nichols et al., 2019). The long-term

[4] Buprenorphine and methadone are predominantly used to treat opioid use disorder.

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use of benzodiazepines is currently discouraged in favor of using antidepressant medications, behavioral treatments, or psychotherapy (Driot et al., 2019; Platt et al., 2016) for many of these indications, but, nevertheless, benzodiazepines are still commonly prescribed for long periods of time by many clinicians (Tanguay et al., 2018).

Preliminary descriptive analyses of available data will be required to determine and finalize the selection of the treatment strategies for each target trial in order to ensure that the analyses intended to emulate the target trials include sufficient numbers of patients who received each strategy across the VA during the 2010–2017 period. After those preliminary descriptive analyses, strategies may include any combination of specific patterns within these broad categories: (1) opioid and benzodiazepine pharmacotherapy (together or separately), (2) non-opioid, non-benzodiazepine pharmacotherapies, (3) non-pharmacological therapies, and (4) changes in treatment monitoring and frequency.

As patients will repeatedly present to care, those treatment strategies can be considered as options at every clinic visit. For example, in usual care, opioids might be continued at one visit, physical therapy started at the next visit, and opioids reduced at the next visit, and so on. All of the treatment strategies may be used independently of each other, although some combinations will be more or less common in actual practice. The frequency of visits will also vary depending on the types of strategies pursued and each patient's condition. In the next sections, the committee defines the general treatment strategies to be considered in the treatment initiation and tapering target trials.

Treatment Initiation Target Trial

The committee considered major categories of pharmacologic therapies that are used for pain, which would include anticonvulsants, muscle relaxants, antidepressants, medical cannabis, and topical therapies. Patients could receive one or more of those treatments at baseline, and preliminary analyses could determine whether patients receiving those medications should be included or excluded from the observational study. The committee also considered major categories of non-pharmacological strategies used to address pain, including behavioral interventions, complementary and alternative therapies, exercise therapy, yoga, and physical therapies.

A clinician could decide to increase or decrease the frequency of visits, monitoring, and other treatments based on the patient's response to treatment. The frequency of treatment visits and types of monitoring activities could have a significant impact on the treatment, regardless of the specific treatment strategy, and could correlate with treatment outcomes. The

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approaches to monitoring could include changing the frequency of visits or using such monitoring strategies as urine drug testing or pill counts; these approaches might vary by site or clinic. The ability to include those considerations in the definition of the target trial will be determined by the availability of suitable data in existing VA datasets.

To study the effects of initiating an opioid for chronic pain on mortality outcomes, various approaches could be possible; however, the committee believes that the most useful study would compare opioids to nonsteroidal anti-inflammatory drugs (NSAIDs).[5] A comparison group receiving an active treatment will be more similar to the group treated with opioids in characteristics such as pain severity and access to pain management services, in contrast to a group with a chronic pain diagnosis receiving no treatment. The committee chose non-aspirin NSAIDs (henceforth "NSAIDs") as the comparison treatment, although other comparisons might also be appropriate. Opioids and NSAIDs are both used routinely in the treatment of chronic pain, whereas many other non-opioid analgesics have multiple indications (e.g., gabapentanoids). Additionally, by comparing medications to one another, the study has the advantage of using parallel measurement approaches for both treatment strategies.

In the more specific clinical context sought to be addressed by this study, namely a patient with a chronic pain diagnosis not having used an opioid during the past 90 days while receiving chronic treatment with a benzodiazepine, a clinician could begin long-term therapy with an opioid, an NSAID, or both. The committee defined beginning opioid treatment (or NSAID treatment) for chronic pain as being dispensed one or more prescriptions of an opioid (or NSAID) for at least a 30-day supply over a 30-day period and having a chronic pain diagnosis. Other definitions may be considered. Furthermore, there is a wide range of other pharmacologic and non-pharmacological pain treatment strategies that could be used alone or in combination.

Tapering Target Trial

The goal of tapering is to safely reduce an opioid dosage. Opioid treatment guidelines recommend that the prescriber conduct frequent reassessments of the benefits and potential harms of opioid therapy (Dowell et al., 2016). If the harms have the potential to outweigh the benefits for a particular patient, the prescriber should consider whether it is appropriate to reduce the opioid dosage. The goal of the dosage reduction can be to achieve a complete discontinuation of opioid use after some period

[5] All references to NSAIDs refer to non-aspirin NSAIDs.

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(sometimes termed an "opioid taper"), but maintaining treatment at a lower daily dosage might also be the goal. The decision to taper might be due to a variety of factors, including concerning patient behaviors (e.g., overtaking the medication, illicit substance use) or the provider's desire to reduce opioid-related risk. In some cases a prescriber might believe that an abrupt discontinuation is clinically indicated for a particular patient, but there is no consensus among opioid prescribers on when abrupt discontinuation is appropriate, and there is concern that such abrupt discontinuation may increase the potential for harm in the context of physical or psychological dependence (Dowell et al., 2016). Given the evidence of harm associated with concurrent opioid and benzodiazepine use, including risk of fatal respiratory depression (Dowell et al., 2016), many treatment guidelines stress the need for frequent reassessment, with a goal of eventually discontinuing either the opioid or the benzodiazepine (Dowell et al., 2016; VA/DoD, 2017). As previously noted, the committee focused on the tapering of opioids, because CDC recommends that as the safer and more practical first step (Dowell et al., 2016).

Opioid Dosage Measurement

In the tapering target trial, patients would be eligible for inclusion into the study after their prescribed daily opioid dosage had reached a level that would be likely to induce opioid dependence. This is because opioid use at a lower dosage would be unlikely to require a slow dosage reduction in an effort to avoid withdrawal symptoms. Each patient's care team would be responsible for implementing the treatment strategy to which the patient was randomized over a 3-month period as well as any decisions to deviate from that strategy during the follow-up period. Patients may be prescribed opioids by other clinicians (e.g., surgeons, those in other health care systems) in ways inconsistent with the discontinuation or tapering strategies, but not the continuation strategy, representing an additional form of nonadherence that is often measurable from claims records. The following dosage strategies should be considered:

1. No dosage reduction: Continue opioid dosage at the same level (or ≤5 percent reduction)[6]; increase as indicated for symptoms or tolerance; taper/discontinue if not tolerated. Continuation may be measured as prescribed daily dosage that is the same or greater for month-to-month change throughout the 3 months.

[6] Reductions of less than 5 percent are considered non-meaningful variation based on measurement.

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2. Slow dosage reduction: Reduce dosage by 5 to 10 percent per month on average over 3 months;[7] stop taper and resume or increase dosage if indicated by pain level or if the risks of discontinuation outweigh benefits. This strategy may be identified by a reduction of, on average, 5 to 10 percent each month during the 3-month window and by the absence of month-to-month decreases in any given month consistent with a moderate to fast dosage reduction or complete discontinuation, described below.
3. Moderate to fast dosage reduction: Continue treatment but reduce dosage by more than 10 percent in 1 month; stop taper and resume or increase dosage if indicated by pain level or if the risks of discontinuation outweigh benefits (Darnall et al., 2018; Dowell et al., 2016). This strategy may be identified by a reduction of greater than 10 percent (but less than 100 percent, which would be a complete discontinuation, described below) from 1 month to the next at least once in a 3-month window.
4. Abrupt discontinuation: Stop taking opioids completely; resume use if indicated by pain level or risks of discontinuation outweigh benefits. As an example, this pattern may be measured as a lapse in days covered by prescriptions of at least 14 days within a 3-month window.

TREATMENT ASSIGNMENT

Individuals in the target trial would be randomly assigned to one of the treatment strategies, stratified by baseline dose. As in most pragmatic trials, the assignment would be non-blinded; that is, both patients and their treating physicians would be aware of the assigned treatment strategy. In the emulation of these target trials, treatment assignment is observed based on treatment records, requiring definitions of treatment groups that allow the creation of meaningful treatment groups and also allow for non-adherence to the assigned treatment that would occur in the target trial.

[7] Darnall et al. (2018) uses 5 percent "for up to two dose reductions in one month" as an initial tapering speed, then no more than 10 percent per week. The CDC guideline (Dowell et al., 2016) also notes that tapers slower than 10 percent per week are likely better tolerated than faster tapers and that tapers may have to be started and stopped. Additionally, it is not possible to assess tapering per week when prescriptions are often written for 30 days. Thus, the committee suggests a 5 percent cut-point for slow dosage reductions and 10 percent for fast dosage reductions.

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START AND END OF FOLLOW-UP

For the participants in the target trial, follow-up would start at the time of treatment assignment (for the initiation study, defined as being dispensed one or more prescriptions of an opioid or NSAID for at least a 30-day supply over a 30-day period; for the tapering study, defined as starting one of the defined tapering strategies) and would end at 18 months for the initiation trial or at 6 months for the tapering trial, or when the patient dies, or when the study ends.

OUTCOMES

For the proposed research to be of value to clinicians and patients, it will be necessary for it to include outcomes that are relevant to treatment decisions. As mentioned previously, the committee chose all-cause mortality and death from suicide as the primary outcomes of interest for the proposed target trials. However, in the case of the opioid initiation and tapering studies, many other secondary outcomes could be measured that are related to the potential benefits of treatment as well as to the potential harms.

Other Secondary Measures of Potential Benefits of Treatment

There are existing and common measures, often used in prospective clinical trials, of many outcomes relevant to the use of opioids and benzodiazepines. These outcomes include pain, anxiety, symptoms of PTSD, and the common functions of daily living.

- Pain relief: Patients typically self-report pain intensity level on an 11-point scale (the numeric rating scale ranging from 0 to 10) in the course of the clinical management of pain. A 30 percent change in pain intensity level is considered a clinically significant change (Hanley et al., 2006).
- Anxiety reduction: Several of the major indications for benzodiazepines are forms of anxiety disorders. Anxiety level is often measured with the Generalized Anxiety Disorder (GAD-7) scale. The GAD-7 represents an anxiety measure based on seven items scored from 0 to 3 based on self-report (Jordan et al., 2017).
- PTSD symptoms: Although PTSD is not considered an indication for benzodiazepines under VA clinical guidelines, is it not uncommon for veterans with PTSD to receive benzodiazepines. The PTSD symptom level is routinely measured in VA primary care with the PTSD Checklist. Additionally, some patients receive

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benzodiazepines without a relevant diagnosis in their medical records.

- Improved functioning: For many patients, the ability to carry out the daily activities of living is the goal of pain or anxiety management. General scales of function, such as the Short Form 12 (SF-12), provide an option to measure this domain across treatments and indications. The SF-12 consists of 12 questions that measure eight health domains in order to assess physical and mental health (Huo et al., 2018). For pain specifically, the three-item PEG scale developed by Krebs and colleagues (2009) incorporates measures of both pain intensity and pain-related functioning and is routinely used in the clinical management of pain in the VA. Items in the PEG scale assess average pain intensity (P), interference with enjoyment of life (E), and interference with general activity (G).
- Health care use: Effective pain management would likely reduce the need for increased levels of medical care, while less effective management (either under-treatment or over medication) would likely result in greater use of health care.

Potential Harms of Treatment

The committee also considered the potential adverse effects of treatment, such as measures of mortality, suicide, and overdose.

- All-cause mortality: A fundamental concern about any treatment is the risk of premature mortality. Assessing all-cause mortality as an outcome also has the advantage of avoiding problems with misclassification and missing data inherent to cause-specific mortality outcomes. Cause-of-death codes can be used to differentiate definite self-harm from possible self-harm in order to avoid missing potential cases of suicide.
- Suicide: Suicide is associated with pain as well as with higher prescribed dosages of opioids. Clinicians concerned about excessive restrictions on access to prescribed opioids have hypothesized that patients who have been on long-term opioid therapy are at an increased risk for suicide during and after opioid discontinuation (Darnall et al., 2018; HP3, 2019). In April 2019 the Food and Drug Administration released a drug safety announcement to communicate reports of suicide in patients physically dependent on opioid pain medicines suddenly having their opioids discontinued or the dosages rapidly decreased. The announcement posits that rapid discontinuation can result in uncontrolled pain

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or withdrawal symptoms, which in turn can lead patients to seek other sources of opioid pain medicines, including illicit opioids.

- Overdose: Unintentional opioid overdose is the potential risk of treatment that has driven much of the effort to reduce potentially excessive opioid prescribing, although it is a relatively rare outcome. Evidence that higher prescribed daily dosages are associated with a greater risk of opioid overdose may have led some physicians to taper patients in an effort to reduce overdose risk. Some advocates for a measured approach to opioid prescribing reductions have hypothesized that the population-level increases in heroin and illegally manufactured fentanyl overdoses are a result of patients transitioning to illegal opioid use after opioid discontinuation (Alpert et al., 2018; Cicero and Ellis, 2015; Cicero et al., 2012; Evans et al., 2019; Larochelle et al., 2015).

Other potential harms of treatments include increased depressive symptoms or suicidal ideation precipitated by non-consensual opioid reduction, incident psychiatric illness, opioid use disorder/opioid dependence, and multi-substance use disorder (SUD) (Glanz et al., 2019). Researchers should also consider the potential benefits and harms of NSAIDs in an effort to understand the trade-offs between the different classes of drugs.

CAUSAL CONTRAST

For each of the outcomes listed above, there are two causal contrasts of interest: the intention-to-treat effect and the per-protocol effect.

The intention-to-treat effect is the effect of being assigned to the treatment strategies at baseline, regardless of the treatment that is actually received. Because most individuals will initiate the strategies at the time of randomization, the intention-to-treat effect is effectively the effect of the initiation of the treatment strategy. The magnitude of the intention-to-treat effect depends on the patterns of non-adherence, the association between adherence and prognosis, and other deviations from protocol that occur during the trial. Two trials of the same treatment strategies conducted in the same population could have different intention-to-treat effects if their adherence patterns differed, and both would be internally valid effects of the assignment to treatment.

The per-protocol effect is the effect of receiving the treatment strategies throughout the follow-up as specified in the study protocol (e.g., without non-adherence). The numerical value of the per-protocol effect does not depend on the particular patterns of deviation from protocol that occur during the trial. Two trials of the same treatment strategies conducted in the same population could have different intention-to-treat effects if the

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adherence patterns differed, but they should have the same per-protocol effect.

The intention-to-treat effect estimates capture the impact of initiating one treatment strategy versus another and, thus, is ideal for informing recommendations for initial treatment selection. That is true because intention-to-treat estimates are agnostic to post-randomization treatment decisions—including discontinuation of the treatment strategies of interest, use of concomitant therapies, or any other deviations from protocol (Hernán and Hernández-Díaz, 2012). The intention-to-treat effect combines the effect of the treatment under study with that of other behavioral changes in the patient or physician triggered by the assignment itself. The intention-to-treat effect is widely used because intention-to-treat analyses preserve the randomized assignment in cases of non-adherence and thus protect against confounding (Ranganathan et al., 2016).

On the other hand, the intention-to-treat estimate may be hard to interpret for patients and clinicians who may desire an estimate of the "pure" treatment effect, that is, the effect that would hypothetically be associated with perfect compliance with the assigned treatment strategy. Importantly, when evaluating the harms of treatment, the intention-to-treat effect incorporates both the harms of the treatment if taken as intended and the willingness or ability of patients to adhere to the prescribed therapy. If the goal is to understand the risk of harm for a patient who is adherent, then the intention-to-treat estimate is an inappropriate choice because a risky treatment may appear less risky if patients are poorly adherent. The per-protocol is generally the more conservative estimate when estimating harm (perhaps giving an estimate of harm that is higher than seen in the population as a whole), while the intention-to-treat estimate is generally the conservative estimate when evaluating benefits (perhaps giving an estimate of benefit that is lower than seen in patients who are highly adherent) (Hernán and Hernández-Díaz, 2012; Sheiner and Rubin, 1995). When patient adherence is excellent, there will be little difference between the two estimates. In this setting of evaluating the harms of treatment, the per-protocol estimate directly addresses the question of interest and should be used. There is empirical evidence that, in some settings, the per-protocol effect is closer than the intention-to-treat effect to the sort of effect that patients and investigators are mostly interested in discovering from pragmatic trials, namely, which treatment would be more effective if taken as indicated in the protocol (Hernán and Robins, 2017; Murray et al., 2018). The per-protocol effect is more relevant for a patient who intends to be adherent; an estimate of the "pure" effect of the treatment is easier for a patient and clinician to discuss and understand than an estimate that intermingles the "pure" effect and adherence (Hernán and Robins, 2017). When the intention-to-treat effect is said to be "biased toward the null" or conservative, the implication is that

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the intention-to-treat effect is a biased estimate of the per-protocol effect (Murray et al., 2018). An added advantage of the per-protocol effect is that its interpretation does not depend on a trial-specific degree of adherence, which makes it a more transportable effect. However, the potential benefit that can be received by patients on average will be best represented by the intention-to-treat estimate rather than the per-protocol effect.

STATISTICAL ANALYSIS

Two separate sets of statistical analyses would be conducted after the completion of the target trial, one to estimate the intention-to-treat effect and another one to estimate the per-protocol effect.

An analysis aimed at estimating the intention-to-treat effect is referred to as an intention-to-treat analysis. In a large pragmatic trial with complete follow-up, the intention-to-treat analysis is straightforward: compare the observed outcome distributions between trial arms. That is, under those conditions, the intention-to-treat effect can be validly estimated without an adjustment for prognostic factors. In contrast, as discussed in the next chapter, observational analyses used to emulate the target trial that attempt to emulate intention-to-treat analyses will generally need to be adjusted for prognostic factors that confound the effect of treatment on the outcome.

An analysis aimed at estimating the per-protocol effect is referred to as a per-protocol analysis. Unlike intention-to-treat analyses, per-protocol analyses generally require adjustment for pre- and post-randomization prognostic factors that predict adherence to the protocol. That is, per-protocol analyses of randomized trials can be viewed as observational analyses, which require the same methods and rely on the same assumptions as the analyses of observational datasets.

The protocol of the target trial would therefore need to pre-specify the following three sets of adjustment variables: (1) pre-randomization prognostic factors that (if imbalanced) would need to be adjusted for in intention-to-treat analyses, (2) pre- and post-randomization prognostic factors to adjust for baseline and time-varying confounding in per-protocol analyses, and (3) pre- and post-randomization prognostic factors to adjust for potential selection bias due to loss to follow-up in both intention-to-treat and per-protocol analyses. Set 1 will generally be included in set 2. The variables in sets 2 and 3 will also be necessary to adjust for confounding and selection bias in observational analyses, which will be described in Chapter 3.

In addition, both intention-to-treat and per-protocol analyses could, in the target trial, be conducted in the following pre-specified sub-groups of patients:

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- Patients with coexisting medical illnesses, especially those with treatments that limit the safety of non-opioid analgesics;
- Patients with psychiatric illness, particularly those with poorly controlled mood symptoms or a history of suicide attempts;
- Patients with SUD, particularly in those patients with concern for active substance use;
- Patients who prefer certain treatment strategies over others (e.g., patients who do not want to engage in behavioral approaches and who prefer medications); and
- Patients with a pain treatment history and a history of overdose with prescribed opioids, benzodiazepines, or other sedating medications (e.g., gabapentin) or illicit drugs (e.g., heroin).

It should be noted that the purpose of the sub-group analyses is to identify treatment effect heterogeneity across different groups of patients rather than to adjust for confounding and selection bias. Some of the variables used to explore this potential effect modification might also be included in the three sets of variables needed to adjust for confounding and selection bias. The sub-groups listed here will be explained in further detail in Chapter 3 in the discussion on why those same variables should be adjusted for confounding in the observational emulation of the target trials.

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3

Observational Emulation of the Target Trials and Practical Considerations

The previous chapter described an approach to addressing the research questions through the specification of the protocol of hypothetical target trials for both opioid initiation and tapering. The next step in investigating comparative effectiveness and safety questions would be to conduct the target trials, or, if this is not possible, to attempt to emulate the target trials using analyses of observational data. This chapter outlines a general procedure for emulation of the opioid initiation and tapering target trials described in Chapter 2, using Department of Veterans Affairs (VA) databases. While this chapter does not define a specific analysis strategy, as the committee was not charged with conducting the actual analyses and did not review the VA's databases, it does lay out considerations of how to emulate each of the components of the protocol of the target trial: eligibility criteria, treatment strategies, treatment assignment, follow-up, outcomes, causal contrasts, and statistical analysis plan.

Before the committee describes the emulation procedures for each component of the target trials, it is important to note that the target trials described in the previous chapter (see Table 2-3) were chosen among several trials that could reasonably be considered to address the research questions. For instance, variations of the target trials' eligibility criteria or treatment strategies could be justifiable or even necessary because the available VA datasets might not include all information needed to emulate the target trials previously described. Additionally, although the focus of the research questions is concomitant opioid and benzodiazepine prescription, variations could also include asking the same research questions among

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individuals who had been prescribed opioids only, without benzodiazepines; however, this was outside the committee's scope.

The process of specifying and emulating the target trial is an iterative process guided by data constraints, with the final analysis being a compromise that is likely to differ from the originally proposed target trial. Therefore, this and the previous chapter should be viewed as guidance on how to structure the specifications of a relevant target trial and how to describe the observational data analyses to carry out the emulation of that trial. The committee begins by briefly describing possible data sources.

DATA SOURCES

Potential sources for data key to the observational emulation of the target trials from 2010 through 2017 are the VA Corporate Data Warehouse (CDW), the outpatient prescription data from the VA's Pharmacy Benefits Management Services, and the Centers for Disease Control and Prevention's National Death Index (NDI). The CDW data can be used to identify those veterans receiving services who have relevant health conditions, such as pain conditions and opioid use disorders, noted during medical encounters. These data include treatment use, demographic characteristics, and clinical diagnoses for all patients seen at VA facilities. The NDI contains information on individuals' date and cause of death, such as the underlying cause of death and detailed information about the death, as well as identifiers such as name and social security number (Ilgen et al., 2016). Those data originate from state vital statistics offices and are based on the results of medical examiner or coroner investigations. The VA purchases mortality data from the NDI so that the date of death and cause of death can be known for VA patients and linked to medical records data (Lin et al., 2019). Other possibly useful data sources include the Operation Enduring Freedom, Operation Iraqi Freedom, and Operation New Dawn rosters, which can be used to obtain service information and fill in missing race and ethnicity data, and the VA Suicide Prevention Applications Network database, for use in identifying non-fatal suicide events (attempts, serious suicidal ideation).

OVERVIEW OF THE EMULATION PROCEDURE

In this section, the committee describes a procedure for the emulation of the two target trials (see Chapter 2) that will estimate the effect of opioid initiation and tapering strategies on patient outcomes.

The emulation procedure starts by identifying a cohort of patients in the VA who are eligible for the initiation and tapering studies at some time point during the period of interest. That time point then defines the start of follow-up time (baseline). It is important to note that, in the observational

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data, patients might be eligible for both studies, although with different baseline times; this situation is illustrated in Figure 3-1. A patient on benzodiazepines but not opioids could be initially eligible for the initiation emulation (left side of Figure 3-1) and then, after initiating and remaining on opioids for at least 90 days, for the tapering study (right side of Figure 3-1). Dotted lines on Figure 3-1 depict other possible trajectories. In cases where a single patient is eligible at multiple times for the same study, one of the multiple eligibility time points could be chosen at random to serve as baseline for that patient, or, alternatively, multiple eligible time points could be included in the emulation.[1]

[1] See Hernán and Robins (2016) for further discussion.

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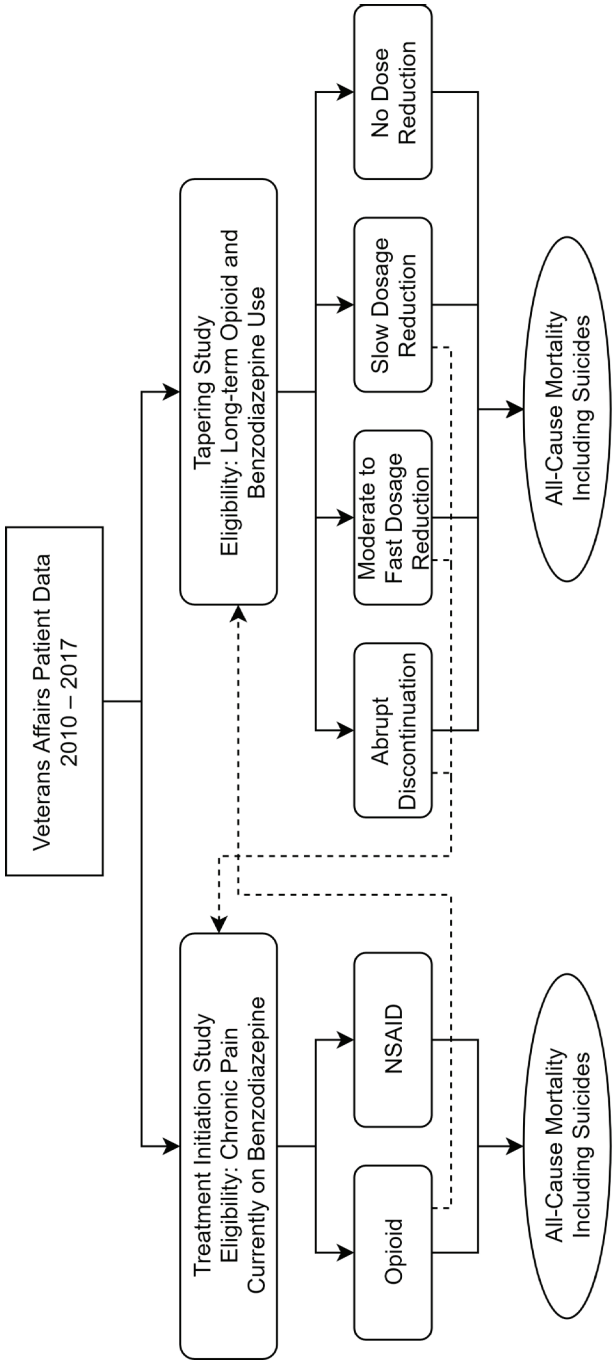

FIGURE 3-1 Opioid treatment initiation and tapering study schematic.
NOTE: NSAID = nonsteroidal anti-inflammatory drug.

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The next step is to assign the eligible patients to the treatment strategies that are consistent with their baseline data. Because VA patients were not randomly assigned to these treatment strategies, the analysis should include adjustments for the potential confounding factors—prognostic factors that are imbalanced across treatment strategies—to approximate the estimates that would arise through randomization as closely as possible. The availability of information on these factors is essential for the success of the emulation procedure. Finally, the outcome distribution is compared between groups defined by their treatment strategies, after appropriate adjustment for pre- and post-baseline confounding factors.

EMULATING THE INITIATION AND TAPERING TARGET TRIALS

Tables 3-1 and 3-2 reiterate the specification of the components of the target initiation and tapering target trials, already described in Table 2-3, and delineate the emulation procedures using available observational data. That is, the target trial columns of Tables 3-1 and 3-2 replicate the relevant columns in Table 2-3, and the last column in each of the tables outlines the proposed observational analyses to emulate the eligibility criteria, treatment strategies, treatment assignment, start and end of follow-up, outcomes, causal contrasts, and statistical analysis of the target trials. Table 3-1 addresses the opioid initiation trial emulation, while Table 3-2 addresses the opioid tapering trial emulation.

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TABLE 3-1 Opioid Initiation Target Trial Emulation

Study Component	Target Trial	Emulation Using Observational Data
Eligibility criteria	Chronic pain diagnosis No prescriptions for opioids or non-aspirin NSAIDS in the past 90 days Long-term benzodiazepine therapy (defined based on pilot data) Exclude: Individuals with serious illness[a] Individuals prescribed opioids used for treatment of opioid use disorder Individuals with surgery or acute painful injury within the past 90 days[b]	Data to determine the use of analgesics during the past 90 days and the use of benzodiazepines will come from pharmacy fills and will require information specifically on fill dates, dose, and supply duration. Data for the diagnoses of chronic pain, serious illnesses, surgeries, or acute painful injuries will come from the medical visit records. Opioid use for opioid use disorder treatment will be measured through a combination of pharmacy fills (for buprenorphine) and clinic codes for opioid treatment programs.
Treatment strategies	(a) Initiation of treatment with an opioid and continuation for 1 year, unless not tolerated by the participant (b) Initiation of treatment with a non-aspirin NSAID and continuation for 1 year, unless not tolerated by the participant	Patients will be assigned to the strategies consistent with their pharmacy fill data, based on initiation at baseline with an opioid or NSAID. Adherence to the strategy is defined by continued fills during the year after baseline. An example of non-adherence would be if a patient could not tolerate over-sedation from opioid use and discontinued as a result.
Treatment assignment	Individual randomization	Assumed to be random conditional on baseline confounders, including, but not limited to —Medical illnesses —Mental health diagnoses —Pain intensity —Substance use disorder (SUD) diagnoses —History of overdose with prescribed opioid —Medication history —Age Diagnoses associated with clinical visits in VA medical records will be used to define these variables.

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TABLE 3-1 Continued

Study Component	Target Trial	Emulation Using Observational Data
Start and end of follow-up	Start of follow-up (baseline): time of assignment to a treatment strategy End of follow-up: the earliest of 18 months, death, or the administrative end of follow-up (end of the study)	Start of follow-up (baseline): time of assignment to a treatment strategy. End of follow-up: the earliest of 18 months, the date of death based on National Death Index records, or the administrative end of follow-up.
Outcomes	(a) All-cause mortality (b) Death from suicide	Deaths ascertained from National Death Index data, with all-cause mortality measured as a death record with a date of death and suicide deaths as those records with underlying cause of death recorded as ICD-10 codes X60–X84, Y87.0, *U03.[c]
Causal contrast	(a) Intention-to-treat effect (b) Per-protocol effect	Observational analog of the intention-to-treat effect: this effect may be close to null and therefore relatively uninformative because adherence to the assigned treatment strategies is expected to be low in the observational data. Observational analog of the per-protocol effect.

continued

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TABLE 3-1 Continued

Study Component	Target Trial	Emulation Using Observational Data
Statistical analysis	Intention-to-treat analysis: check for balance on key variables, e.g., mental health diagnoses and SUDs. Per-protocol analysis: patients will be censored at the time they deviate from their assigned strategy. To adjust for the potential selection bias induced by censoring, inverse probability weighting will be used. The weights will be a function of the baseline and post-baseline (time-varying) confounders. Both analyses may require further adjustment for selection bias due to loss to follow-up. Pre-specified sub-groups to be examined for potential effect modification include, e.g., those with pain severity, history of overdose, history of suicide attempt.	Intention-to-treat analysis: same as in target trial, except that an individual may have multiple eligibility points, and adjustment for baseline confounders is required. Per-protocol analysis: same, except that a single subject may have multiple eligibility points. All variables will be obtained from medical records, including clinic visit information, diagnoses, and pharmacy records.

[a] Serious illness is defined by Kelley and Bollens-Lund (2018) as a health condition that carries a high risk of mortality and negatively affects a person's daily functioning. The committee recommends operationalizing this as any of the following conditions: cancer, chronic obstructive pulmonary disease, congestive heart failure, dementia, or severe neurologic disorder (e.g., amyotrophic lateral sclerosis, multiple sclerosis).

[b] 90 days was chosen to minimize the likelihood of opioids being prescribed for acute rather than chronic pain conditions. However, the committee acknowledges that the choice of 90 as opposed to 30 or 60 is arbitrary.

[c] The researchers who perform the study should determine whether this definition is sufficiently accurate for their purposes.

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TABLE 3-2 Opioid Tapering Target Trial Emulation

Study Component	Target Trial	Emulation Using Observational Data
Eligibility criteria	Long-term opioid therapy defined as 3+ opioid fills ≥21 days apart in a ≥84-day period for ≥84-day supply (Larochelle et al., 2016) Average opioid MME[a]/day is ≥30 over the prior 84 days[b] Long-term benzodiazepine therapy (defined based on pilot data) Exclude: Individuals with serious illness[c] Individuals prescribed opioids for the treatment of opioid use disorder Individuals with surgery or acute painful injury within the 90 days prior to baseline	Data to determine opioid use will come from pharmacy fills and will require information specifically on fill dates, dose, and supply duration. Data for diagnoses qualifying as serious illnesses will come from the medical visit records. Opioid use for opioid use disorder treatment will be measured through a combination of pharmacy fills (for buprenorphine) and clinic codes for opioid treatment programs.
Treatment strategies	(a) No dosage reduction: ≤5% average decrease per month for 3 months (b) Slow dosage reduction[d]: >5% but ≤10% average decrease per month for 3 months (c) Moderate to fast dosage reduction: >10% average decrease per month for 3 months (d) Complete discontinuation within 3 months from baseline Participants who cannot tolerate their assigned dosage change will be excused from following their assigned strategy. Percentage of taper is relative to opioid dose at baseline and is calculated over the next 3 months. After that period, dosage is left to the physician's discretion.	The treatment strategy to which a participant is assigned is determined by the average change in opioid dose during the 3-month period after baseline. This will minimize the impact of changes that are due to non-clinical reasons, as those changes should be followed by a correction (e.g., early prescription fill due to patient vacation, followed by a late fill). Tapering treatment strategies are defined the same as in the target trial. An example of non-adherence would be if a patient's pain worsened and functioning declined and the patient returned to the original dosage after starting a taper.

continued

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TABLE 3-2 Continued

Study Component	Target Trial	Emulation Using Observational Data
Treatment assignment	Individual randomization	Assumed to be random conditional on the baseline confounders, including —Medical illnesses —Mental health diagnoses —Substance use disorder (SUD) diagnoses —History of overdose with prescribed opioid —Age Diagnoses associated with clinical visits in VA medical records will be used to define these variables.
Start and end of follow-up	Start of follow-up (baseline): time of assignment to a treatment strategy End of follow-up: the earliest of 6 months, death, or the administrative end of follow-up (end of the study)	Start of follow-up (baseline): time of assignment to a treatment strategy. End of follow-up: the earliest of 6 months, the date of death based on National Death Index records, or the administrative end of follow-up.
Outcomes	(a) All-cause mortality (b) Death from suicide	Deaths will be ascertained from National Death Index data, with all-cause mortality measured as a death record with a date of death and suicide deaths as those records with underlying cause of death recorded as ICD-10 codes X60–X84, Y87.0, *U03.[e]
Causal contrast	(a) Intention-to-treat effect (b) Per-protocol effect	Observational analog of the intention-to-treat effect: this effect may be close to null and therefore relatively uninformative because adherence to the assigned treatment strategies is expected to be low in the observational data. Observational analog of the per-protocol effect.

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TABLE 3-2 Continued

Study Component	Target Trial	Emulation Using Observational Data
Statistical analysis	Intention-to-treat analysis: check for balance on key variables, e.g., mental health diagnoses and SUDs. Per-protocol analysis: patients will be censored at the time they deviate from their assigned strategy. To adjust for the potential selection bias induced by censoring, inverse probability weighting will be used. The weights will be a function of the baseline and post-baseline (time-varying) confounders. Both analyses may require further adjustment for selection bias due to loss to follow-up. Pre-specified sub-groups to be examined for potential effect modification include, e.g., patients with pain severity, history of overdose, or history of suicide attempt.	Intention-to-treat analysis: N/A Per-protocol analysis: same as in target trial, except that a single subject may contribute two clones. All variables will be obtained from medical records, including clinic visit information, diagnoses, and pharmacy records.

[a] MME = morphine milligram equivalent.

[b] This threshold was used because labeling for OxyContin extended release defines opioid tolerant as consuming 30 MME/day. Researchers might consider a lower dose threshold if the purpose is to include anyone who could be considered for a taper.

[c] Serious illness is defined by Kelley and Bollens-Lund (2018) as a health condition that carries a high risk of mortality and negatively affects a person's daily functioning. The committee recommends operationalizing this as any of the following conditions: cancer, chronic obstructive pulmonary disease, congestive heart failure, dementia, or severe neurologic disorder (e.g., amyotrophic lateral sclerosis, multiple sclerosis).

[d] Speed of tapering: there is no generally accepted rate of tapering speed (i.e., rate of dosage decrease per week/month); options would need to be explored using pilot data. The tapering speeds proposed for this trial should not be considered medical guidance.

[e] The researchers who perform the study should determine whether this definition is sufficiently accurate for their purposes.

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Tables 3-1 and 3-2 describe an initial emulation strategy that has not been evaluated and would likely require modification after an initial review of the available data. It is important to remember that the process of specifying a target trial is necessarily iterative: after the initial set of design choices for the target trial are made (as shown in Chapter 2), an examination of the available observational data may indicate that the components of the target trial need to be modified. For example, a proposed definition of the eligibility criteria might initially include a characteristic that is found to be unavailable in the observational data. This process could then be repeated until the specified components of the target trial and the available data are consistent with each other or until it is determined that the only target trials that could be emulated using the available data are of little interest. Importantly, this process should not involve any evaluation of the outcomes of interest.

TREATMENT STRATEGIES

Emulating the initiation and tapering target trials requires using information from VA pharmacy data to determine the treatment strategy. The pharmacy data contain information on medications filled and dispensed to VA patients, either in VA facilities or through mail order, with data fields such as the date dispensed, days supplied, number of units, and dose per unit. This section outlines the major considerations related to measurement treatment strategies from pharmacy records.

The patterns of medication use that can be derived from these data may be thought of as either (a) the prescribed course of treatment, if the goal is to draw inferences about the effects of assignment to treatment strategies (intention-to-treat), or (b) patients' actual medication consumption, if the goal is to draw causal inferences about the effects of the medication strategy (per-protocol). Measurement choices must address the fact that some patients will have highly variable medication use patterns, which may not appear consistent with any specific treatment strategy because of changes made to the treatment plan over time. Furthermore, even some relatively stable patterns of prescribing and medication use may appear variable because of the reliance on dispensing data, for example, if patients choose to fill their prescriptions on different days each month.

For the initiation study, one can assume that the date of initiation is the date that an opioid or nonsteroidal anti-inflammatory drug (NSAID) medication was first dispensed. Prescriptions that are written and never filled by the patient are not included in the pharmacy data, which is a limitation if one seeks to study the deviations from assignment that would occur early after randomization in the target trial.

The challenges of measuring treatment strategies are even greater for the tapering study, which relies on calculating medication dosages in order

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to differentiate between strategies. Calculating monthly averages[2] of daily opioid dosages, rather than calculating dosages that vary from day to day, should reduce some non-informative variability. Figure 3-2 illustrates multiple hypothetical trajectories of opioid use patterns over time that are relevant to this study, with the vertical axis representing dose and the horizontal axis representing time. The top several trajectories depict monthly averaged dosages over the observation period from which the intended course of treatment is relatively easy to infer and that are consistent with protocols for the tapering target trial. The last trajectory demonstrates the type of variability from month to month that is often present in opioid dispensing–based measurement and from which the intended course of treatment is difficult to infer. There are likely many other trajectories than those shown, especially taking into account concurrent benzodiazepine use. The trajectories might also be stratified, for example, by pain severity over time.

[2] The committee intended that treatment months would be the unit of measurement, meaning for each patient, time would be measured as 30-day periods, starting at the point of the initial medication fill relevant to the study. Of note, the most common number of days supplied of opioid fills in VA pharmacy records is 30 days.

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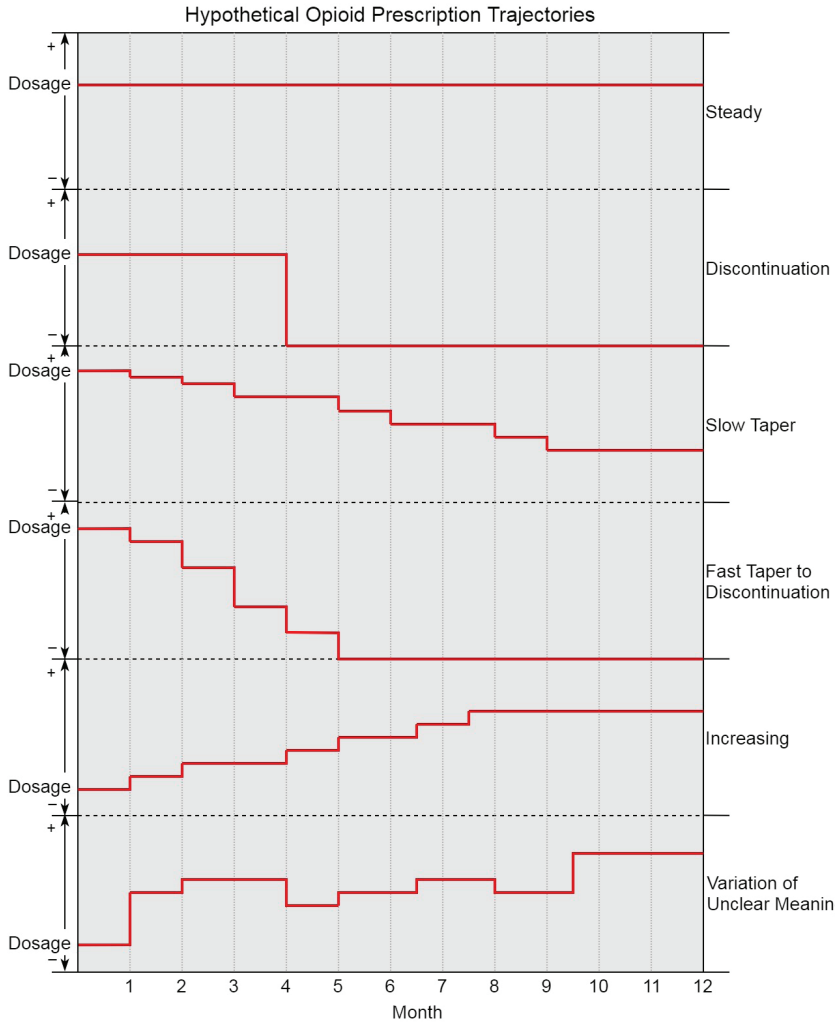

FIGURE 3-2 Hypothetical opioid prescription trajectories.

The specification of the treatment strategies for the target trial should be mindful of the various combinations of treatment strategies that a single patient might experience over time and must be realistic in order to avoid comparisons that are not relevant for clinical decision making or that are hopelessly confounded. Sensitivity analyses can assess the impact of measurement decisions on the study conclusions. For example, alternative measurements of treatment strategy may assume that medications prescribed to be taken "as needed" are taken by the patient at a faster (e.g., maximum

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allowed under the prescription instructions) or slower (e.g., half as often as allowed) pace.

CONFOUNDING VARIABLES

In designing the analyses of observational data, it is important to consider confounders that may alter the impact of the intervention—opioid tapering or initiation—on the primary outcomes of all-cause mortality and suicide. Those confounders can be thought of as factors that are predictive of the receipt of a particular treatment strategy and also risk factors for one of the outcomes (Kyriacou and Lewis, 2016). Confounding, if not adjusted for, can bias or even reverse the direction of the estimate of the treatment effect. For example, if an analysis of the association between patient outcomes and treatment strategy was conducted using a dataset in which there was confounding by indication, and if the analysis failed to include a good measurement for the indication for treatment as a covariate in the analyses or to control for this confounding in some other way (e.g., limiting the analysis to individuals with the indication), the estimate of the association would be biased and possibly qualitatively incorrect. Because the proposed studies use time-dependent exposure classification (i.e., allow treatment status to vary over time), the measurement of the relevant confounders has to be considered not only at baseline but also at each visit during follow-up (see Statistical Analysis in Tables 3-1 and 3-2).

Confounders may be either observed (measured) or unobserved (unmeasured). Furthermore, a confounder may be measured with error, which then results in residual confounding. For example, a physician's impression that a patient is misusing his or her opioids—an impression that is likely to affect the choice of treatment strategy and may be correlated with other patient characteristics that affect outcome—would be an unmeasured confounder if the physician impression is not recorded in the medical record or is otherwise unavailable to the investigator. It would be partially measured if it were recorded in some medical records but not others or if only indirect indications of the physician's impression were available. It would be measured inaccurately, at best, because the physician's impression about misuse is unlikely to be a fully accurate measure of whether a patient is truly misusing the opioids. Common statistical models can only adjust for measured confounders, and the adjustment will be highly dependent on the quality and consistency of the measurement of the confounder. Under strong assumptions, other statistical methods (e.g., instrumental variable analysis) may be able to adjust for unmeasured confounding, but these methods are not generally applicable to the comparison of treatment strategies sustained in time, like the ones under consideration here.

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Below, a number of potential confounders are provided, both those likely to be measured and those unlikely to be measured consistently or at all. While the goal was to make this list as comprehensive as possible, the committee acknowledges that there are likely to be unanticipated confounders. For each example provided below, the committee considers how it might relate to opioid initiation and tapering and to outcomes of suicide and all-cause mortality.

Examples of Measured Confounders

Medical Illnesses

Co-existing medical illness may affect the opioid treatment approach in several ways. First, such medical illnesses as end-stage renal disease and cirrhosis can limit the safety of other analgesic options, such as NSAIDs and acetaminophen, making the use of opioids potentially more appropriate than some alternatives (Chandok and Watt, 2010; Hartmann et al., 2010; Klinge et al., 2018; O'Connor and Corcoran, 2012). Such medical illnesses as cancer, dementia, congestive heart failure, and chronic obstructive pulmonary disease may also limit patients' prognoses, making the long-term risk of opioids a less important consideration. Therefore, medical illness is more likely to be associated with opioid initiation and less likely to be associated with opioid tapering (Platt, 2010). Medical illness is also associated with increased all-cause mortality and with suicide (Ilgen et al., 2016).

Psychiatric Illnesses

Psychiatric illnesses, including depression, are associated with a substantially increased risk of suicide in veterans (Ilgen et al., 2010). Coexisting psychiatric illness, particularly in patients with poorly controlled mood symptoms or a history of suicide attempt, increases the risk of opioid-related harms (Maloney et al., 2007). However, there is a well-documented phenomenon of adverse selection where patients with mental health and substance use comorbidities are more likely to be prescribed opioids, most likely because of clinicians' desire to treat emotional, in addition to physical, pain (Quinn et al., 2017; Sullivan and Howe, 2013; Sullivan et al., 2005). It is also possible that psychiatric illness influences the likelihood of opioid tapering. Clinicians may be more likely to initiate tapering in response to uncontrolled psychiatric symptoms in some cases or, in other cases, less likely to initiate tapering because of the challenge of managing pain in patients with psychiatric comorbidities. Psychiatric illness is associated with both increased all-cause mortality and increased suicide risk (Chesney et al., 2014; Ilgen et al., 2016).

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Opioid Misuse Behaviors

Opioid misuse behaviors include such things as running out of opioids early, missing appointments, and taking opioids for symptoms other than pain. Even if the patient does not have a diagnosable opioid use disorder, the risk of continuing opioids in the setting of those behaviors may be greater than the benefits. Some opioid misuse behaviors are able to be identified from medical chart data (Kim et al., 2012). For example, the risk may exceed the benefit if a patient has multiple episodes of lost or stolen medication, which may appear in the medical records as "early" or redundant refills (Sehgel et al., 2012). Therefore, patients with opioid misuse might be more likely to be withdrawn from opioids, and many clinics have policies that recommend tapering in those situations (Kahan et al., 2011). Due to other comorbidities such as a psychiatric illness that may contribute to opioid misuse, these patients might also have increased all-cause mortality and risk of suicide.

Substance Use Disorders

Substance use disorders (SUDs) increase the risk of opioid-related harms, particularly in patients who are of concern for active substance use (including opioid use disorder and other SUDs (Mark and Parish, 2019). However, as described above, "adverse selection" may mean that those patients are more likely to be initiated on opioids and less likely to be tapered (Merrill et al., 2012; Sullivan and Howe, 2013). These patients also have increased all-cause mortality and risk of suicide (Bohnert and Ilgen, 2019; Bohnert et al., 2010, 2017). Although SUD diagnoses are included in medical records data, it is likely that this method of measurement both misses cases and incorrectly classifies individuals as having a SUD who would not meet the diagnostic criteria for such a disorder.

History of Overdose

Whether intentional or unintentional, opioid overdose has been associated with a higher risk of future opioid overdose (Boscarino et al., 2016). It is also likely associated with tapering (Chang et al., 2018), although recent studies suggest that most patients who have had an overdose with a prescribed opioid are re-started on that same opioid (NASEM, 2017). Given the comorbidities that are more prevalent in patients with a history of prescribed opioid overdose (psychiatric illness, opioid misuse, substance use), this group likely has higher all-cause mortality and suicide risk than patients with no history of overdose. Overdoses treated outside of the VA system are unlikely to be recorded and available for measurement.

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Examples of Unobserved or Poorly Measured Confounders

Clinician Perception of Pain Etiology

Although guidelines caution against this approach (Hooten et al., 2017), the perception that a patient has a "legitimate" reason to have pain (e.g., cancer, severe injury) versus pain conditions perceived as having a less clear etiology (e.g., back pain, fibromyalgia) might influence the decision to choose one treatment instead of another (e.g., opioids instead of NSAIDS and cognitive behavioral therapy) (Collett, 2001; Sluka and Clauw, 2016). Pain etiology could also relate to suicide and all-cause mortality. For example, Ilgen et al. (2013) showed that psychogenic pain, which could be viewed as non-legitimate, was associated with suicide after adjusting for other psychiatric diagnoses. Diabetes, which could be viewed as a "legitimate" cause of neuropathic pain (Schreiber, 2015), is associated with increased all-cause mortality (Cheng et al., 2016).

Pain Treatment History

Long-term opioid treatment is typically reserved for patients who have tried and failed with multiple other pain treatments (HHS, 2016). However, the "and failed" is often subjective and is not systematically captured in the medical record (Palmer et al., 2015).

Opioid Misuse Behaviors

Although some opioid misuse behaviors are easily found in the medical record (e.g., having gone to multiple clinicians for opioid prescriptions, missed appointments, illicit substance use), others are not consistently documented (angry or aggressive behavior related to opioids, asking for a specific opioid by name) (Ives et al., 2006; Palmer et al., 2015). Opioid misuse, whether documented in the patient record or not, may lead clinicians to withhold or taper opioids, and is also associated with an increased risk of overdose-related mortality (Fields, 2011).

Patient Treatment Preferences

Although participation in the proposed target trial, and thus opioid dosage reduction, would be voluntary, it is unknown what proportion of VA patients who experienced opioid tapering during the years of the proposed observational study did so voluntarily. It is important to note that tapering a patient off opioids because he or she wants to reduce the dose or discontinue opioids is likely different from tapering a patient for other

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reasons, such as clinic-specific policies or prescriber concerns that a patient is diverting medications or experiencing harms from opioid use (Frank et al., 2016; Glajchen, 2001; Hadlandsmyth et al., 2018). Patient willingness to participate might be related to potential adverse events of the treatment strategies, possibly due to a correlation with other factors such as opioid misuse and mental health conditions.

STATISTICAL ANALYSIS

At baseline, patients will be assigned to the treatment strategy that is compatible with their observed data. Then the observational analog of the intention-to-treat analysis will be similar to that of the intention-to-treat analysis of the target trial (if the trial were actually conducted); that is, it will be done by comparing the outcome distributions between groups defined by the treatment strategy assigned at baseline. The main difference between how the target trial and observational analog would be analyzed is that the observational analysis will require an adjustment for baseline covariates that are imbalanced across the different treatment strategies. However, if adherence to the treatment strategy assigned at baseline is low, which often is the case with patients prescribed opioids and benzodiazepines, the intention-to-treat and per-protocol effects are likely to be very different, and the preferred estimate will depend on the goal of the analysis. As discussed in Chapter 2, clinicians and patients may find the per-protocol estimates to be more relevant in informing their individual clinical decision making (Hernán and Robins, 2017). Thus, while the intention-to-treat estimate is potentially important in informing recommendations for treatment strategies, the per-protocol effect is likely to be a more practical inferential target. The observational analog of the per-protocol analysis would be essentially identical to a non-naive per-protocol analysis of the target trial (if the trial were actually conducted). Such a per-protocol analysis will require adequate adjustment for both baseline and post-baseline (time-varying) confounders. This adjustment could be carried out via g-methods, such as the g-formula (see Keil et al., 2014; Robins et al., 2007) or inverse probability (IP) weighting (see Hernán et al., 2006; Robins et al., 2000).

If IP weighting is used, patients will be censored if and when they deviated from their initial treatment strategy. For example, consider a patient in the initiation trial who is assigned to opioid initiation at time 0 but discontinues treatment after 4 months. The patient would be then censored at month 4, whereas uncensored individuals at that time will be weighted by the inverse of their probability of remaining uncensored. Because the definition of censoring depends deterministically on the observed treatment, the denominator of the IP weights is defined by

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the time-varying probability of treatment, which needs to be estimated as a function of baseline and post-baseline confounders at prior times (Robins et al., 2000).

Censored patients could become eligible once again for the target trial at a later point. A statistically efficient way to handle multiple eligibility periods in the analysis is to include a copy of a patient's data in the analysis for each instance of multiple eligibility, assigning a different "time 0" and treatment strategy to each record that aligns with an eligibility event. This approach requires that the estimation of standard errors adjust for correlations due to repeated measures within patients (Hernán and Robins, 2016). While the committee cannot give a definitive recommendation about the final analytic strategy without pilot data, it is quite likely that this will be the preferable approach.

In the tapering trial, a patient's data at baseline may be compatible with more than one treatment strategy. To handle this problem, a copy (clone) of a patient's data for each possible treatment strategy compatible with the patient's data at a given time point would be included in the analysis. Clones are then censored when their data stop being compatible with their particular treatment strategy.[3]

Sample Size

Assessing the magnitude of an effect that would be detectable at a given level of significance and statistical power provides context for how conclusive one might expect the analysis to be before conducting it, and it provides context for the interpretation of results. Key inputs for evaluating the adequacy of the sample size for conducting an informative analysis include the number of eligible patients per analysis, the comparability of patients across the treatment strategy groups, the expected value of the outcome, the size of a clinically meaningful effect of one treatment strategy versus another on the outcome, and the variation in the outcome. That assessment of the magnitude of an effect is illustrated by considering all-cause mortality in the context of the dosage reduction study. Krebs et al. (2011) report an all-cause mortality rate of 0.066 per patient-year in a cohort of patients with pain who were prescribed methadone or morphine and whose estimated conditional probabilities of receiving methadone versus morphine equaled or exceeded 0.10. Given that rate, the committee provides an illustration of the role of outcome prevalence on the sample size required to detect a clinically meaningful effect. Consider a simple comparison of two independent groups where the power is estimated using an independent two-sample test of proportions with continuity correction (Fleiss et al.,

[3] See Hernán and Robins (2016) for further discussion.

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2003). To illustrate, assume the clinically meaningful difference to detect is a difference in mortality relative risk of 1.2 between two treatment strategies. However, prior to emulating the target trial, investigators should form their own assessment of the most clinically meaningful difference in relative risks upon which to base a power calculation. To detect a relative risk of mortality of 1.2 for one group versus another with 80 percent power at alpha = 0.05 (two-sided test) would require 15,110 patients across both groups. If this sample size of patients is not available for analysis, then the emulation will be under-powered and the result inconclusive.

In such a case, one might consider whether the outcome should instead be treated as a secondary outcome. However, when the outcome is rare, large sample sizes are required to detect clinically meaningful effects. That is an even greater concern for outcomes such as suicide. Ilgen et al. (2016) found a suicide rate of 44 per 100,000 person-years in a cohort followed after an initial opioid prescription fill. Given this rate, consider again a simple independent two-group comparison where group assignment is assigned randomly and the groups are of equal size. To detect a relative risk of mortality of 1.2 for one group versus another with 80 percent power at alpha = 0.05 (two-sided test), about 2.2 million patients across both groups would be required. However, the number of patients required is likely to be larger than that, given that the treatment strategies to be compared are unlikely to be of equal size. Vanderlip et al. (2014) found 7.5 percent of patients with chronic pain who initiated long-term opioid therapy had discontinued by 90 days later. If those under the strategy of discontinuation were compared with all others, the sample sizes required would be 570,000 for the discontinuation group and 7.6 million for the group of all others. The scenario for which the committee illustrates sample size considerations is simplified relative to the proposed emulation, and considering additional factors might increase or decrease sample size requirements relative to the illustration provided here. Nevertheless, the calculations demonstrate the challenge posed by examining rare outcomes.

Limitations

The approach described in this chapter, namely the emulation of particular initiation and tapering target trials using observational data and analyses, comes with limitations that relate to the risk of bias in nonrandomized studies of interventions (Sterne et al., 2016). The domains of potential bias include bias due to confounding, bias in the selection of participants into the study, bias in the classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in the measurement of outcomes, and bias in the selection of the reported results. Here, the committee focuses discussion on bias from measurement

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(i.e., the misclassification of exposures/interventions and outcomes) and bias from confounding factors.

Measurement Bias

Misclassification of treatment strategy The classification of intervention status in both the initiation and the tapering studies is based on dispensing information from the VA's Pharmacy Benefits Management Services. Because for most veterans co-payments are low or zero, veterans have strong financial incentives to obtain outpatient prescriptions through the VA system. The dispensing information is highly accurate (Aspinall et al., 2016) and is a step closer to ingestion than prescribing information. Thus, the exposure information, in this type of observational data, is often better than that in a randomized controlled trial, where all that is typically known is the prescriber's intent. Nonetheless, automated prescription records indicate medications dispensed, not ingested, which may result in non-differential overestimation of ingestion, especially for symptomatic treatments, and thus a dilution of findings. In addition, the misclassification of opioid exposure due to access to illicit sources of opioids is of concern. Over-the-counter NSAIDs could also be a confounding variable, one that is more likely in the opioid exposure group.

For the tapering study specifically, the appropriate classification of the intervention categories represents a specific challenge as it requires inference of the intended treatment strategy (e.g., continuation, slow taper, fast taper, etc.) from multiple consecutive prescription fills (see Table 3-2).

Misclassification of outcomes (primary) All-cause mortality is ascertainable in the data with great accuracy. The NDI is regarded as the most authoritative source of death information for the U.S. population and includes more than 99 percent of all deaths in the United States (Lash and Silliman, 2001; Patterson and Bilgrad, 1986; Rich-Edwards et al., 1994; Sathiakumar et al., 1998). Suicide mortality, however, is likely subject to misclassification due to the misattribution of the intent of the injury causing death (Rockett et al., 2018; Stone et al., 2017).

Confounding

Prescribers and patients make decisions regarding opioid initiation and tapering strategies in light of the patient's characteristics and preferences and the prescriber's clinical experience. When such factors are also risk factors for the study outcomes (i.e., confounders), they might bias the results. A hypothetical example would be psychiatric conditions, which could affect the likelihood of treatment with opioids and benzodiazepines

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and also the likelihood of suicide. The observational study will adjust for baseline and post-baseline confounders via IP weighting as described above. Residual confounding remains a threat to the validity of results to the extent that confounders are inaccurately measured or unmeasured (see above for a discussion of key confounding factors, including those that are likely unmeasured in the VA data). To address residual confounding, the committee proposes using quantitative sensitivity analysis for unmeasured or poorly measured confounding factors (e.g., opioid misuse behaviors) to estimate the strength of residual confounding that would be necessary to explain the observed association (Schneeweiss, 2006).

Limited Statistical Power

As illustrated above, the sample size required to conduct a test with sufficient statistical power to compare treatment strategies is very large for a low-prevalence outcome such as suicide. One must assess a priori whether there would be a sufficient number of patients in the database to detect a clinically meaningful effect when emulating the target trial.

Generalizability

The interpretation of findings from the emulation of the target trial using observational data must take into account how generalizable the study's findings would be. For example, the proposed trial emulation would be applied to data from 2010 to 2017, so trends in opioid use and prescribing practices along with changing responses to opioid misuse and prescribing practices might reduce the generalizability of findings to future time periods. Furthermore, the study would use data from the VA population, so findings might not be generalizable beyond the VA because there are major demographic differences between VA users and other populations, with the VA population being more male and older on average than the broader population (NCVAS, 2019). Steps could be taken to enhance generalizability, such as by examining the treatment effects of interest within subgroups (e.g., by gender) or by weighting to match the demographics of the broader population (Stuart et al., 2015). Such steps are useful for enhancing generalizability with respect to the observable differences between the study population and the broader population, but they will not address unobservable differences.

CONCLUSIONS

Randomized trials are the preferred method for quantifying the causal effects of treatments on clinical outcomes. However, trials often are not

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possible for a variety of reasons, such as cost, ethics, and logistics, and the results from the trials that are feasible might have limited applicability in routine clinical settings. In those cases, analyses of existing observational data can be conducted to emulate the "target trial" of interest. An explicit emulation of the target trial—the hypothetical pragmatic randomized trial that would estimate the effect of interest, if conducted—mitigates or clarifies some of the limitations of studies using observational data. The committee described the rationale, advantages, and limitations of such an approach in Chapter 2.

The committee chose to describe two hypothetical target trials and sample emulation procedures for investigating the effects of (1) opioid initiation and (2) opioid dosage tapering in patients receiving chronic benzodiazepine treatment, and the committee developed protocols and analytic strategies for those trials, while recognizing that many other studies are of potential interest. The object of the trials is to determine preferred approaches for opioid initiation or tapering strategies for patients participating in the trials, while taking into account the potential limitations of the available observational dataset.

The committee emphasizes that the examples of studies in this report are only two of the possible target trials, chosen because they not only most directly address the Statement of Task, but also are the minimum number of studies needed to address the task. Adjustments to the proposed studies would likely be necessary after examining the observational data and determining how best to approach the studies and analyze the data. Many other studies would also be of interest beyond the outcomes of mortality and suicide in the population of veterans treated with opioids and benzodiazepines. For example, standardized self-report measures of pain, social and emotional functioning, depression, anxiety, and co-prescription of other central nervous system depressant medications could be examined to determine the effects of these factors on patient functioning over time. Examining the clinical and functional outcomes of veterans prescribed only opioids or only benzodiazepines would also be informative. The VA medical record contains a wealth of clinical information that could be analyzed to determine the potential benefits, as well as risks, to patients with a wide variety of characteristics who are prescribed opioids and benzodiazepines.

The committee views the proposed analysis plans and any related investigations as an excellent opportunity to use the rich VA clinical databases to elucidate the connections among important clinical conditions, treatment outcomes, and changes in opioid and benzodiazepine prescribing practices over the years 2010–2017. Significant changes in prescribing practice occurred over that period, so comparisons of the outcomes of different treatment strategies could yield important insights into best treatment practices. For example, because of understandable concerns about

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high-dosage opioid treatment, many practitioners in the United States have dramatically curtailed opioid prescribing in recent years in response to increasing rates of opioid use disorder (NASEM, 2017), yet that leaves many patients struggling to cope with chronic pain problems for which they had previously relied on opioid medication. The proposed observational studies has the potential to reveal important insights that could help health care providers improve chronic pain treatment by beginning to understand the most appropriate role of opioid treatment in a comprehensive program of chronic pain management.

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