December 1, 2015

TO: National Quality Forum

FROM: RAND Health

SUBJECT: Request for Ad Hoc Review of NQF 0004 (Initiation and Engagement of Alcohol and Other Drug Dependence Treatment)

This memo requests an ad hoc review of NQF 0004 (Initiation and Engagement of Alcohol and Other Drug Dependence Treatment). NQF 0004 is a two-part measure that consists of the proportion of patients with an initial diagnosis of alcohol or other drug dependence that receive (1) treatment within 14 days of the initial diagnosis, and (2) follow-up treatment within 30 days thereafter. In this memo, we present evidence that the current definition of "treatment" is incomplete, as it only includes psychosocial interventions, but not medication-assisted treatment (MAT). In other words, patients receiving MAT only would be misclassified based on the current definition.

We propose that the measure definition for NQF 0004 be changed so receiving psychosocial treatment only, MAT only, or both psychosocial treatment and MAT would meet the numerator criteria. Based on recent conversations with NQF staff, we understand that there is no plan for a systematic re-evaluation of NQF 0004 in the near future. Therefore, this memo is a request for an ad hoc review of NQF 0004 in order to align the measure definition with current evidence.

This memo provides evidence supporting a "material change" to the measure and therefore, a need for an ad hoc review of NQF 0004, including:

1. Guideline recommendations that support use of MAT for treatment of alcohol or opioid dependence.
2. Evidence from a targeted literature search on the proportion of psychosocial care being provided outside of the formal healthcare system, and therefore, not captured by claims data.

In a subsequent memo to be sent later, we will present empirical results from an analysis of claims data of the effect of changing the measure definitions. This will provide an estimate of the misclassification based on current definitions.

Exhibit 1 in this memo is an excerpt from the *current* Evidence Form for NQF 0004, written by the National Committee for Quality Assurance (NCQA) and submitted to NQF on February 28, 2013. The guideline recommendations cited in this form support the use of psychosocial care for patients with alcohol and other drug dependence, as reflected in the current definition of "treatment". Two of the guidelines that are cited in the current NQF Evidence Form submitted by NCQA, the Department of Veteran Affairs/Department of Defense (VA/DoD) guideline (VA/DoD, 2009) and the American Psychiatric Association (APA) guideline (APA, 2006), support a change in NQF 0004 to include MAT as an appropriate treatment option for patients with alcohol and opioid dependence. The recommendations

on MAT from the VA/DoD and APA guidelines are provided in Exhibits 2 and 3, respectively, for alcohol dependence and in Exhibits 4 and 5, respectively, for opioid dependence.

This memo also includes recommendations from several other clinical practice guidelines, which are not cited in the NQF 0004 Evidence Form, that support the use of MAT for patients with alcohol or opioid dependence. Exhibits 6 through 8 in this memo contain the exact wording of the recommendations for the use of MAT for *alcohol dependence* from three additional guidelines published between 2011 and 2015:

- Substance Abuse and Mental Health Services Administration and National Institute on Alcohol Abuse and Alcoholism, Medication for the Treatment of Alcohol Use Disorder: A Brief Guide. HHS Publication No. (SMA) 15-4907. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2015a. Available November 19, 2015, at http://store.samhsa.gov/shin/content/SMA15-4907/SMA15-4907.pdf
- British Association for Psychopharmacology (BAP): Lingford-Hughes AR, Welch S, Peters L, Nutt DJ. BAP updated guidelines: evidence-based guidelines for the pharmacological management of substance abuse, harmful use, addiction and co-morbidity: recommendations from BAP. J Psychopharmacol 2012; 26: 899–952. Available November 19, 2015, at http://www.bap.org.uk/pdfs/BAPaddictionEBG_2012.pdf
- National Institute for Health and Clinical Excellence (NICE). 2011. Alcohol-use disorders: diagnosis, assessment and management of harmful drinking and alcohol dependence. National Clinical Practice Guideline 115. National Collaborating Centre for Mental Health commissioned by the National Institute for Health & Clinical Excellence. Available November 19, 2015, at http://www.nice.org.uk/guidance/cg115/evidence

In total, the five guidelines (these three plus those from VA/DoD and APA) recommend that the clinician consider prescribing an FDA-approved medication (i.e., acamprosate calcium, disulfiram, oral naltrexone, or extended-release injectable naltrexone) in treating patients with alcohol dependence. Four of the five guidelines on alcohol dependence recommend that the pharmacological treatment be provided in conjunction with some type of psychosocial treatment. Three of the five organizations issuing these guidelines rated the strength of the recommendation and/or graded the supporting evidence; of these, the 2012 British Association for Psychopharmacology guideline on pharmacological management of substance abuse is the most recent.

Exhibits 9 through 17 in this memo contain the exact wording of the recommendations for the use of MAT for *opioid dependence* from nine additional guidelines, which are not cited in the NQF 0004 Evidence Form, published between 2005 and 2015:

- Substance Abuse and Mental Health Services Administration. Clinical Use of Extended-Release Injectable Naltrexone in the Treatment of Opioid Use Disorder: A Brief Guide. HHS Publication No. (SMA) 14-4892R. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2015b. Available November 19, 2015 at

http://store.samhsa.gov/product/Clinical-Use-of-Extended-Release-Injectable-Naltrexone-in-the-Treatment-of-Opioid-Use-Disorder-A-Brief-Guide/SMA14-4892R

- American Society of Addiction Medicine (ASAM), 2015. The National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use. Available November 19, 2015 at http://www.asam.org/docs/default-source/practice-support/guidelines-and-consensus-docs/national-practice-guideline.pdf
- British Association for Psychopharmacology (BAP): Lingford-Hughes AR, Welch S, Peters L, Nutt DJ. BAP updated guidelines: evidence-based guidelines for the pharmacological management of substance abuse, harmful use, addiction and co-morbidity: recommendations from BAP. J Psychopharmacol 2012; 26: 899–952. Available November 19, 2015, at http://www.bap.org.uk/pdfs/BAPaddictionEBG_2012.pdf
- World Federation of Societies of Biological Psychiatry (WFSBP): Soyka M, Kranzler HR, van den Brink W, Krystal J, Möller H-J, Kasper W. The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Substance Use and Related Disorders. Part 2: Opioid dependence. World J Biological Psychiatry 2011; 12:160–187. Available November 19, 2015, at http://www.wfsbp.org/fileadmin/user_upload/Treatment_Guidelines/Guidelines_Addiction_Part_2.pdf
- Centre for Addiction and Mental Health (CAMH): Handford C, Kahan M, Srivastava A, Cirone S, Sanghera S, Palda V. Buprenorphine/naloxone for opioid dependence: clinical practice guideline [Internet].Centre for Addiction and Mental Health; 2011. Available November 19, 2015 at https://knowledgex.camh.net/primary_care/guidelines_materials/Documents/buprenorphine_naloxone_gdlns2011.pdf
- World Health Organization, 2009. Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence. Available November 19, 2015 at http://www.who.int/substance_abuse/publications/opioid_dependence_guidelines.pdf
- National Institute for Health and Clinical Excellence (NICE), 2007a. Methadone and buprenorphine for the management of opioid dependence. Technology appraisal guidance. 24 January 2007a. Available November 19, 2015, at http://www.nice.org.uk/guidance/ta114
- National Institute for Health and Clinical Excellence (NICE). 2007b. Naltrexone for the management of opioid dependence. Technology appraisal guidance. 24 January 2007b. Available November 19, 2015, at http://www.nice.org.uk/guidance/ta115
- Substance Abuse and Mental Health Services Administration Center for Substance Abuse Treatment. Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs. Treatment Improvement Protocol (TIP) Series 43. HHS Publication No. (SMA) 12-4214. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2005. Available November 19, 2015 at http://store.samhsa.gov/shin/content//SMA12-4214/SMA12-4214.pdf

In total, the eleven guidelines (these nine plus those from VA/DoD and APA) recommend that the clinician consider prescribing one of the FDA-approved medications (i.e., buprenorphine, methadone, oral naltrexone, or extended-release injectable naltrexone) in treating opioid dependence. Seven of the

eleven guidelines on opioid dependence recommend that the pharmacological treatment be provided in conjunction with some type of psychosocial treatment. Six of the eleven organizations issuing these guidelines rated the strength of the recommendation and/or graded the supporting evidence; of these, the 2012 British Association for Psychopharmacology guideline on pharmacological management of substance abuse is the most recent. These recommendations for opioid dependence together with those for alcohol dependence offer strong guideline support for MAT being included in the definition of treatment for alcohol and other drug dependence in the NQF 0004 measure.

As mentioned above, the majority of guidelines in Exhibits 2 through 17 recommend that MAT be provided in conjunction with psychosocial treatment. In other words, patients on MAT should also have psychosocial treatment and therefore, it might be argued that the failure to include MAT in the measure definition might not affect measure results. However, this assumes that psychosocial treatment is captured properly. NQF 0004 relies on claims data to identify psychosocial treatment, which means that treatment received outside of the formal healthcare system, such as self-help groups, and treatment paid by the patient outside of his/her insurance will not be captured.

To estimate the frequency of treatment received outside of the formal healthcare system, this memo includes the results of a targeted literature search to estimate the frequency with which those with alcohol dependence seek psychosocial treatment outside the formal health care system. Two studies identified by our search (Exhibit 18) indicate high levels of participation in 12-Step programs such as Alcoholics Anonymous. According to a study by Dawson et al. (2006), 26 percent of those with alcohol dependence had ever sought help for alcohol problems. Of those who had sought treatment, 12 percent had participated in 12-Step programs only, 22 percent had received formal treatment only, and 67 percent had participated in both a 12-Step program and received formal treatment. Another study (Grant et al., 2015) found only 8 percent with a 12-month alcohol use disorder had sought treatment for their alcohol dependence in the previous 12 months; 59 percent of those who sought treatment reported receiving treatment from a 12-Step program. The same study reported 20 percent of those with a lifetime alcohol use disorder had sought treatment for alcohol dependence, of which 78 percent reported receiving treatment from a 12-Step program. We conclude that a meaningful proportion of patients with MAT will receive psychosocial support outside the formal health care system, and claims data are not able to capture that.

Finally, in the Appendix, we supplement the guideline recommendations with detailed information from five Cochrane reviews cited in the 2012 BAP guidelines to support recommendations regarding MAT.

Exhibit 1. Guideline Recommendations Cited in the Current Evidence Form for NQF 0004 (Initiation and Engagement of Alcohol and Other Drug Dependence Treatment)

1c.16 Quote verbatim, the specific guideline recommendation *(Including guideline # and/or page #)*:
American Psychiatric Association (APA): "Outpatient treatment of substance use disorders is appropriate for patients whose clinical condition or environmental circumstances do not require a more intensive level of care [I]. As in other treatment settings, a comprehensive approach is optimal, using, where indicated, a variety of psychotherapeutic and pharmacological interventions along with behavioral monitoring [I]"

Michigan Quality Improvement Consortium 2009: Schedule appropriate follow-up within 30 days to re-assess and support behavior change.

VA/DoD 2009: Offer referral to specialty SUD care for addiction treatment if the patient:

- May benefit from additional evaluation or motivational interviewing regarding his/her substance use and related problems
- Has tried and been unable to change substance use on his/her own or does not respond to repeated brief intervention
- Has been diagnosed with substance dependence
- Has previously been treated for an alcohol or other substance use disorder

USPSTF 2004: The USPSTF recommends screening and behavioral counseling interventions to reduce alcohol misuse by adults, including pregnant women, in primary care settings

1c.17 Clinical Practice Guideline Citation:
APA: Work Group on Substance Use Disorders, Kleber HD, Weiss RD, Anton RF, Rounsaville BJ, George TP, Strain EC, Greenfield SF, Ziedonis DM, Kosten TR, Hennessy G, O´Brien CP, Connery HS, American Psychiatric Association Steering Committee on Practice Guidelines, McIntyre JS, Charles SC, Anzia DJ, Nininger JE, Cook IA, Summergrad P, Finnerty MT, Woods SM, Johnson BR, Yager J, Pyles R, Lurie L, Cross CD, Walker RD, Peele R, Barnovitz MA, Gray SH, Shemo JP, Saxena S, Tonnu T, Kunkle R, Albert AB, Fochtmann LJ, Hart C, Regier D. Treatment of patients with substance use disorders, second edition. American Psychiatric Association. Am J Psychiatry 2006 Aug;163(8 Suppl):5-82.

Michigan: Michigan Quality Improvement Consortium. Screening, diagnosis and referral for substance use disorders. Southfield (MI): Michigan Quality Improvement Consortium; 2009

VA/DOD: Department of Veteran Affairs, Department of Defense. VA/DoD clinical practice guideline for management of substance use disorders (SUD). Washington (DC): Department of Veteran Affairs, Department of Defense; 2009 Aug. 158 p.

U.S. Preventive Services Task Force. Screening and Behavioral Counseling Interventions in Primary Care to Reduce Alcohol Misuse: Recommendation Statement. April 2004.
http://www.uspreventiveservicestaskforce.org/3rduspstf/alcohol/alcomisrs.htm

1c.18 National Guideline Clearinghouse or other URL:
http://www.uspreventiveservicestaskforce.org/3rduspstf/alcohol/alcomisrs.htm

1c.19 Grading of Strength of Guideline Recommendation. Has the recommendation been graded? Yes

1c.20 If guideline recommendation graded, identify the entity that graded the evidence including balance of

representation and any disclosures regarding bias: USPSTF/VA-DOD/MQIC/APA

1c.21 **System Used for Grading the Strength of Guideline Recommendation:** Other

1c.22 **If other, identify and describe the grading scale with definitions:** APA Rating Scheme for the Strength of the Recommendation
Each recommendation is identified as meriting one of three categories of endorsement, based on the level of clinical confidence regarding the recommendation, as indicated by a bracketed Roman numeral after the statement. The three categories are as follows:
[I] Recommended with substantial clinical confidence.
[II] Recommended with moderate clinical confidence.
[III] May be recommended on the basis of individual circumstances.
Method for Rating Strength of Recommendation
Expert Consensus
MQIC Rating Scheme for the Strength of the Recommendation
A. Randomized controlled trials
B. Controlled trials, no randomization
C. Observational studies
D. Opinion of expert panel
Method for Rating Strength of Recommendation
External Peer Review
Internal Peer Review

VA/DoD Rating Scheme for the Strength of the Recommendation
A A strong recommendation that the clinicians provide the intervention to eligible patients.
Good evidence was found that the intervention improves important health outcomes and concludes that benefits substantially outweigh harm.
B A recommendation that clinicians provide (the service) to eligible patients.
At least fair evidence was found that the intervention improves health outcomes and concludes that benefits outweigh harm.
C No recommendation for or against the routine provision of the intervention is made.
At least fair evidence was found that the intervention can improve health outcomes, but concludes that the balance of benefits and harms is too close to justify a general recommendation.
D Recommendation is made against routinely providing the intervention to asymptomatic patients.
At least fair evidence was found that the intervention is ineffective or that harms outweigh benefits.
I The conclusion is that the evidence is insufficient to recommend for or against routinely providing the intervention.
Evidence that the intervention is effective is lacking, or poor quality, or conflicting, and the balance of benefits and harms cannot be determined.
Method for Rating Strength of Recommendation
Peer Review

1c.23 **Grade Assigned to the Recommendation:** Grades are included in Section 1c.16

1c.24 **Rationale for Using this Guideline Over Others:** Used multiple guidelines to find areas of consistency in guidelines supporting this measure.

Exhibit 2. Guideline Recommendations Not in Current Evidence Form for NQF 0004 That Support Medication-Assisted Treatment of Alcohol Dependence: Department of Veteran Affairs, Department of Defense (VA/DOD), 2009

1a.4. CLINICAL PRACTICE GUIDELINE RECOMMENDATION

1a.4.1. Guideline citation (*including date*) and **URL for guideline** (*if available online*):
Department of Veteran Affairs, Department of Defense (VA/DOD). VA/DoD clinical practice guideline for management of substance use disorders (SUD). Washington (DC): Department of Veteran Affairs, Department of Defense; 2009 Aug. Available November 19, 2015, at http://www.healthquality.va.gov/guidelines/MH/sud/sud_full_601f.pdf

1a.4.2. Identify guideline recommendation number and/or page number and **quote verbatim, the specific guideline recommendation**.

Department of Veteran Affairs, Department of Defense (VA/DOD), 2009:

- Routinely consider oral naltrexone, an opioid antagonist, and/or acamprosate for patients with alcohol dependence. [A] (Module P, page 67)
- Medications should be offered in combined with addiction-focused counseling. [A] (Module P, page 67)
- Injectable naltrexone should be considered when medication adherence is a significant concern in treating alcohol dependence and should be combined with addiction-focused counseling. [A] (Module P, page 67)
- If patient does not respond to one of the approved medications, a trial on one of the other approved medications is warranted. (Module P, page 67)
- Because of the risk of significant toxicity and limited evidence of effectiveness, risk and benefits of disulfiram should be considered and disulfiram should only be used when abstinence is the goal and when combined with addiction-focused counseling. [B] The informed consent discussion with the patient should be documented. (Module P, page 67)
- Dosing of these pharmacotherapies should be consistent with medication trials and recommendations in appropriate drug references. (Module P, page 67)

1a.4.3. Grade assigned to the quoted recommendation with definition of the grade:
The VA Guideline (2009) assigned strength of recommendation ratings to each recommendation. **[A]** is defined as "A strong recommendation that the clinicians provide the intervention to eligible patients. Good evidence was found that the intervention improves important health outcomes and concludes that benefits substantially outweigh harm." **[B]** is defined as "A recommendation that clinicians provide (the service) to eligible patients. At least fair evidence was found that the intervention improves health outcomes and concludes that benefits outweigh harm." **[C]** is defined as "No recommendation for or against the routine provision of the intervention is made. At least fair evidence was found that the intervention can improve health outcomes, but concludes that the balance of benefits and harms is too close to justify a general recommendation." **[D]** is defined as "Recommendation is made against routinely providing the intervention. At least fair evidence was found that the intervention is ineffective or that harms outweigh benefits." **[I]** is defined as "The conclusion is that the evidence is insufficient to recommend for or against routinely providing the intervention. Evidence that the intervention is effective is lacking, or poor quality, or conflicting, and the balance of benefits and harms cannot be determined."

1a.4.4. Provide all other grades and associated definitions for recommendations in the grading system. (*Note: If separate grades for the strength of the evidence, report them in section 1a.7.*)
See section 1a.4.3 for all grades and associated definitions.

1a.4.5. Citation and URL for methodology for grading recommendations (*if different from 1a.4.1*)**:**
See section 1a.4.1 for guideline citation.

1a.4.6. If guideline is evidence-based (rather than expert opinion), are the details of the quantity, quality, and consistency of the body of evidence available (e.g., evidence tables)?

☐ Yes → ***complete section 1a.7***

☐ No → ***report on another systematic review of the evidence in sections 1a.6 and 1a.7; if another review does not exist, provide what is known from the guideline review of evidence in 1a.7***

Exhibit 3. Guideline Recommendations Not in Current Evidence Form for NQF 0004 That Support Medication-Assisted Treatment of Alcohol Dependence: American Psychiatric Association (APA), 2006

1a.4. CLINICAL PRACTICE GUIDELINE RECOMMENDATION

1a.4.1. Guideline citation (*including date*) and **URL for guideline** (*if available online*):

American Psychiatric Association (APA) Work Group on Substance Use Disorders, Kleber HD, Weiss RD, Anton RF, Rounsaville BJ, George TP, Strain EC, Greenfield SF, Ziedonis DM, Kosten TR, Hennessy G, O´Brien CP, Connery HS, American Psychiatric Association Steering Committee on Practice Guidelines, McIntyre JS, Charles SC, Anzia DJ, Nininger JE, Cook IA, Summergrad P, Finnerty MT, Woods SM, Johnson BR, Yager J, Pyles R, Lurie L, Cross CD, Walker RD, Peele R, Barnovitz MA, Gray SH, Shemo JP, Saxena S, Tonnu T, Kunkle R, Albert AB, Fochtmann LJ, Hart C, Regier D. Treatment of patients with substance use disorders, second edition. American Psychiatric Association. Am J Psychiatry 2006 Aug;163(8 Suppl):5-82. Available November 19, 2015 at http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/substanceuse.pdf

1a.4.2. Identify guideline recommendation number and/or page number and **quote verbatim, the specific guideline recommendation**.

American Psychiatric Association (APA), 2006:

- Specific pharmacotherapies for alcohol-dependent patients have well-established efficacy and moderate effectiveness. Naltrexone may attenuate some of the reinforcing effects of alcohol [I], although data on its long-term efficacy are limited. The use of long-acting, injectable naltrexone may promote adherence, but published research is limited and FDA approval is pending. Acamprosate, a γ-aminobutyric acid (GABA) analog that may decrease alcohol craving in abstinent individuals, may also be an effective adjunctive medication in motivated patients who are concomitantly receiving psychosocial treatment [I]. Disulfiram is an effective adjunct to a comprehensive treatment program for reliable, motivated patients whose drinking may be triggered by events that suddenly increase alcohol craving [II]. (page 13)

1a.4.3. Grade assigned to the quoted recommendation with definition of the grade:

The APA Guideline assigned one of three categories of endorsement to each recommendation, based on the level of clinical confidence. The categories are: [I] Recommended with substantial clinical confidence; [II] Recommended with moderate clinical confidence; and [III] May be recommended on the basis of individual circumstances.

1a.4.4. Provide all other grades and associated definitions for recommendations in the grading system. (*Note: If separate grades for the strength of the evidence, report them in section 1a.7.*)

See section 1a.4.3 for all grades and associated definitions.

1a.4.5. Citation and URL for methodology for grading recommendations (*if different from 1a.4.1*)**:**

See section 1a.4.1 for guideline citation.

1a.4.6. If guideline is evidence-based (rather than expert opinion), are the details of the quantity, quality, and consistency of the body of evidence available (e.g., evidence tables)?

☐ Yes → ***complete section 1a.7***

☐ No → ***report on another systematic review of the evidence in sections 1a.6 and 1a.7; if another review does not exist, provide what is known from the guideline review of evidence in 1a.7***

Exhibit 4. Guideline Recommendations Not in Current Evidence Form for NQF 0004 That Support Medication-Assisted Treatment of Opioid Dependence: Department of Veteran Affairs/Department of Defense (VA/DOD), 2009

1a.4. CLINICAL PRACTICE GUIDELINE RECOMMENDATION

1a.4.1. Guideline citation (*including date*) and **URL for guideline** (*if available online*):
Department of Veteran Affairs, Department of Defense (VA/DOD). VA/DoD clinical practice guideline for management of substance use disorders (SUD). Washington (DC): Department of Veteran Affairs, Department of Defense; 2009 Aug. Available November 19, 2015, at http://www.healthquality.va.gov/guidelines/MH/sud/sud_full_601f.pdf

1a.4.2. Identify guideline recommendation number and/or page number and **quote verbatim, the specific guideline recommendation**.

Department of Veteran Affairs, Department of Defense (VA/DOD), 2009:

- Provide access to opioid agonist treatment (OAT) for all opioid dependent patients, under appropriate medical supervision and with concurrent addiction-focused psychosocial treatment as indicated. [A] (Module P, page 55)
- Strongly recommend methadone or sublingual buprenorphine/naloxone maintenance as first line treatments due to their documented efficacy in improving retention and reducing illicit opioid use and craving. [A] (Module P, page 55)
- Appropriate psychosocial interventions should be provided as part of the opioid agonist therapy (OAT). [A] (Module P, page 59)
- Consider monitored administration of naltrexone maintenance in highly motivated opioid dependent patients. [C] (Module P, page 64)
- Consider opioid agonist treatment (OAT) or long-term therapeutic community before naltrexone as first line approaches for chronic opioid dependent patients. (Module P, page 64)

1a.4.3. Grade assigned to the quoted recommendation with definition of the grade:
The VA Guideline (2009) assigned strength of recommendation ratings to each recommendation. **[A]** is defined as "A strong recommendation that the clinicians provide the intervention to eligible patients. Good evidence was found that the intervention improves important health outcomes and concludes that benefits substantially outweigh harm." **[B]** is defined as "A recommendation that clinicians provide (the service) to eligible patients. At least fair evidence was found that the intervention improves health outcomes and concludes that benefits outweigh harm." **[C]** is defined as "No recommendation for or against the routine provision of the intervention is made. At least fair evidence was found that the intervention can improve health outcomes, but concludes that the balance of benefits and harms is too close to justify a general recommendation." **[D]** is defined as "Recommendation is made against routinely providing the intervention. At least fair evidence was found that the intervention is ineffective or that harms outweigh benefits." **[I]** is defined as "The conclusion is that the evidence is insufficient to recommend for or against routinely providing the intervention. Evidence that the intervention is effective is lacking, or poor quality, or conflicting, and the balance of benefits and harms cannot be determined."

1a.4.4. Provide all other grades and associated definitions for recommendations in the grading system. (*Note: If separate grades for the strength of the evidence, report them in section 1a.7.*)
See section 1a.4.3 for all grades and associated definitions.

1a.4.5. Citation and URL for methodology for grading recommendations (*if different from 1a.4.1*)**:**
See section 1a.4.1 for guideline citation.

1a.4.6. If guideline is evidence-based (rather than expert opinion), are the details of the quantity, quality, and consistency of the body of evidence available (e.g., evidence tables)?

☐ Yes → ***complete section 1a.7***

☐ No → ***report on another systematic review of the evidence in sections 1a.6 and 1a.7; if another review does not exist, provide what is known from the guideline review of evidence in 1a.7***

Exhibit 5. Guideline Recommendations Not in Current Evidence Form for NQF 0004 That Support Medication-Assisted Treatment of Opioid Dependence: American Psychiatric Association (APA), 2006

1a.4. CLINICAL PRACTICE GUIDELINE RECOMMENDATION

1a.4.1. Guideline citation (*including date*) and **URL for guideline** (*if available online*):
American Psychiatric Association (APA) Work Group on Substance Use Disorders, Kleber HD, Weiss RD, Anton RF, Rounsaville BJ, George TP, Strain EC, Greenfield SF, Ziedonis DM, Kosten TR, Hennessy G, O´Brien CP, Connery HS, American Psychiatric Association Steering Committee on Practice Guidelines, McIntyre JS, Charles SC, Anzia DJ, Nininger JE, Cook IA, Summergrad P, Finnerty MT, Woods SM, Johnson BR, Yager J, Pyles R, Lurie L, Cross CD, Walker RD, Peele R, Barnovitz MA, Gray SH, Shemo JP, Saxena S, Tonnu T, Kunkle R, Albert AB, Fochtmann LJ, Hart C, Regier D. Treatment of patients with substance use disorders, second edition. American Psychiatric Association. Am J Psychiatry 2006 Aug;163(8 Suppl):5-82. Available November 19, 2015 at http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/substanceuse.pdf

1a.4.2. Identify guideline recommendation number and/or page number and **quote verbatim, the specific guideline recommendation**.
American Psychiatric Association (APA), 2006:

- Maintenance treatment with methadone or buprenorphine is appropriate for patients with a prolonged history (>1 year) of opioid dependence [I]. The goals of treatment are to achieve a stable maintenance dose of opioid agonist and facilitate engagement in a comprehensive program of rehabilitation [I]. Maintenance treatment with naltrexone is an alternative strategy [I], although the utility of this strategy is often limited by lack of patient adherence and low treatment retention. (page 14)

1a.4.3. Grade assigned to the quoted recommendation with definition of the grade:
The APA Guideline assigned one of three categories of endorsement to each recommendation, based on the level of clinical confidence. The categories are: [I] Recommended with substantial clinical confidence; [II] Recommended with moderate clinical confidence; and [III] May be recommended on the basis of individual circumstances.

1a.4.4. Provide all other grades and associated definitions for recommendations in the grading system. (*Note: If separate grades for the strength of the evidence, report them in section 1a.7.*)
See section 1a.4.3 for all grades and associated definitions.

1a.4.5. Citation and URL for methodology for grading recommendations (*if different from 1a.4.1*)**:**
See section 1a.4.1 for guideline citation.

1a.4.6. If guideline is evidence-based (rather than expert opinion), are the details of the quantity, quality, and consistency of the body of evidence available (e.g., evidence tables)?
☐ Yes → ***complete section 1a.7***
☐ No → ***report on another systematic review of the evidence in sections 1a.6 and 1a.7; if another review does not exist, provide what is known from the guideline review of evidence in 1a.7***

Exhibit 6. Guideline Recommendations Not in Current Evidence Form for NQF 0004 That Support Medication-Assisted Treatment of Alcohol Dependence: Substance Abuse and Mental Health Services Administration (SAMHSA), 2015a

1a.4. CLINICAL PRACTICE GUIDELINE RECOMMENDATION

1a.4.1. Guideline citation (*including date*) and **URL for guideline** (*if available online*):
Substance Abuse and Mental Health Services Administration and National Institute on Alcohol Abuse and Alcoholism, Medication for the Treatment of Alcohol Use Disorder: A Brief Guide. HHS Publication No. (SMA) 15-4907. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2015a. Available November 19, 2015, at http://store.samhsa.gov/shin/content/SMA15-4907/SMA15-4907.pdf

1a.4.2. Identify guideline recommendation number and/or page number and **quote verbatim, the specific guideline recommendation**.
SAMHSA, 2015a:
Clinicians should consider prescribing one of these medications [i.e., acamprosate calcium, disulfiram, oral naltrexone, extended-release injectable naltrexone] when treating a patient who is dependent on alcohol or who has stopped drinking but is experiencing problems including cravings or relapses. Patients with moderate or severe alcohol use disorder, including those who have physiologic dependence or who are experiencing cravings and have not improved in response to psychosocial approaches alone, are particularly strong candidates for medication-assisted treatment. (page 2)

Medications should be prescribed as part of a comprehensive treatment approach that includes counseling and other psychosocial therapies (through referral to a psychiatrist, psychologist, or professional counselor) and social supports (through participation in Alcoholics Anonymous and other mutual-help programs). (page 2)

1a.4.3. Grade assigned to the quoted recommendation with definition of the grade:
SAMHSA, 2015, Medication for the Treatment of Alcohol Use Disorder: A Brief Guide:
The recommendations were not graded.

1a.4.4. Provide all other grades and associated definitions for recommendations in the grading system. (*Note: If separate grades for the strength of the evidence, report them in section 1a.7.*)
The recommendations were not graded.

1a.4.5. Citation and URL for methodology for grading recommendations (*if different from 1a.4.1*)**:**
The recommendations were not graded.

1a.4.6. If guideline is evidence-based (rather than expert opinion), are the details of the quantity, quality, and consistency of the body of evidence available (e.g., evidence tables)?
☐ Yes → ***complete section 1a.7***
☐ No → ***report on another systematic review of the evidence in sections 1a.6 and 1a.7; if another review does not exist, provide what is known from the guideline review of evidence in 1a.7***

Exhibit 7. Guideline Recommendations Not in Current Evidence Form for NQF 0004 That Support Medication-Assisted Treatment of Alcohol Dependence: British Association for Psychopharmacology (BAP) (Lingford-Hughes, 2012)

1a.4. CLINICAL PRACTICE GUIDELINE RECOMMENDATION

1a.4.1. Guideline citation (*including date*) and **URL for guideline** (*if available online*):
British Association for Psychopharmacology (BAP): Lingford-Hughes AR, Welch S, Peters L, Nutt DJ. BAP updated guidelines: evidence-based guidelines for the pharmacological management of substance abuse, harmful use, addiction and co-morbidity: recommendations from BAP. J Psychopharmacol 2012; 26: 899–952. Available November 19, 2015 at http://www.bap.org.uk/pdfs/BAPaddictionEBG_2012.pdf

1a.4.2. Identify guideline recommendation number and/or page number and **quote verbatim, the specific guideline recommendation**.
British Association for Psychopharmacology (BAP) (Lingford-Hughes, 2012):
- Acamprosate can be used to improve abstinence rates (A). It should be continued if the person starts drinking, since there is evidence that acamprosate reduces alcohol consumption (A), at least for a period to assess whether there is overall patient benefit attributable to acamprosate. (page 11)
- Naltrexone can be used to reduce risk of lapse becoming a relapse, but there is less evidence to support its use in maintaining abstinence (A). Naltrexone may therefore be a better choice if someone is 'sampling' alcohol regularly but wishes to be abstinent. (page 11)
- For acamprosate and naltrexone there is no consistent evidence to suggest which types of patient will respond, and relapse prevention medication should be offered to/considered for everyone who is alcohol dependent wanting to be abstinent (A). (page 11)
- Disulfiram is effective if intake is witnessed. Disulfiram can be offered as a treatment option for patients who intend to maintain abstinence, and for whom there are no contraindications (B). (page 11)
- Baclofen should be considered if a patient wants to be abstinent , has high levels of anxiety and has not benefited from or is unable to take acamprosate, naltrexone or disulfiram (C). (page 11)
- SSRIs should be avoided, or used with caution in type 2 alcoholism (B). (page 11)

1a.4.3. Grade assigned to the quoted recommendation with definition of the grade:
Strength of recommendation is defined as **[A]** directly based on category I evidence (from meta-analysis of randomized controlled trials (Ia) or evidence from at least one randomized controlled trial (Ib)); **[B]** directly based on category II evidence (evidence from at least one controlled study without randomization (IIa) or evidence from at least one other type of quasi-experimental study (IIb) or extrapolated recommendation from category I evidence); **[C]** directly based on category III evidence (evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies) or extrapolated recommendation from category I or II evidence; **[D]** directly based on category IV evidence (evidence from expert committee reports or opinions and/or clinical experience of respected authorities) or extrapolated recommendation from category I, II or III evidence; **[S]**: Standard of care (BAP: Lingford-Hughes et al., 2012).

1a.4.4. Provide all other grades and associated definitions for recommendations in the grading system. (*Note: If separate grades for the strength of the evidence, report them in section 1a.7.*)
See section 1a.4.3 for all grades and associated definitions.

1a.4.5. Citation and URL for methodology for grading recommendations (*if different from 1a.4.1*)**:**
See section 1a.4.1 for guideline citation.

1a.4.6. If guideline is evidence-based (rather than expert opinion), are the details of the quantity, quality, and consistency of the body of evidence available (e.g., evidence tables)?
☐ Yes → ***complete section 1a.7***
☐ No → ***report on another systematic review of the evidence in sections 1a.6 and 1a.7; if another review does not exist, provide what is known from the guideline review of evidence in 1a.7***

Exhibit 8. Guideline Recommendations Not in Current Evidence Form for NQF 0004 That Support Medication-Assisted Treatment of Alcohol Dependence: National Institute for Health and Clinical Excellence (NICE), 2011

1a.4. CLINICAL PRACTICE GUIDELINE RECOMMENDATION

1a.4.1. Guideline citation (*including date*) and **URL for guideline** (*if available online*):

National Institute for Health and Clinical Excellence (NICE). 2011. Alcohol-use disorders: diagnosis, assessment and management of harmful drinking and alcohol dependence. National Clinical Practice Guideline 115. National Collaborating Centre for Mental Health commissioned by the National Institute for Health & Clinical Excellence. Available November 19, 2015, at http://www.nice.org.uk/guidance/cg115/evidence

1a.4.2. Identify guideline recommendation number and/or page number and **quote verbatim, the specific guideline recommendation**.

National Institute for Health and Clinical Excellence (NICE), 2011:

- 7.15.1.1 After a successful withdrawal for people with moderate and severe alcohol dependence, consider offering acamprosate or oral naltrexone in combination with an individual psychological intervention (cognitive behavioural therapies, behavioural therapies or social network and environment-based therapies) focused specifically on alcohol misuse. (page 424)
- 7.16.5.1 For harmful drinkers and people with mild alcohol dependence who have not responded to psychological interventions alone, or who have specifically requested a pharmacological intervention, consider offering acamprosate [6] or oral naltrexone in combination with an individual psychological intervention (cognitive behavioural therapies, behavioural therapies or social network and environment-based therapies) or behavioural couples therapy. (page 429)
- 8.3.6.1 After a successful withdrawal for people with moderate and severe alcohol dependence, consider offering acamprosate or oral naltrexone in combination with an individual psychological intervention (cognitive behavioural therapies, behavioural therapies or social network and environment-based therapies) focused specifically on alcohol misuse. (page 454)
- 8.3.6.2 After a successful withdrawal for people with moderate and severe alcohol dependence, consider offering acamprosate or oral naltrexone in combination with behavioural couples therapy to service users who have a regular partner and whose partner is willing to participate in treatment. (page 454)
- 8.3.6.3 After a successful withdrawal for people with moderate and severe alcohol dependence, consider offering disulfiram in combination with a psychological intervention to service users who:
  - have a goal of abstinence but for whom acamprosate and oral naltrexone are not suitable, or
  - prefer disulfiram and understand the relative risks of taking the drug. (page 455)
- 8.3.7.9 After a careful review of the risks and benefits, specialists may consider offering acamprosate [15] or oral naltrexone in combination with cognitive behavioural therapy to young people aged 16 and 17 years who have not engaged with or benefited from a multicomponent treatment programme. (page 458)

1a.4.3. Grade assigned to the quoted recommendation with definition of the grade:

The recommendations were not graded.

1a.4.4. Provide all other grades and associated definitions for recommendations in the grading system. (*Note: If separate grades for the strength of the evidence, report them in section 1a.7.*)

The recommendations were not graded.

1a.4.5. Citation and URL for methodology for grading recommendations (*if different from 1a.4.1*)**:**

The recommendations were not graded.

1a.4.6. If guideline is evidence-based (rather than expert opinion), are the details of the quantity, quality, and consistency of the body of evidence available (e.g., evidence tables)?

☐ Yes → ***complete section 1a.7***

☐ No → ***report on another systematic review of the evidence in sections 1a.6 and 1a.7; if another review does not exist, provide what is known from the guideline review of evidence in 1a.7***

Exhibit 9. Guideline Recommendations Not in Current Evidence Form for NQF 0004 That Support Medication-Assisted Treatment of Opioid Dependence: Substance Abuse and Mental Health Services Administration (SAMHSA), 2015b

1a.4. CLINICAL PRACTICE GUIDELINE RECOMMENDATION

1a.4.1. Guideline citation (*including date*) and **URL for guideline** (*if available online*):
Substance Abuse and Mental Health Services Administration. Clinical Use of Extended-Release Injectable Naltrexone in the Treatment of Opioid Use Disorder: A Brief Guide. HHS Publication No. (SMA) 14-4892R. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2015b. Available October 29, 2015 at http://store.samhsa.gov/product/Clinical-Use-of-Extended-Release-Injectable-Naltrexone-in-the-Treatment-of-Opioid-Use-Disorder-A-Brief-Guide/SMA14-4892R

1a.4.2. Identify guideline recommendation number and/or page number and **quote verbatim, the specific guideline recommendation**.

Substance Abuse and Mental Health Services Administration (SAMHSA), 2015b:

- All medications for the treatment of the opioid use disorder should be prescribed as part of a comprehensive treatment approach that includes counseling and other psychosocial therapies delivered by a psychiatrist, psychologist, or professional counselor, as well as social support through participation in Narcotics Anonymous (NA) and other mutual-help programs. Health care providers who choose to offer medication-assisted treatment in their office practices need to understand the nature of the underlying disorder, the specific actions of each available medication (and the associated contraindications or cautions), and the importance of careful patient selection and monitoring. (page 3)
- Clinical Recommendations. Although no definitive research supports which patients benefit most from extended-release injectable naltrexone, patients in the following categories may be good candidates for such treatment.
  - Patients who have not had treatment success with methadone or buprenorphine: Depending on the reasons for treatment failure, individuals with an opioid use disorder who have not been successfully treated with methadone or buprenorphine may benefit from medically supervised withdrawal followed by a trial of extended-release injectable naltrexone. (page 8)
  - Patients who have a high degree of motivation for abstinence: Individuals who are highly motivated to achieve and maintain abstinence from opioids may be good candidates for treatment with extended-release injectable naltrexone. This category includes people who are required to demonstrate abstinence on urine drug screens, such as individuals in programs for impaired health care professionals, parolees, probationers, and airline pilots. (page 8)
- Some patients respond to psychosocial interventions or medication therapy alone, but most patients need both. The different approaches (medication-assisted treatment, professional counseling, and mutual-help groups) are complementary. They support the same goals while addressing different aspects of opioid use disorder: neurobiological, psychological, and social. (page 9)
- Offering the full range of effective treatments maximizes patient choice and outcomes, because no single approach is universally successful. Many studies show that the combination of pharmacologic and nonpharmacologic interventions may be more effective than either approach used alone. (page 9)

1a.4.3. Grade assigned to the quoted recommendation with definition of the grade:
The recommendations were not graded.

1a.4.4. Provide all other grades and associated definitions for recommendations in the grading system. (*Note: If separate grades for the strength of the evidence, report them in section 1a.7.*)
The recommendations were not graded.

1a.4.5. Citation and URL for methodology for grading recommendations (*if different from 1a.4.1*)**:**
The recommendations were not graded.

1a.4.6. If guideline is evidence-based (rather than expert opinion), are the details of the quantity, quality, and consistency of the body of evidence available (e.g., evidence tables)?
☐ Yes → ***complete section 1a.7***

☐ No → ***report on another systematic review of the evidence in sections 1a.6 and 1a.7; if another review does not exist, provide what is known from the guideline review of evidence in 1a.7***

Exhibit 10. Guideline Recommendations Not in Current Evidence Form for NQF 0004 That Support Medication-Assisted Treatment of Opioid Dependence: American Society of Addiction Medicine (ASAM), 2015

1a.4. CLINICAL PRACTICE GUIDELINE RECOMMENDATION

1a.4.1. Guideline citation (*including date*) and **URL for guideline** (*if available online*):

American Society of Addiction Medicine (ASAM). 2015. The National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use. Available November 19, 2015 at http://www.asam.org/docs/default-source/practice-support/guidelines-and-consensus-docs/national-practice-guideline.pdf

1a.4.2. Identify guideline recommendation number and/or page number and **quote verbatim, the specific guideline recommendation**.

American Society of Addiction Medicine (ASAM), 2015:

- Methadone is a treatment option recommended for patients who are physiologically dependent on opioids, able to give informed consent, and who have no specific contraindications for agonist treatment when it is prescribed in the context of an appropriate plan that includes psychosocial intervention. (page 17)
- Psychosocial treatment, though sometimes minimally needed, should be implemented in conjunction with the use of methadone in the treatment of opioid use disorder. (page 17)
- Buprenorphine is recommended for the treatment of opioid use disorder. Buprenorphine relieves drug cravings without producing the euphoria or dangerous side effects of other opioids. In addition to its pharmacological properties, an important feature of buprenorphine is its ability to be prescribed in office-based treatment settings. (page 84)
- Psychosocial treatment should be implemented in conjunction with the use of buprenorphine in the treatment of opioid use disorder. (page 92)
- Naltrexone is a recommended treatment in preventing relapse in opioid use disorder. Oral formula naltrexone may be considered for patients where adherence can be supervised or enforced. Extended-release injectable naltrexone may be more suitable for patients who have issues with adherence. (page 98)
- Psychosocial treatment is recommended in conjunction with treatment with naltrexone. The efficacy of naltrexone use in conjunction with psychosocial treatment has been established, whereas the efficacy of extended-release injectable naltrexone without psychosocial intervention has not been established. (page 99)

1a.4.3. Grade assigned to the quoted recommendation with definition of the grade:

The recommendations were not graded.

1a.4.4. Provide all other grades and associated definitions for recommendations in the grading system. (*Note: If separate grades for the strength of the evidence, report them in section 1a.7.*)

The recommendations were not graded.

1a.4.5. Citation and URL for methodology for grading recommendations (*if different from 1a.4.1*)**:**

The recommendations were not graded.

1a.4.6. If guideline is evidence-based (rather than expert opinion), are the details of the quantity, quality, and consistency of the body of evidence available (e.g., evidence tables)?

☐ Yes → ***complete section 1a.7***

☐ No → ***report on another systematic review of the evidence in sections 1a.6 and 1a.7; if another review does not exist, provide what is known from the guideline review of evidence in 1a.7***

Exhibit 11. Guideline Recommendations Not in Current Evidence Form for NQF 0004 That Support Medication-Assisted Treatment of Opioid Dependence: British Association for Psychopharmacology (BAP) (Lingford-Hughes, 2012)

1a.4. CLINICAL PRACTICE GUIDELINE RECOMMENDATION

1a.4.1. Guideline citation (*including date*) and **URL for guideline** (*if available online*):
British Association for Psychopharmacology (BAP): Lingford-Hughes AR, Welch S, Peters L, Nutt DJ. BAP updated guidelines: evidence-based guidelines for the pharmacological management of substance abuse, harmful use, addiction and co-morbidity: recommendations from BAP. J Psychopharmacol 2012; 26: 899–952. Available November 19, 2015, at http://www.bap.org.uk/pdfs/BAPaddictionEBG_2012.pdf

1a.4.2. Identify guideline recommendation number and/or page number and **quote verbatim, the specific guideline recommendation**.

British Association for Psychopharmacology (BAP) (Lingford-Hughes, 2012):

- MMT is an appropriate treatment option for opioid-dependent patients. It is effective in reducing heroin use, injecting, and sharing of injecting equipment (A). (page 14)
- BMT is an appropriate treatment option for opioid-dependent patients. It is effective in reducing heroin use (A). (page 14)
- Both methadone and buprenorphine are effective treatments. Opioid-dependent patients should be offered either medication, guided by patient choice and safety considerations. (A). (page 14)
- MMT or BMT should be provided in conjunction with psychosocial interventions such as regular counselling (B). (page 14)
- Oral naltrexone treatment should be considered for formerly opioid-dependent people who are highly motivated to remain abstinent (D). (page 16)

1a.4.3. Grade assigned to the quoted recommendation with definition of the grade:
Strength of recommendation is defined as **[A]** directly based on category I evidence (from meta-analysis of randomized controlled trials (Ia) or evidence from at least one randomized controlled trial (Ib)); **[B]** directly based on category II evidence (evidence from at least one controlled study without randomization (IIa) or evidence from at least one other type of quasi-experimental study (IIb) or extrapolated recommendation from category I evidence); **[C]** directly based on category III evidence (evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies) or extrapolated recommendation from category I or II evidence; **[D]** directly based on category IV evidence (evidence from expert committee reports or opinions and/or clinical experience of respected authorities) or extrapolated recommendation from category I, II or III evidence; **[S]**: Standard of care (BAP: Lingford-Hughes et al., 2012).

1a.4.4. Provide all other grades and associated definitions for recommendations in the grading system. (*Note: If separate grades for the strength of the evidence, report them in section 1a.7.*)
See section 1a.4.3 for all grades and associated definitions.

1a.4.5. Citation and URL for methodology for grading recommendations (*if different from 1a.4.1*)**:**
See section 1a.4.1 for guideline citation.

1a.4.6. If guideline is evidence-based (rather than expert opinion), are the details of the quantity, quality, and consistency of the body of evidence available (e.g., evidence tables)?

☐ Yes → ***complete section 1a.7***

☐ No → ***report on another systematic review of the evidence in sections 1a.6 and 1a.7; if another review does not exist, provide what is known from the guideline review of evidence in 1a.7***

Exhibit 12. Guideline Recommendations Not in Current Evidence Form for NQF 0004 That Support Medication-Assisted Treatment of Opioid Dependence: World Federation of Societies of Biological Psychiatry (WFSBP), 2011

1a.4. CLINICAL PRACTICE GUIDELINE RECOMMENDATION

1a.4.1. Guideline citation (*including date*) and **URL for guideline** (*if available online*):
World Federation of Societies of Biological Psychiatry (WFSBP): Soyka M, Kranzler HR, van den Brink W, Krystal J, Möller H-J, Kasper W. The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Substance Use and Related Disorders. Part 2: Opioid dependence. World J Biological Psychiatry 2011; 12:160–187. Available November 19, 2015, at http://www.wfsbp.org/fileadmin/user_upload/Treatment_Guidelines/Guidelines_Addiction_Part_2.pdf

1a.4.2. Identify guideline recommendation number and/or page number and **quote verbatim, the specific guideline recommendation**.
World Federation of Societies of Biological Psychiatry (WFSBP) (2011):

- Methadone is the standard medication for the treatment of opioid dependence [RG1]. Its efficacy can be enhanced when combined with contingency management [RG1]. (page 168)
- Buprenorphine and buprenorphine/naloxone are standard medications for the treatment of opioid dependence. [RG1] Whether the combination of buprenorphine and naloxone has advantages over buprenorphine alone requires empirical validation. There are no indications that adding contingency management to buprenorphine maintenance treatment enhances its effectiveness [RG1]. (page 171)
- Oral naltrexone is not a first line treatment for opioid dependence [RG1]. However, oral naltrexone might be effective in a small subgroup of highly motivated and well-integrated patients [RG3]. Retention in naltrexone treatment is usually poor. (page 172)
- Although depot naltrexone is now approved and available in the United States for the treatment of opioid dependence, additional studies are needed to define more clearly its clinical efficacy over the long term. Naltrexone implants cannot yet be recommended for clinical use because although there are promising efficacy data for them, safety concerns remain and require further evaluation. (page 173)
-

1a.4.3. Grade assigned to the quoted recommendation with definition of the grade:
The recommendation grades are defined as follows: RG1=Category A evidence (Full Evidence From Controlled Studies) and good risk-benefit ratio; RG2=Category A evidence (Full Evidence From Controlled Studies) and moderate risk-benefit ratio; RG3=Category B evidence (Limited Positive Evidence From Controlled Studies); RG4=Category C evidence (Evidence from Uncontrolled Studies or Case Reports/Expert Opinion); RG5=Category D evidence (Inconsistent results).

1a.4.4. Provide all other grades and associated definitions for recommendations in the grading system. (*Note: If separate grades for the strength of the evidence, report them in section 1a.7.*)
See section 1a.4.3 for all grades and associated definitions.

1a.4.5. Citation and URL for methodology for grading recommendations (*if different from 1a.4.1*)**:**
See section 1a.4.1 for guideline citation.

1a.4.6. If guideline is evidence-based (rather than expert opinion), are the details of the quantity, quality, and consistency of the body of evidence available (e.g., evidence tables)?
☐ Yes → ***complete section 1a.7***
☐ No → ***report on another systematic review of the evidence in sections 1a.6 and 1a.7; if another review does not exist, provide what is known from the guideline review of evidence in 1a.7***

Exhibit 13. Guideline Recommendations Not in Current Evidence Form for NQF 0004 That Support Medication-Assisted Treatment of Opioid Dependence: Centre for Addiction and Mental Health (CAMH), 2011

1a.4. CLINICAL PRACTICE GUIDELINE RECOMMENDATION

1a.4.1. Guideline citation (*including date*) and **URL for guideline** (*if available online*):
Centre for Addiction and Mental Health (CAMH): Handford C, Kahan M, Srivastava A, Cirone S, Sanghera S, Palda V. Buprenorphine/naloxone for opioid dependence: clinical practice guideline [Internet].Centre for Addiction and Mental Health; 2011. Available November 19, 2015 at https://knowledgex.camh.net/primary_care/guidelines_materials/Documents/buprenorphine_naloxone_gdlns2011.pdf

1a.4.2. Identify guideline recommendation number and/or page number and **quote verbatim, the specific guideline recommendation**.
Centre for Addiction and Mental Health (CAMH), 2011:

- Once a patient is diagnosed with opioid dependence and is deemed appropriate for opioid agonist treatment, prescribers are encouraged to consider prescribing either buprenorphine/naloxone or methadone in order to increase retention in treatment and decrease opioid misuse. (Level I, Grade A) (page 22)

1a.4.3. Grade assigned to the quoted recommendation with definition of the grade:
Levels of evidence are defined as follows: I=Evidence from randomized, controlled trial(s); II-1=Evidence from controlled trial(s) without randomization; II-2=Evidence from cohort or case-control analytic studies, preferably from more than one centre or research group; II-3 Evidence from comparisons between times or places with or without the intervention; dramatic results in uncontrolled experiments could be included here; III=Opinions of respected authorities, based on clinical experience; descriptive studies or reports of expert committees.
Grades of recommendation are defined as follows: A=There is good evidence to recommend the action; B=There is fair evidence to recommend the action; C=The existing evidence is conflicting and does not allow making a recommendation for or against the use of the action; however, other factors may influence decisionmaking; D=There is fair evidence to recommend against the action; E=There is good evidence to recommend against the action; I=There is insufficient evidence (in quantity and/or quality) to make a recommendation; however, other factors may influence decision-making.

1a.4.4. Provide all other grades and associated definitions for recommendations in the grading system. (*Note: If separate grades for the strength of the evidence, report them in section 1a.7.*)
See section 1a.4.3 for all grades and associated definitions.

1a.4.5. Citation and URL for methodology for grading recommendations (*if different from 1a.4.1*)**:**
See section 1a.4.1 for guideline citation.

1a.4.6. If guideline is evidence-based (rather than expert opinion), are the details of the quantity, quality, and consistency of the body of evidence available (e.g., evidence tables)?
☐ Yes → ***complete section 1a.7***
☐ No → ***report on another systematic review of the evidence in sections 1a.6 and 1a.7; if another review does not exist, provide what is known from the guideline review of evidence in 1a.7***

Exhibit 14. Guideline Recommendations Not in Current Evidence Form for NQF 0004 That Support Medication-Assisted Treatment of Opioid Dependence: World Health Organization (WHO), 2009

1a.4. CLINICAL PRACTICE GUIDELINE RECOMMENDATION

1a.4.1. Guideline citation (*including date*) and **URL for guideline** (*if available online*):
World Health Organization. 2009. Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence. Available November 19, 2015 at http://www.who.int/substance_abuse/publications/opioid_dependence_guidelines.pdf

1a.4.2. Identify guideline recommendation number and/or page number and **quote verbatim, the specific guideline recommendation**.

World Health Organization (WHO), 2009:

- For the pharmacological treatment of opioid dependence, clinicians should offer opioid withdrawal, opioid agonist maintenance and opioid antagonist (naltrexone) treatment, but most patients should be advised to use opioid agonist maintenance treatment. (Strength of recommendation=strong; Quality of evidence=low to moderate) (page 29)
- For opioid-dependent patients not commencing opioid agonist maintenance treatment, consider antagonist pharmacotherapy using naltrexone following the completion of opioid withdrawal. (Strength of recommendation = standard; Quality of evidence = low) (page 29)

1a.4.3. Grade assigned to the quoted recommendation with definition of the grade:
As recommended in the GRADE system, recommendations were divided into two strengths, here termed as "strong" or "standard" recommendations. Strong recommendations are those for which: most individuals should receive the intervention, assuming that they have been informed about and understand its benefits, harms and burdens; most individuals would want the recommended course of action and only a small proportion would not; the recommendation could unequivocally be used for policy making. Standard recommendations are those for which: most individuals would want the suggested course of action, but an appreciable proportion would not; values and preferences vary widely; policy making will require extensive debates and involvement of many stakeholders.

In the GRADE system, evidence is classified as "high", "moderate", "low" or "very low". Definitions are as follows: High=Further research is very unlikely to change confidence in the estimate of effect; Moderate=Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate; Low=Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate; Very low=Any estimate of effect is very uncertain.

1a.4.4. Provide all other grades and associated definitions for recommendations in the grading system. (*Note: If separate grades for the strength of the evidence, report them in section 1a.7.*)
See section 1a.4.3 for all grades and associated definitions.

1a.4.5. Citation and URL for methodology for grading recommendations (*if different from 1a.4.1*)**:**
See section 1a.4.1 for guideline citation.

1a.4.6. If guideline is evidence-based (rather than expert opinion), are the details of the quantity, quality, and consistency of the body of evidence available (e.g., evidence tables)?

☐ Yes → ***complete section 1a.7***

☐ No → ***report on another systematic review of the evidence in sections 1a.6 and 1a.7; if another review does not exist, provide what is known from the guideline review of evidence in 1a.7***

Exhibit 15. Guideline Recommendations Not in Current Evidence Form for NQF 0004 That Support Medication-Assisted Treatment of Opioid Dependence: National Institute for Health and Clinical Excellence (NICE), 2007a

1a.4. CLINICAL PRACTICE GUIDELINE RECOMMENDATION

1a.4.1. Guideline citation (*including date*) and **URL for guideline** (*if available online*):
National Institute for Health and Clinical Excellence (NICE). 2007a. Methadone and buprenorphine for the management of opioid dependence. Technology appraisal guidance. 24 January 2007a. Available November 19, 2015, at nice.org.uk/guidance/ta114

1a.4.2. Identify guideline recommendation number and/or page number and **quote verbatim, the specific guideline recommendation**.

National Institute for Health and Clinical Excellence (NICE), 2007a:

- 1.1 Methadone and buprenorphine (oral formulations), using flexible dosing regimens, are recommended as options for maintenance therapy in the management of opioid dependence. (page 3)
- 1.2 The decision about which drug to use should be made on a case by case basis, taking into account a number of factors, including the person's history of opioid dependence, their commitment to a particular long-term management strategy, and an estimate of the risks and benefits of each treatment made by the responsible clinician in consultation with the person. If both drugs are equally suitable, methadone should be prescribed as the first choice. (page 3)
- 1.3 Methadone and buprenorphine should be administered daily, under supervision, for at least the first 3 months. Supervision should be relaxed only when the patient's compliance is assured. Both drugs should be given as part of a programme of supportive care. (page 3)

1a.4.3. Grade assigned to the quoted recommendation with definition of the grade:
The recommendations were not graded.

1a.4.4. Provide all other grades and associated definitions for recommendations in the grading system. (*Note: If separate grades for the strength of the evidence, report them in section 1a.7.*)
The recommendations were not graded.

1a.4.5. Citation and URL for methodology for grading recommendations (*if different from 1a.4.1*)**:**
The recommendations were not graded.

1a.4.6. If guideline is evidence-based (rather than expert opinion), are the details of the quantity, quality, and consistency of the body of evidence available (e.g., evidence tables)?

☐ Yes → ***complete section 1a.7***

☐ No → ***report on another systematic review of the evidence in sections 1a.6 and 1a.7; if another review does not exist, provide what is known from the guideline review of evidence in 1a.7***

Exhibit 16. Guideline Recommendations Not in Current Evidence Form for NQF 0004 That Support Medication-Assisted Treatment of Opioid Dependence: National Institute for Health and Clinical Excellence (NICE). 2007b

1a.4. CLINICAL PRACTICE GUIDELINE RECOMMENDATION

1a.4.1. Guideline citation (*including date*) and **URL for guideline** (*if available online*):
National Institute for Health and Clinical Excellence (NICE). 2007b. Naltrexone for the management of opioid dependence. Technology appraisal guidance. 24 January 2007b. Available November 19, 2015, at nice.org.uk/guidance/ta115

1a.4.2. Identify guideline recommendation number and/or page number and **quote verbatim, the specific guideline recommendation**.
National Institute for Health and Clinical Excellence (NICE), 2007b:

- 1.1 Naltrexone is recommended as a treatment option in detoxified formerly opioid dependent people who are highly motivated to remain in an abstinence programme. (page 3)
- 1.2 Naltrexone should only be administered under adequate supervision to people who have been fully informed of the potential adverse effects of treatment. It should be given as part of a programme of supportive care. (page 3)
- 1.3 The effectiveness of naltrexone in preventing opioid misuse in people being treated should be reviewed regularly. Discontinuation of naltrexone treatment should be considered if there is evidence of such misuse. (page 3)

1a.4.3. Grade assigned to the quoted recommendation with definition of the grade:
The recommendations were not graded.

1a.4.4. Provide all other grades and associated definitions for recommendations in the grading system. (*Note: If separate grades for the strength of the evidence, report them in section 1a.7.*)
The recommendations were not graded.

1a.4.5. Citation and URL for methodology for grading recommendations (*if different from 1a.4.1*)**:**
The recommendations were not graded.

1a.4.6. If guideline is evidence-based (rather than expert opinion), are the details of the quantity, quality, and consistency of the body of evidence available (e.g., evidence tables)?
☐ Yes → ***complete section 1a.7***
☐ No → ***report on another systematic review of the evidence in sections 1a.6 and 1a.7; if another review does not exist, provide what is known from the guideline review of evidence in 1a.7***

Exhibit 17. Guideline Recommendations Not in Current Evidence Form for NQF 0004 That Support Medication-Assisted Treatment of Opioid Dependence: Substance Abuse and Mental Health Services Administration (SAMHSA), 2005

1a.4. CLINICAL PRACTICE GUIDELINE RECOMMENDATION

1a.4.1. Guideline citation (*including date*) and **URL for guideline** (*if available online*):
Substance Abuse and Mental Health Services Administration Center for Substance Abuse Treatment. Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs. Treatment Improvement Protocol (TIP) Series 43. HHS Publication No. (SMA) 12-4214. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2005. Available November 19, 2015 at http://store.samhsa.gov/shin/content//SMA12-4214/SMA12-4214.pdf

1a.4.2. Identify guideline recommendation number and/or page number and **quote verbatim, the specific guideline recommendation**.

Substance Abuse and Mental Health Services Administration (SAMHSA), 2005:

- OTPs [opioid treatment programs] can provide several treatment options:
- Maintenance treatment combines pharmacotherapy with a full program of assessment, psychosocial intervention, and support services; it is the approach with the greatest likelihood of long-term success for many patients. (page 5)
- Medical maintenance treatment is provided to stabilize patients and may include long-term provision of methadone, buprenorphine, LAAM, or naltrexone, with a reduction in clinic attendance and other services. A patient can receive medical maintenance at an OTP, after he or she is stabilized fully. The patient usually must complete a comprehensive treatment program first. The decision about whether to provide medical maintenance must be made by a licensed practitioner. A designated medication unit (e.g., physician's office, pharmacy, long-term care facility) affiliated with an OTP can provide some medical maintenance services. To reduce clinic attendance—a key feature of medical maintenance—patients must qualify, subject to variations in State regulations (which may be more stringent than Federal regulations), to receive 7- to 14-day supplies of methadone for take-home dosing after 1 year of continuous treatment and 15- to 30-day supplies after 2 years of continuous treatment in an OTP (if additional criteria are satisfied [see chapter 5]) (42 CFR, Part 8 § 12(h); Federal Register 66:4079). (page 5-6)
- Maintenance treatment with methadone or buprenorphine is appropriate for patients with a prolonged history (>1 year) of opioid dependence [I]. The goals of treatment are to achieve a stable maintenance dose of opioid agonist and facilitate engagement in a comprehensive program of rehabilitation [I]. Maintenance treatment with naltrexone is an alternative strategy [I], although the utility of this strategy is often limited by lack of patient adherence and low treatment retention. (page 14)

1a.4.3. Grade assigned to the quoted recommendation with definition of the grade:
The recommendations were not graded.

1a.4.4. Provide all other grades and associated definitions for recommendations in the grading system. (*Note: If separate grades for the strength of the evidence, report them in section 1a.7.*)
The recommendations were not graded.

1a.4.5. Citation and URL for methodology for grading recommendations (*if different from 1a.4.1*)**:**
The recommendations were not graded.

1a.4.6. If guideline is evidence-based (rather than expert opinion), are the details of the quantity, quality, and consistency of the body of evidence available (e.g., evidence tables)?

☐ Yes → ***complete section 1a.7***

☐ No → ***report on another systematic review of the evidence in sections 1a.6 and 1a.7; if another review does not exist, provide what is known from the guideline review of evidence in 1a.7***

Exhibit 18. Results of Targeted Literature Review on Psychosocial Treatment for Alcohol and Other Drug Dependence Outside the Formal Health Care System

1a.8 OTHER SOURCE OF EVIDENCE

If source of evidence is NOT from a clinical practice guideline, USPSTF, or systematic review, please describe the evidence on which you are basing the performance measure.

1a.8.1 What process was used to identify the evidence?

Targeted literature search

1a.8.2. Provide the citation and summary for each piece of evidence.

The so-called "12-Step programs" for treating substance abuse, such as Alcoholics Anonymous (AA) and Narcotics Anonymous (NA), have become an important component of substance abuse treatment in the United States and worldwide. AA's worldwide membership grew from 2 members in 1935 to over 2 million in 1990. In recent years, its worldwide membership has fluctuated around 2 million (Alcoholics Anonymous, 2015a). In 2015, AA reported almost 1.3 million members and 60,000 groups in the US (Alcoholics Anonymous, 2015b). No comparable data for NA could be identified, although NA reports more than 63,000 weekly meetings worldwide (Narcotics Anonymous, 2014).

Two studies reported data on the frequency of psychosocial treatment outside the formal health care system, which would not be identifiable through claims data:

Dawson et al. (2006): This study presents the results of the first wave of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), conducted in 2001-2002. Of the 4,422 individuals with DSM-IV alcohol dependence in the past year that made up the sample, only 25.6% of them had ever sought help for alcohol problems. Of the entire sample, 3.0% had participated in 12-Step programs only (11.7% of those seeking treatment), 5.6% had received formal treatment only (21.9% of those seeking treatment), and 17.1% had both participated in a 12-Step program and received formal treatment (66.8% of those seeking treatment). This study was funded by the Intramural Research Program of the National Institutes of Health, National Institute on Alcohol Abuse and Alcoholism.

Grant et al. (2015): This study presents the results of the third wave of the NESARC, conducted in 2012-2013. Investigators interviewed a representative sample of 36,309 US adults on their alcohol drinking habits. In this sample, 13.9% and 29.1% of respondents had alcohol use disorders (AUDs) in the past 12 months and their lifetime, respectively, (DSM-5 definition of AUD). Of those with 12-month DSM-5 AUDs, only 7.7% had sought treatment in the previous 12 months, of which 59.0% reported receiving treatment from a 12-Step program. Of those with lifetime DSM-5 AUDs, 19.8% had sought treatment, of which 77.7% reported receiving treatment from a 12-Step program. This study was supported by the National Institute on Alcohol Abuse and Alcoholism (NIAAA), the National Institute on Drug Abuse, the National Institutes of Health, and by the Intramural Research Program of the NIAAA.

In conclusion, the high percentage of those seeking treatment who attend 12-step program meetings (78.5% [Dawson et al., 2006] and 59.0-77.7% [Grant et al., 2015]) indicates that a meaningful proportion of patients with MAT will receive psychosocial support outside the formal health care system, and claims data are not able to capture that.

References

Alcoholics Anonymous. (2015a, May 2015). Estimated Worldwide AA Individual and Group Membership. Retrieved November 12, 2015, from http://www.aa.org/assets/en_US/smf-132_en.pdf

Alcoholics Anonymous. (2015b, May 2015). Estimates of AA Groups and Members as of January 1, 2015. Retrieved November 12, 2015, from http://www.aa.org/assets/en_US/smf-53_en.pdf

Dawson, Deborah A, Grant, Bridget F, Stinson, Frederick S, & Chou, Patricia S. (2006). Estimating the effect of help-seeking on achieving recovery from alcohol dependence. *Addiction, 101*(6), 824-834.

Grant, Bridget F, Goldstein, Risë B, Saha, Tulshi D, Chou, S Patricia, Jung, Jeesun, Zhang, Haitao, . . . Huang, Boji.

(2015). Epidemiology of DSM-5 alcohol use disorder: results from the national epidemiologic survey on alcohol and related conditions III. *JAMA psychiatry, 72*(8), 757-766.
Narcotics Anonymous. (2014). Information about NA. Retrieved November 12, 2015, from https://www.na.org/admin/include/spaw2/uploads/pdf/PR/Information_about_NA.pdf

Appendix A

Exhibit A.1. Guideline Recommendations Not in Current Evidence Form for NQF 0004 That Support Medication-Assisted Treatment of Alcohol Dependence: British Association for Psychopharmacology (BAP) (Lingford-Hughes, 2012)

1a.4. CLINICAL PRACTICE GUIDELINE RECOMMENDATION

1a.4.1. Guideline citation (*including date*) and **URL for guideline** (*if available online*):
British Association for Psychopharmacology (BAP): Lingford-Hughes AR, Welch S, Peters L, Nutt DJ. BAP updated guidelines: evidence-based guidelines for the pharmacological management of substance abuse, harmful use, addiction and co-morbidity: recommendations from BAP. J Psychopharmacol 2012; 26: 899–952. Available November 19, 2015 at http://www.bap.org.uk/pdfs/BAPaddictionEBG_2012.pdf

1a.4.2. Identify guideline recommendation number and/or page number and **quote verbatim, the specific guideline recommendation**.
British Association for Psychopharmacology (BAP) (Lingford-Hughes, 2012) (page 11):

- Acamprosate can be used to improve abstinence rates (A). It should be continued if the person starts drinking, since there is evidence that acamprosate reduces alcohol consumption (A), at least for a period to assess whether there is overall patient benefit attributable to acamprosate.
- Naltrexone can be used to reduce risk of lapse becoming a relapse, but there is less evidence to support its use in maintaining abstinence (A). Naltrexone may therefore be a better choice if someone is 'sampling' alcohol regularly but wishes to be abstinent.
- For acamprosate and naltrexone there is no consistent evidence to suggest which types of patient will respond, and relapse prevention medication should be offered to/considered for everyone who is alcohol dependent wanting to be abstinent (A).
- Disulfiram is effective if intake is witnessed. Disulfiram can be offered as a treatment option for patients who intend to maintain abstinence, and for whom there are no contraindications (B).
- Baclofen should be considered if a patient wants to be abstinent, has high levels of anxiety and has not benefited from or is unable to take acamprosate, naltrexone or disulfiram (C).
- SSRIs should be avoided, or used with caution in type 2 alcoholism (B).

1a.4.3. Grade assigned to the quoted recommendation with definition of the grade:
Strength of recommendation is defined as **[A]** directly based on category I evidence (from meta-analysis of randomized controlled trials (Ia) or evidence from at least one randomized controlled trial (Ib)); **[B]** directly based on category II evidence (evidence from at least one controlled study without randomization (IIa) or evidence from at least one other type of quasi-experimental study (IIb) or extrapolated recommendation from category I evidence); **[C]** directly based on category III evidence (evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies) or extrapolated recommendation from category I or II evidence; **[D]** directly based on category IV evidence (evidence from expert committee reports or opinions and/or clinical experience of respected authorities) or extrapolated recommendation from category I, II or III evidence; **[S]**: Standard of care (BAP: Lingford-Hughes et al., 2012).

1a.4.4. Provide all other grades and associated definitions for recommendations in the grading system. (*Note: If separate grades for the strength of the evidence, report them in section 1a.7.*)
See section 1a.4.3 for all grades and associated definitions.

1a.4.5. Citation and URL for methodology for grading recommendations (*if different from 1a.4.1*)**:**
See section 1a.4.1 for guideline citation.

1a.4.6. If guideline is evidence-based (rather than expert opinion), are the details of the quantity, quality, and consistency of the body of evidence available (e.g., evidence tables)?

☐ Yes → ***complete section 1a.7***

☐ No → ***report on another systematic review of the evidence in sections 1a.6 and 1a.7; if another review does not exist, provide what is known from the guideline review of evidence in 1a.7***

Exhibit A.2. Systematic Reviews Cited by the British Association for Psychopharmacology (BAP) Guideline on Pharmacological Management of Substance Abuse: Acamprosate for alcohol dependence (Rosner et al., 2010a)

1a.7. FINDINGS FROM SYSTEMATIC REVIEW OF BODY OF THE EVIDENCE SUPPORTING THE MEASURE
If more than one systematic review of the evidence is identified above, you may choose to summarize the one (or more) for which the best information is available to provide a summary of the quantity, quality, and consistency of the body of evidence. Be sure to identify which review is the basis of the responses in this section and if more than one, provide a separate response for each review.
Systematic review on:
Rösner S, Hackl-Herrwerth A, Leucht S, et al. (2010a) Acamprosate for alcohol dependence. Cochrane Database Syst Rev 9: CD004332.

1a.7.1. What was the specific structure, treatment, intervention, service, or intermediate outcome addressed in the evidence review? Treatment of alcohol dependence with acamprosate was the focus of the review.

1a.7.2. Grade assigned for the quality of the quoted evidence with definition of the grade: The systematic review did not grade the evidence.

1a.7.3. Provide all other grades and associated definitions for strength of the evidence in the grading system. The systematic review did not grade the evidence.

1a.7.4. What is the time period covered by the body of evidence? (*provide the date range, e.g., 1990-2010*). Date range: 1990 - 2006

QUANTITY AND QUALITY OF BODY OF EVIDENCE
1a.7.5. How many and what type of study designs are included in the body of evidence? (*e.g., 3 randomized controlled trials and 1 observational study*) Twenty-four RCTs were included in the review. Eighteen of the 24 RCTs employed a multicenter design, and 6 trials, a single-center design.

1a.7.6. What is the overall quality of evidence across studies in the body of evidence? (*discuss the certainty or confidence in the estimates of effect particularly in relation to study factors such as design flaws, imprecision due to small numbers, indirectness of studies to the measure focus or target population*) "Within the acamprosate trials included in the review, various features of the study design have been adequately implemented to ensure a high level of validity: Patients were randomly assigned to treatment groups to prevent selection bias. Active medication and placebo with identical appearance were used to mask treatment allocation and to reduce the general susceptibility of outcomes to bias effects; objective measures of drinking were considered…either to validate patient-reported outcomes or as a discrete outcome criteria [sic] in the majority of studies." "Nevertheless, some uncertainties still persist. …The poor reporting of the study design mainly concerns the methods used for generating random sequences, the specification of person groups included in the blinding process and the methods applied for allocation concealment."

ESTIMATES OF BENEFIT AND CONSISTENCY ACROSS STUDIES IN BODY OF EVIDENCE
1a.7.7. What are the estimates of benefit—magnitude and direction of effect on outcome(s) across studies in the body of evidence? (*e.g., ranges of percentages or odds ratios for improvement/ decline across studies, results of meta-analysis, and statistical significance*) The results are based on 6915 patients in 24 RCTs. "Compared to placebo, acamprosate was shown to significantly reduce the risk of any drinking RR 0.86 (95% CI 0.81 to 0.91); NNT 9.09 (95% CI 6.66 to 14.28) and to significantly increase the cumulative abstinence

duration MD 10.94 (95% CI 5.08 to 16.81), while secondary outcomes (gammaglutamyltransferase, heavy drinking) did not reach statistical significance."
RR= risk ratio, CI=confidence interval, NNT=number needed to treat, MD=mean difference

1a.7.8. What harms were studied and how do they affect the net benefit (benefits over harms)?
"Diarrhea was the only side effect that was more frequently reported under acamprosate than placebo RD 0.11 (95% 0.09 to 0.13); NNTB 9.09 (95% CI 7.69 to 11.11)." Other side effects that did not differ were abdominal pain, constipation, nausea, vomiting, gastrointestinal symptoms, headache, pruritus, vertigo, and several others."

UPDATE TO THE SYSTEMATIC REVIEW(S) OF THE BODY OF EVIDENCE
1a.7.9. If new studies have been conducted since the systematic review of the body of evidence, provide for <u>each</u> new study: 1) citation, 2) description, 3) results, 4) impact on conclusions of systematic review.

Exhibit A.3. Systematic Reviews Cited by the British Association for Psychopharmacology (BAP) Guideline on Pharmacological Management of Substance Abuse: Opioid antagonists for alcohol dependence (Rosner et al., 2010b)

1a.7. FINDINGS FROM SYSTEMATIC REVIEW OF BODY OF THE EVIDENCE SUPPORTING THE MEASURE
If more than one systematic review of the evidence is identified above, you may choose to summarize the one (or more) for which the best information is available to provide a summary of the quantity, quality, and consistency of the body of evidence. Be sure to identify which review is the basis of the responses in this section and if more than one, provide a separate response for each review.
Systematic review:
Rösner S, Hackl-Herrwerth A, Leucht S, et al. (2010b) Opioid antagonists for alcohol dependence. Cochrane Database Syst Rev 12: CD001867.

1a.7.1. What was the specific structure, treatment, intervention, service, or intermediate outcome addressed in the evidence review? Treatment of alcohol dependence with opioid antagonists was the focus of the review.

1a.7.2. Grade assigned for the quality of the quoted evidence with definition of the grade: The systematic review did not grade the evidence.

1a.7.3. Provide all other grades and associated definitions for strength of the evidence in the grading system. The systematic review did not grade the evidence.

1a.7.4. What is the time period covered by the body of evidence? (*provide the date range, e.g., 1990-2010*). Date range: 1992-2009

QUANTITY AND QUALITY OF BODY OF EVIDENCE
1a.7.5. How many and what type of study designs are included in the body of evidence? (*e.g., 3 randomized controlled trials and 1 observational study*) Fifty randomized controlled trials were included in the review. Fourteen of the 50 were multicenter trials and 36 were single center.

1a.7.6. What is the overall quality of evidence across studies in the body of evidence? (*discuss the certainty or confidence in the estimates of effect particularly in relation to study factors such as design flaws, imprecision due to small numbers, indirectness of studies to the measure focus or target population*) "Various features of the study design, which have been implemented in the naltrexone and nalmefene trials included in the review, ensure a high methodological quality of the primary database: To prevent selection bias, patients were randomly assigned to treatment groups, to mask treatment allocation, active medication and placebo with identical appearance were used and to reduce the general susceptibility of outcomes to bias effects, objective measures of drinking were considered … either to validate patient-reported outcomes or as a discrete outcome criteria [sic] in the majority of studies." "Nevertheless, some uncertainties persist. As specific features of the study designs were omitted from trial reports, it remains unclear whether these have not been implemented or whether they were implemented, but not reported … poor reporting concerned the methods used for generating random sequences, the exact specification of person groups included in the blinding process and the methods applied for allocation concealment. Particularly the latter, unclear concealment, has repeatedly been shown to be associated with bias effects in various fields of clinical research."

ESTIMATES OF BENEFIT AND CONSISTENCY ACROSS STUDIES IN BODY OF EVIDENCE

1a.7.7. What are the estimates of benefit—magnitude and direction of effect on outcome(s) across studies in the body of evidence? (*e.g., ranges of percentages or odds ratios for improvement/ decline across studies, results of meta-analysis, and statistical significance*) The results are based on 7793 patients in 50 RCTs. "[N]altrexone reduced the risk of heavy drinking to 83% of the risk in the placebo group RR 0.83 (95% CI 0.76 to 0.90) and decreased drinking days by about 4%, MD -3.89 (95% CI -5.75 to -2.04). Significant effects were also demonstrated for the secondary outcomes of the review including heavy drinking days, MD - 3.25 (95% CI -5.51 to -0.99), consumed amount of alcohol, MD - 10.83 (95% CI -19.69 to -1.97) and gamma-glutamyltransferase, MD -10.37 (95% CI -18.99 to -1.75), while effects on return to any drinking, RR 0.96 (95 CI 0.92 to 1.00) missed statistical significance." MD=mean difference

1a.7.8. What harms were studied and how do they affect the net benefit (benefits over harms)? "Side effects of naltrexone were mainly gastrointestinal problems (e.g. nausea: RD 0.10; 95% CI 0.07 to 0.13) and sedative effects (e.g. daytime sleepiness: RD 0.09; 95% CI 0.05 to 0.14)." RD=risk difference

UPDATE TO THE SYSTEMATIC REVIEW(S) OF THE BODY OF EVIDENCE

1a.7.9. If new studies have been conducted since the systematic review of the body of evidence, provide for each new study: 1) citation, 2) description, 3) results, 4) impact on conclusions of systematic review.

Exhibit A.4. Guideline Recommendations Not in Current Evidence Form for NQF 0004 That Support Medication-Assisted Treatment of Opioid Dependence: British Association for Psychopharmacology (BAP) (Lingford-Hughes, 2012)

1a.4. CLINICAL PRACTICE GUIDELINE RECOMMENDATION

1a.4.1. Guideline citation (*including date*) and **URL for guideline** (*if available online*):
British Association for Psychopharmacology (BAP): Lingford-Hughes AR, Welch S, Peters L, Nutt DJ. BAP updated guidelines: evidence-based guidelines for the pharmacological management of substance abuse, harmful use, addiction and co-morbidity: recommendations from BAP. J Psychopharmacol 2012; 26: 899–952. Available November 19, 2015 at http://www.bap.org.uk/pdfs/BAPaddictionEBG_2012.pdf

1a.4.2. Identify guideline recommendation number and/or page number and **quote verbatim, the specific guideline recommendation**.
British Association for Psychopharmacology (BAP) (Lingford-Hughes, 2012):

- MMT is an appropriate treatment option for opioid dependent patients. It is effective in reducing heroin use, injecting, and sharing of injecting equipment (A).
- MMT is more effective at doses in the range 60–120 mg than at lower doses. Following safe induction of methadone treatment (see Department of Health Guidelines), consideration should be given to higher maintenance doses (A).
- BMT is an appropriate treatment option for opioid-dependent patients. It is effective in reducing heroin use (A).
- Buprenorphine should be prescribed at doses of 8 mg or higher when used for maintenance treatment (B), and preferably at doses over 12 mg (D).
- Where concerns over diversion are paramount, buprenorphine/ naloxone combinations may be preferred (B).
- Both methadone and buprenorphine are effective treatments. Opioid-dependent patients should be offered either medication, guided by patient choice and safety considerations. (A).
- MMT or BMT should be provided in conjunction with psychosocial interventions such as regular counselling (B).
- Oral naltrexone treatment should be considered for formerly opioid-dependent people who are highly motivated to remain abstinent (D).
-

1a.4.3. Grade assigned to the quoted recommendation with definition of the grade:
Strength of recommendation is defined as **[A]** directly based on category I evidence (from meta-analysis of randomized controlled trials (Ia) or evidence from at least one randomized controlled trial (Ib)); **[B]** directly based on category II evidence (evidence from at least one controlled study without randomization (IIa) or evidence from at least one other type of quasi-experimental study (IIb) or extrapolated recommendation from category I evidence); **[C]** directly based on category III evidence (evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies) or extrapolated recommendation from category I or II evidence; **[D]** directly based on category IV evidence (evidence from expert committee reports or opinions and/or clinical experience of respected authorities) or extrapolated recommendation from category I, II or III evidence; **[S]**: Standard of care (BAP: Lingford-Hughes et al., 2012).

1a.4.4. Provide all other grades and associated definitions for recommendations in the grading system. (*Note: If separate grades for the strength of the evidence, report them in section 1a.7.*)
See section 1a.4.3 for all grades and associated definitions.

1a.4.5. Citation and URL for methodology for grading recommendations (*if different from 1a.4.1*)**:**
See section 1a.4.1 for guideline citation.

1a.4.6. If guideline is evidence-based (rather than expert opinion), are the details of the quantity, quality, and consistency of the body of evidence available (e.g., evidence tables)?

☐ Yes → ***complete section 1a.7***

☐ No → ***report on another systematic review of the evidence in sections 1a.6 and 1a.7; if another review does not exist, provide what is known from the guideline review of evidence in 1a.7***

Exhibit A.5. Systematic Reviews Cited by the British Association for Psychopharmacology (BAP) Guideline on Pharmacological Management of Substance Abuse: Methadone maintenance therapy for opioid dependence (Mattick et al., 2009)

1a.7. FINDINGS FROM SYSTEMATIC REVIEW OF BODY OF THE EVIDENCE SUPPORTING THE MEASURE
If more than one systematic review of the evidence is identified above, you may choose to summarize the one (or more) for which the best information is available to provide a summary of the quantity, quality, and consistency of the body of evidence. Be sure to identify which review is the basis of the responses in this section and if more than one, provide a separate response for each review.
Systematic review on methadone:
Mattick RP, Breen C, Kimber J, et al. (2009) Methadone maintenance therapy versus no opioid replacement for opioid dependence. Cochrane Database Syst Rev 3: CD002209.

1a.7.1. What was the specific structure, treatment, intervention, service, or intermediate outcome addressed in the evidence review? Treatment of opioid dependence with methadone maintenance treatment was the focus of the review.

1a.7.2. Grade assigned for the quality of the quoted evidence with definition of the grade:
The systematic review graded the evidence for five outcomes:
Retention in treatment – Old studies (before 2000): high
Retention in treatment – New studies (2000 and after): high
Morphine positive urine or hair analysis: high
Criminal activity: moderate
Mortality: moderate

High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

1a.7.3. Provide all other grades and associated definitions for strength of the evidence in the grading system. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

1a.7.4. What is the time period covered by the body of evidence? (*provide the date range, e.g., 1990-2010*). Date range: 1969-2008

QUANTITY AND QUALITY OF BODY OF EVIDENCE
1a.7.5. How many and what type of study designs are included in the body of evidence? (*e.g., 3 randomized controlled trials and 1 observational study*) Eleven randomized clinical trials were included in the review.

1a.7.6. What is the overall quality of evidence across studies in the body of evidence? (*discuss the certainty or confidence in the estimates of effect particularly in relation to study factors such as design flaws, imprecision due to small numbers, indirectness of studies to the measure focus or target population*)
Five of the studies were deemed to have adequate sequence generation for randomization. One study was determined to have in adequate sequence generation for randomization. One of the five adequate studies also had

adequate concealment of allocation, as did two additional studies.
"Of the eleven studies included in this review, two were placebo-controlled trials. Both of these studies were double-blind but [one] did not provide sufficient data to be confident about the concealment of allocation. The remaining studies were not blinded. All studies addressed the issue of incomplete outcome data adequately and were independently deemed by reviewers to be free of other major bias."

ESTIMATES OF BENEFIT AND CONSISTENCY ACROSS STUDIES IN BODY OF EVIDENCE

1a.7.7. What are the estimates of benefit—magnitude and direction of effect on outcome(s) <u>across studies</u> in the body of evidence? (*e.g., ranges of percentages or odds ratios for improvement/ decline across studies, results of meta-analysis, and statistical significance*) The results are based on 1969 patients in 11 randomized clinical trials. "Methadone appeared statistically significantly more effective than non-pharmacological approaches in retaining patients in treatment and in the suppression of heroin use as measured by self report and urine/hair analysis (6 RCTs, RR = 0.66 95%CI 0.56-0.78), but not statistically different in criminal activity (3 RCTs, RR=0.39; 95%CI: 0.12-1.25) or mortality (4 RCTs, RR=0.48; 95%CI: 0.10-2.39)." RR=risk ratio

1a.7.8. What harms were studied and how do they affect the net benefit (benefits over harms)?
No harms were discussed in the systematic review.

UPDATE TO THE SYSTEMATIC REVIEW(S) OF THE BODY OF EVIDENCE

1a.7.9. If new studies have been conducted since the systematic review of the body of evidence, provide for <u>each</u> new study: 1) citation, 2) description, 3) results, 4) impact on conclusions of systematic review.

Exhibit A.6. Systematic Review Cited by the British Association for Psychopharmacology (BAP) Guideline on Pharmacological Management of Substance Abuse: Oral naltrexone maintenance treatment for opioid dependence (Minozzi et al., 2011)

1a.7. FINDINGS FROM SYSTEMATIC REVIEW OF BODY OF THE EVIDENCE SUPPORTING THE MEASURE
If more than one systematic review of the evidence is identified above, you may choose to summarize the one (or more) for which the best information is available to provide a summary of the quantity, quality, and consistency of the body of evidence. Be sure to identify which review is the basis of the responses in this section and if more than one, provide a separate response for each review.
Systematic review on methadone:
Minozzi S, Amato L, Vecchi S, et al. (2011) Oral naltrexone maintenance treatment for opioid dependence. Cochrane Database Syst Rev 4: CD001333.

1a.7.1. What was the specific structure, treatment, intervention, service, or intermediate outcome addressed in the evidence review? Prevention of relapse in opioid addicts following detoxification using naltrexone maintenance treatment.

1a.7.2. Grade assigned for the quality of the quoted evidence with definition of the grade: The systematic review did not grade the evidence.

1a.7.3. Provide all other grades and associated definitions for strength of the evidence in the grading system. The systematic review did not grade the evidence.

1a.7.4. What is the time period covered by the body of evidence? (*provide the date range, e.g., 1990-2010*). Date range: 1976-2008

QUANTITY AND QUALITY OF BODY OF EVIDENCE

1a.7.5. How many and what type of study designs are included in the body of evidence? (*e.g., 3 randomized controlled trials and 1 observational study*) Thirteen randomised controlled trials were included in this review.

1a.7.6. What is the overall quality of evidence across studies in the body of evidence? (*discuss the certainty or confidence in the estimates of effect particularly in relation to study factors such as design flaws, imprecision due to small numbers, indirectness of studies to the measure focus or target population*)
"The majority of the studies where [sic] not of high quality. Only two studies reported information about sequence generation and only three about allocation concealment. Eight out of thirteen studies were double blind, the other were open trial. Nevertheless we think that this did not introduce bias in the main outcomes addressed in this review, because the retention in treatment is an objective measure and abstinence is assessed by urine analysis in all trials. Incomplete outcome data was addressed correctly in the majority of the studies and in any case it does not introduce bias for the outcome retention and retention and abstinence which are the main outcomes on which the review is focused."

ESTIMATES OF BENEFIT AND CONSISTENCY ACROSS STUDIES IN BODY OF EVIDENCE

1a.7.7. What are the estimates of benefit—magnitude and direction of effect on outcome(s) across studies in the body of evidence? (*e.g., ranges of percentages or odds ratios for improvement/*

decline across studies, results of meta-analysis, and statistical significance)

The results are based on 13 studies of 1158 patients. "Comparing naltrexone versus placebo or no pharmacological treatments, no statistically significant difference were [sic] noted for all the primary outcomes considered. The only outcome statistically significant in favour of naltrexone is reincarceration, RR 0.47 (95% CI 0.26-0.84), but results come only from two studies. Considering only studies were [sic] patients were forced to adherence a statistical significant difference in favour of naltrexone was found for retention and abstinence, RR 2.93 (95%CI 1.66-5.18)." RR=risk ratio

1a.7.8. What harms were studied and how do they affect the net benefit (benefits over harms)?

Four of the 13 studies reported side effects (varied by study but included abdominal discomfort, sleep disturbances, loss of appetite, diarrhea, and nausea), but there was no statistically significant difference between treatment and control groups.

UPDATE TO THE SYSTEMATIC REVIEW(S) OF THE BODY OF EVIDENCE

1a.7.9. If new studies have been conducted since the systematic review of the body of evidence, provide for <u>each</u> new study: 1) citation, 2) description, 3) results, 4) impact on conclusions of systematic review.

Exhibit A.7. Systematic Review Cited by the British Association for Psychopharmacology (BAP) Guideline on Pharmacological Management of Substance Abuse: Buprenorphine maintenance therapy for opioid dependence (Mattick et al., 2014)

1a.7. FINDINGS FROM SYSTEMATIC REVIEW OF BODY OF THE EVIDENCE SUPPORTING THE MEASURE
If more than one systematic review of the evidence is identified above, you may choose to summarize the one (or more) for which the best information is available to provide a summary of the quantity, quality, and consistency of the body of evidence. Be sure to identify which review is the basis of the responses in this section and if more than one, provide a separate response for each review.
Systematic review on methadone:
Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database of Systematic Reviews 2014, Issue 2. Art. No.: CD002207. DOI: 10.1002/14651858.CD002207.pub4. (Note that this is an update of the systematic review cited by the BAP guideline.)

1a.7.1. What was the specific structure, treatment, intervention, service, or intermediate outcome addressed in the evidence review? Treatment of opioid dependence using buprenorphine maintenance and methadone maintenance.

1a.7.2. Grade assigned for the quality of the quoted evidence with definition of the grade: The systematic review graded the evidence for five outcomes:
Retention in treatment: high
Morphine-positive urines: moderate
Self-reported heroin use: moderate
Cocaine-positive urines: moderate
Benzodiazepine-positive urines: moderate

High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

1a.7.3. Provide all other grades and associated definitions for strength of the evidence in the grading system. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

1a.7.4. What is the time period covered by the body of evidence? (*provide the date range, e.g., 1990-2010*). Date range: 1992-2010

QUANTITY AND QUALITY OF BODY OF EVIDENCE
1a.7.5. How many and what type of study designs are included in the body of evidence? (*e.g., 3 randomized controlled trials and 1 observational study*) Thirty-one randomized controlled trials were included in this review.

1a.7.6. What is the overall quality of evidence across studies in the body of evidence? (*discuss the certainty or confidence in the estimates of effect particularly in relation to study factors such as design flaws, imprecision due to small numbers, indirectness of studies to the measure focus or target population*)

"The clinical trials represented in this review are of reasonable quality, and whilst many of them did not fully explain how randomization was concealed, they appear to have used doses which are clinicallyrelevant and to have treated participants for significant periods of time. Moreover, despite the tendency of randomised studies to include selected populations, characteristics of drug users enrolled in the studies included in this review appear to be heterogeneous enough to allow generalisability of the results across different clinical and cultural settings. Based on the nature of the trials, it would appear the external validity or generalisability of the results is quite good, particularly from those trials which have used large sample sizes and adequate doses."

ESTIMATES OF BENEFIT AND CONSISTENCY ACROSS STUDIES IN BODY OF EVIDENCE

1a.7.7. What are the estimates of benefit—magnitude and direction of effect on outcome(s) across studies in the body of evidence? (*e.g., ranges of percentages or odds ratios for improvement/ decline across studies, results of meta-analysis, and statistical significance*)

The results are based on 5430 patients in 31 RCTs. "There is high quality of evidence that buprenorphine was superior to placebo medication in retention of participants in treatment at all doses examined. Specifically, buprenorphine retained participants better than placebo: at low doses (2 - 6 mg), 5 studies, 1131 participants, risk ratio (RR) 1.50; 95% confidence interval (CI) 1.19 to 1.88; at medium doses (7 - 15 mg), 4 studies, 887 participants, RR 1.74; 95% CI 1.06 to 2.87; and at high doses (≥ 16 mg), 5 studies, 1001 participants, RR 1.82; 95% CI 1.15 to 2.90. However, there is moderate quality of evidence that only high-dose buprenorphine (≥ 16 mg) was more effective than placebo in suppressing illicit opioid use measured by urinanalysis in the trials, 3 studies, 729 participants, standardised mean difference (SMD) -1.17; 95% CI -1.85 to -0.49, notably, low-dose, (2 studies, 487 participants, SMD 0.10; 95% CI -0.80 to 1.01), and medium-dose, (2 studies, 463 participants, SMD -0.08; 95% CI -0.78 to 0.62) buprenorphine did not suppress illicit opioid use measured by urinanalysis better than placebo."

1a.7.8. What harms were studied and how do they affect the net benefit (benefits over harms)?

"Few studies reported adverse events; two studies compared adverse events statistically, finding no difference between methadone and buprenorphine, except for a single result indicating more sedation among those using methadone." Adverse events reported by the two studies included but were not limited to: sedation, insomnia, headache, depression, sweating, and dyspepsia.

UPDATE TO THE SYSTEMATIC REVIEW(S) OF THE BODY OF EVIDENCE

1a.7.9. If new studies have been conducted since the systematic review of the body of evidence, provide for each new study: 1) citation, 2) description, 3) results, 4) impact on conclusions of systematic review.