

## Evidence-based Practice Center Systematic Review Protocol

Project Title: Comparative Effectiveness of Strategies to De-escalate Aggressive Behavior in Psychiatric Patients in Acute Care Settings

### I. Background and Objectives for the Systematic Review

Aggressive behavior is understood to mean using actual physical violence toward self, others, or property, or making specific imminent verbal threats.<sup>1</sup> In the health care setting, approaches for actively aggressive patients have historically involved using either seclusion (involuntary placement of a patient in a locked room or area from which the patient is not allowed to leave) or restraints (involuntary administration of mechanical, pharmacologic, or physical interventions, which is seen as more restrictive than seclusion); these practices continue today.<sup>2,3</sup> Since the late 1990s, the Centers for Medicaid & Medicare Services (CMS)—formerly known as the Health Care Financing Administration (HCFA)<sup>3</sup> and the Joint Commission<sup>4</sup>—have required that seclusion and restraints must be used only for a behavior that “jeopardizes the immediate physical safety of the patient, a staff member, or others”<sup>5</sup> (including other patients) and when less restrictive measures have failed.

Despite organizations’ guidelines advocating limitations of seclusion or restraints as much as possible,<sup>6</sup> data in the United States and Europe show that 10 percent to 30 percent of patients (from adolescent and young adult to elderly) admitted to acute psychiatric units receive these interventions.<sup>7-9</sup> Behaviors indicating the potential need for these types of interventions occur in both acute care settings (such as public and private mental hospitals, state mental hospitals, emergency departments, Veterans Affairs hospitals, and medical or surgical units in general hospitals) and chronic care settings (such as nursing homes and psychiatric residential treatment facilities).<sup>10</sup> Although psychotic disorders account for 44 percent of individuals requiring seclusion or restraint (or both), multiple psychiatric diagnoses, including substance misuse and delirium, are associated with aggression in health care settings.<sup>10-12</sup> In addition, in some acute care settings (e.g., the emergency department) the psychiatric diagnosis may not yet be clear or patients may not have been formally diagnosed; treatment decisions are then often based on the presence of psychiatric symptoms including aggressive behaviors. Although dementia is frequently associated with aggression and the use of seclusion and restraints,<sup>13</sup> individuals with dementia are often managed in chronic care settings; a separate report is covering this evidence.<sup>14</sup> Our review will focus on adults in acute care settings and will involve inpatients with any psychiatric diagnosis, including delirium and substance misuse (but not dementia), and patients in emergency departments with severe psychiatric symptomatology.

Several factors underscore the significance of the decision to use seclusion or restraints. First, a key clinical and policy question is how to best balance the benefits and risks of (a) seclusion or restraints with those of (b) various alternatives to seclusion and restraints.<sup>7</sup> Benefits of seclusion and restraints can include reduced physical risk to the patient, other patients, and staff; quick reduction of aggressive behaviors; and increased

likelihood of receiving treatment that effectively treats the psychiatric disorder (if the aggression is preventing proper treatment). Potential harms include increased physical harm to the patient (severe and even fatal side effects,<sup>15</sup> with estimates of 50 to 150 seclusion- or restraint-related deaths annually<sup>16</sup>), other patients (e.g., by assault), and staff; perceived punishment of patients and loss of dignity; re-traumatization of some patients; potentially new traumatic effects of such coercion; and future aversion to returning to the hospital even if a patient is in great need (e.g., is suicidal).

Second, discussion continues as to whether an evidence base even exists to support the use of seclusion or restraints.<sup>7, 17-20</sup> Finally, usual care (often represented in comparative studies as whatever was done before a new intervention was tried) varies substantially. Given these considerable potential harms and the availability of alternative strategies (briefly described below), most guidelines, as well as regulatory agencies (e.g. CMS, the Joint Commission, as previously mentioned) now recommend using seclusion and restraints only as a last resort.<sup>10, 21-28</sup>

Given the concern about the application of seclusion and restraints, much interest has focused on the use of alternative approaches in place of seclusion and restraints. Most of these alternatives are strongly influenced by the National Association of State Mental Health Program Directors' (NASMHPD's) Six Core Strategies.<sup>29</sup> These principles are (1) leadership toward organization change, (2) use of data to inform change, (3) workforce development (strongly influenced by the principles of trauma-informed care),<sup>30</sup> (4) use of seclusion and restraint prevention tools, (5) consumer roles in inpatient settings, and (6) debriefing techniques. Such approaches appear to be comprehensive, noninvasive, low risk, and they offer promising results.<sup>31</sup>

These Six Core Strategies ultimately aim to decrease aggressive behavior. Strategies to prevent aggressive behavior can involve general strategies (applied to a whole group, usually via policy) or specific strategies (applied to specific individuals who are at increased risk of becoming aggressive), and those aimed at de-escalating or managing aggressive behavior, once it has already developed.

*Preventing aggressive behavior (general strategies):* The vast majority of patients who are admitted to an acute care health setting because of a psychiatric illness or are being treated in an emergency department because of severe psychiatric symptomatology are at some increased risk of aggression relative to the general population. Preventive strategies to reduce the likelihood of becoming acutely aggressive focus on providing a calm environment in which aggression is less likely to develop and they tend to focus on the entire unit. These approaches include milieu-based changes such as sensory rooms, which provide a calm and supportive environment for patients,<sup>32</sup> and staffing changes, such as increased staff-to-patient ratios,<sup>24</sup> specific staff training programs,<sup>33</sup> or peer-based interventions.<sup>34</sup> For example, one program introduced a 12-hour staff training program focused on previously identified barriers to reducing the use of seclusion or restraints.<sup>33</sup> These barriers for the staff included fear, prejudices, hopelessness, and negative attitudes. The focus of the peer-based intervention was to build trust and confidence in the patient and engage the patient on a mutual level.<sup>34</sup> The strengths of such approaches are that they are collaborative and low risk to patients and staff.<sup>35</sup> They also can help address the risk in groups harder to identify as being at risk of acute aggression—those who isolate themselves and withdraw from the milieu.<sup>36</sup>

*Preventing aggressive behavior (specific strategies):* Agitation, commonly, although not always, precedes aggression, and specific strategies to prevent aggression often try to intercede at the point of agitation. If a patient becomes agitated (exemplified by behaviors such as pacing, yelling, verbal threats, or threatening gestures toward others), the patient is generally thought to be at increased risk of aggressive behavior, including physical violence. For agitated patients, the goal of an intervention is to decrease that agitation to prevent aggressive behavior. Early agitation often resolves with the use of supportive (often referred to as nonconfrontational) language and other verbal de-escalation techniques to help diffuse the interpersonal interaction. The use of restrictive interventions, such as restraints, at this early stage may only further escalate the situation.<sup>24</sup> More serious agitation may require cognitive behavioral techniques aimed at helping the patient manage his or her emotions and distress, so as to regain control of behavior. Such aggression prevention approaches<sup>37</sup> form the basis of guidelines for managing agitated patients in different settings.<sup>38-42</sup>

Pharmacologic intervention treating the underlying psychiatric illness is also a common specific strategy employed to prevent aggressive behavior. A case in point might be increasing the dose or adding an as-needed dose of an antipsychotic medication for a patient with a history of aggression and schizophrenia to decrease current reactivity and impulsivity and, thereby, the risk for current aggression. When successful, such medication-based steps can help prevent aggression.<sup>42</sup>

Furthermore, recognizing triggers for aggressive behavior can inform prevention strategies by identifying individualized patterns that can be addressed. For example, certain sensory stimuli, such as excessive noise, can trigger aggression in some patients and could theoretically be addressed by offering ear plugs or headphones to those individuals. Similarly, paranoid patients may benefit from having only prepackaged foods on their meal tray to decrease agitation related to concerns about poisoning.

*Managing acute aggression:* If a patient does become actively aggressive (i.e., exhibiting actual physical violence toward property, self, or others, or making specific imminent verbal threats), either seclusion or restraints or alternative strategies can be used. In this case, alternatives can include Emergency Response Teams (which encompass Behavioral Emergency Response Teams,<sup>43</sup> Rapid Response Teams,<sup>43</sup> and Psychiatric Emergency Response Teams<sup>11</sup>) and pharmacologic interventions aimed at rapidly reducing agitation (rather than treating the underlying illness).

The latter include, for example, the medication protocols described in the emergency department-focused Project BETA (Best Practices in Evaluation and Treatment of Agitation).<sup>44</sup> These involve U.S. Food and Drug Administration (FDA)-approved medications whose indications specifically include use for agitation in adults (olanzapine, ziprasidone, aripiprazole, and inhaled loxapine)<sup>45-48</sup> and those that do not have formal approval for these purposes (e.g., haloperidol, risperidone, and lorazepam).

A final factor highlighting this issue's importance is the fact that the use of seclusion and restraints is closely followed as a quality-of-care measure, particularly for psychiatric patients in hospital settings.<sup>49</sup> The International Quality Indicator Project defines the frequency of use as an indicator of quality of care.<sup>50</sup> The Joint Commission reported in 2010 more than 200 deaths related to seclusion or restraints over a prior 5-year period<sup>51</sup>; the organization collects publically available, comparative data on patient hours of seclusion and restraints for acute care hospitals that offer hospital-based inpatient

psychiatric services (HBIPS-2, HBIPS-3); it also includes time in seclusion or in restraints as part of its inpatient psychiatric services core measure for accreditation.<sup>52</sup> Some state psychiatric hospital systems have undertaken comprehensive efforts to reduce use of seclusion and restraints and collected data on their progress. For example, in Pennsylvania from 1990 to 2000, the rates of seclusion decreased from 4.2 to 0.3 episodes per 1,000 patient days and rates of restraints decreased from 3.5 to 1.2.<sup>53</sup> The authors cite many factors contributing to the change, including advocacy, policy change, staffing ratios, response teams, and second generation antipsychotics. The federal government also gives this issue high priority—the Substance Abuse and Mental Health Services Administration, for one, makes consistent and active efforts to reduce and ultimately abolish the use of seclusion and restraints.<sup>54, 55</sup>

To our knowledge, no systematic review focusing on acute care settings has directly compared either (1) the effectiveness of different available alternative strategies to *prevent aggressive behavior* or (2) the effectiveness of alternative strategies compared with each other or with seclusion and restraints to *de-escalate aggressive behaviors or improve health outcomes for those who are acutely aggressive*. Existing systematic reviews of pharmacological de-escalation strategies often include placebo-controlled studies, focus only on a small subset of our eligible population, and are rarely limited to the acute care setting.

This review focuses on the comparative effectiveness of strategies to de-escalate aggressive behavior in psychiatric patients in acute care settings. In this case, we conceptualize “de-escalate” as including preventing aggressive behaviors *and* reducing the use of seclusion and restraints. We clarify when “de-escalate” refers specifically to actively aggressive behavior.

Based on our preliminary literature search and input from key informants, we appreciate that risk assessment is a crucial step in the process of reducing aggressive behavior and the potential use of seclusion and restraints for psychiatric patients. We understand that a practical need exists to assess the accuracy of available risk assessment tools. Similarly, we appreciate that seclusion and restraints are applied across a span of settings, including chronic care settings, such as skilled nursing facilities and psychiatric residential treatment facilities. Nevertheless, risk assessment and consideration of chronic care settings are beyond the immediate scope of this comparative effectiveness review (CER); thus, we will not specifically address such topics or settings in this project.

## II. The Key Questions

### **Key Questions**

For the purposes of the Key Questions (KQs) posed in this review, we define aggressive behavior as making specific imminent verbal threats or using actual physical violence toward self, others, or property. As discussed above, we focus on patients with any psychiatric diagnosis per Diagnostic and Statistical Manual of Mental Disorders, Third Edition-Revised, Fourth Edition, or Fifth Edition (DSM-III-R, DSM-IV, or DSM-5).<sup>56-58</sup> For our purposes, these include delirium and substance misuse (but not dementia) and, for patients in emergency departments, those displaying severe psychiatric symptomatology. We view effectiveness as including a consideration of both benefits and harms, so we frame our questions to address each, respectively.

We envision a continuum of risk and behavior. Thus, the KQs cover a range of patients, from those with these disorders who may be at risk of aggressive behavior (i.e., are not actively aggressive), in which case interventions are preventive, to those who are actively exhibiting aggressive behaviors. Interventions can occur at any point along this continuum, and they can involve both nonpharmacologic and pharmacologic strategies. The interventions must target a reduction in aggressive behavior or a reduction in the use of seclusion and restraints. Of note, a strong focus of policy has been to reduce the use of seclusion and restraints, underscoring its importance as an outcome.

Accordingly, our two primary comparative outcome benefits are (1) a decrease in aggressive behaviors and (2) a decrease in the use of seclusion and restraints. For patients who are not acutely aggressive (i.e., not threatening the immediate physical safety of themselves, the staff, or others), use of seclusion and restraints is not allowed under current regulatory statutes.<sup>59</sup> Here, the potential outcomes include a reduction in aggressive behaviors or in the eventual use of seclusion and restraints (or both). However, for those who are actively aggressive, use of seclusion and restraints may be an option; in comparative studies where seclusion and restraints are used, reduction in aggressive behaviors will be the primary benefit outcome.

We will also look at longer term, or more final, health outcomes, including improved quality of life, functioning, or patient experience; improved therapeutic relationship; decreased subsequent aggressive behavior; and general resource use or costs. While also important, our scope will not allow us to focus on staff turnover or the sustainability of interventions.

Because of safety concerns in relation to aggressive behavior, our harms outcomes are more inclusive. Also, we note that harms to staff and/or patient might come from the use of seclusion or restraints as well as failure to use seclusion or restraints, so any comparison must account for this possibility.

Acute care settings are defined as public and private mental hospitals, acute care units at state mental hospitals, emergency departments, Veterans Affairs hospitals, and medical or surgical units in general hospitals, where discharge occurs within 35 days of beginning treatment.<sup>60</sup> Stays longer than 35 days would indicate a chronic care setting.

**KQ 1:** Regarding benefits for adult psychiatric patients in acute care settings:

- a. For those without active aggression, what are the comparative benefits of strategies to prevent aggressive behavior?
- b. For those with active aggression, what are the comparative benefits of strategies, including seclusion and restraints, to de-escalate aggressive behavior?
- c. For those with active aggression, what are the comparative benefits of strategies to reduce the use of seclusion and restraints?

**KQ 2:** Regarding harms for adult psychiatric patients in acute care settings:

- a. For those without active aggression, what are the comparative harms of strategies to prevent aggressive behavior?
- b. For those with active aggression, what are the comparative harms of strategies, including seclusion and restraints, to de-escalate aggressive behavior?
- c. For those with active aggression, what are the comparative harms of strategies to reduce the use of seclusion and restraints?

**KQ 3:** What characteristics [of patients (including age, gender, diagnosis, motivation to receive treatment), of intervention components, or of acute care settings] modify the benefits or harms of interventions for psychiatric patients at risk of, or presenting with, active aggression?

For the above KQs, the following PICOTS criteria for populations, interventions, comparators, outcomes, time frames, and settings apply:

### **Population(s)**

- KQs 1 through 3
  - Adult individuals (ages 18 or older) with an identified psychiatric disorder, including substance use disorders and delirium (but not dementia), *or* with severe psychiatric symptomatology, who are at risk of or actively exhibiting active aggression toward self, others, or property.

### **Interventions**

- KQs 1a and 2a: Strategies (early intervention techniques) targeted to reduce the likelihood of active aggression, such as:
  - Supportive language and verbal de-escalation;
  - Milieu-based changes, such as sensory rooms or staffing changes (including increased staff-to-patient ratios), specific staff training programs (including psychoeducation about collaborating with patients to reduce risk of aggression), or peer-based interventions;
  - Adjustments to the primary psychotropic regimen for the purpose of decreasing agitation or preventing aggression; these approaches (adjustments) may include an increase in an antipsychotic or mood stabilizer that treats the underlying psychiatric disorder);
  - Any intervention, or combination of interventions, different from seclusion and restraints that is aimed at preventing aggressive behavior (e.g., implementation of a procedure informed by the NASMHPD's Six Core Strategies).
- KQs 1b, 1c, 2b, and 2c: Strategies targeted to decrease aggression for those who are actively aggressive, such as:
  - Psychiatric Emergency Response Teams
  - Medication protocols that use on- or off-label FDA-approved medications to treat aggressive behavior, such as those described in project BETA
  - Any intervention, or combination of interventions, different from seclusion and restraints that is aimed at decreasing aggressive behavior (e.g., implementation of a procedure informed by NASMHPD's Six Core Strategies).
- KQ 3: Same as KQs 1 and 2.

### **Comparators**

- KQs 1a and 2a:

- Other strategies (early intervention techniques), but not seclusion and restraints, targeted to reduce the likelihood of active aggression, as described above for KQs 1a and 2a
- Usual care, defined as the standard of care for a particular setting before implementation of an intervention designed to decrease the likelihood of active aggression and/or the use of seclusion and restraints
- KQs 1b, 1c, 2b, and 2c:
  - Other strategies targeted to decrease aggression for those who are actively aggressive, as described above for KQs 1b/1c and 2b/2c
  - Seclusion or restraints (for 1b and 2b only):
    - Seclusion (involuntary confinement where individual is physically prevented from leaving)
    - Restraints, whether physical (e.g., any manual method, physical or mechanical device, material, or equipment that immobilizes or reduces the ability of a patient to move freely) or chemical (e.g., a psychotropic drug or medication when it is used as a restriction to manage the patient’s behavior)
  - Usual care, defined as the standard of care for a particular setting before implementation of an intervention designed to decrease aggression and/or the use of seclusion and restraints
- KQ 3: Same as KQs 1 and 2

## Outcomes

- KQs 1a, 1b, and 1c:
  - Intermediate outcomes:
    - Decreased aggression in terms of frequency, severity, or duration (as measured by direct counts or by validated aggression scales)
    - KQs 1a and 1c only: Reduced use of seclusion or restraints (decreased rate, amount, or duration)
    - Other secondary outcomes will be included, including length of time in the emergency department, but to be eligible, studies must report on at least one of the outcomes above
  - Final health outcomes: improved quality of life, functioning, or patient experience; improved therapeutic relationship; decreased subsequent aggressive behavior; decreased subsequent use of seclusion or restraints; general resource use or costs
- KQs 2a, 2b, and 2c: Patient injury or accidental death, staff injury, staff distress, patient psychological trauma (per self-report or clinical assessment); decreased adherence or engagement with treatment by patient; other side effects of interventions (e.g., medication side effects, such as excessive sedation, acute dystonia, and akathisia)
- KQ 3: Same as KQs 1 and 2

**Timing**

- KQs 1 through 3:
  - Imminently or within current episode of care (e.g., inpatient hospitalization, emergency department stay)

**Setting**

- KQs 1 through 3:
  - Acute care settings: emergency department or hospital (e.g., private or public psychiatric hospitals, general medical hospitals at which discharge occurs within 35 days of beginning treatment)

In addition to the foregoing PICOTS, we are considering the following other inclusion or exclusion criteria. Given concerns about risk of bias in observational and noncontrolled trials, and consistent with our prior CER work, we are requiring a total sample size of 100 or greater for any nonrandomized study after discussions with our Technical Expert Panel (TEP).

**Study Design**

- Systematic reviews, with or without meta-analyses
- Randomized controlled trials, including cluster randomized trials
- Nonrandomized controlled trials ( $n \geq 100$ )
- Cohort studies (prospective and retrospective,  $n \geq 100$ )
- Case-control studies ( $n \geq 100$ )
- Single group pre/post studies ( $n \geq 100$ )
- Interrupted time-series designs ( $n \geq 100$ )

**Geographic location**

- Developed countries (“very high” human development index as defined by the United Nations Development Programme)<sup>61</sup>

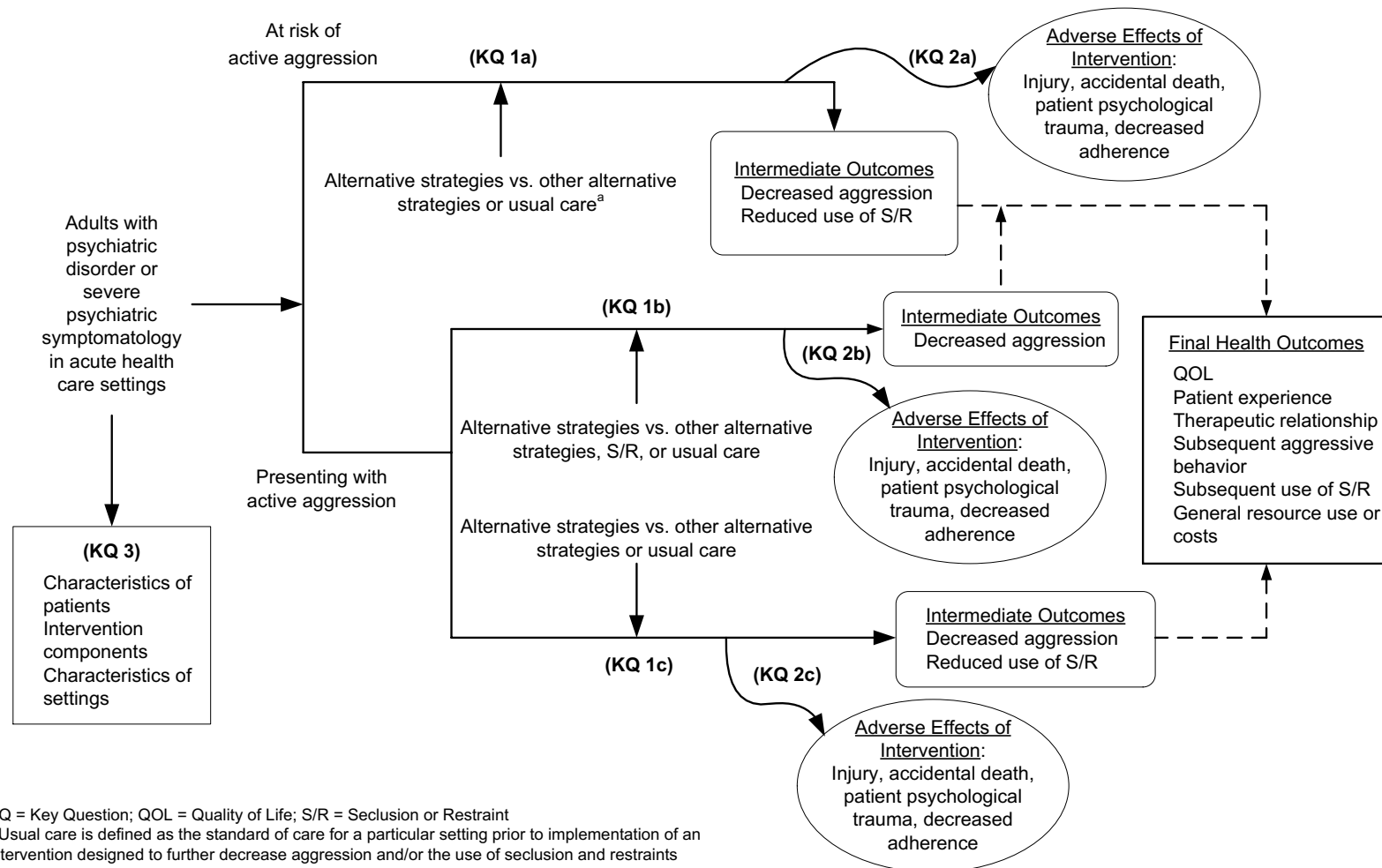
**Language**

- English language only



### III. Analytic Framework

**Figure 1. Analytic framework for comparative effectiveness of strategies to de-escalate aggressive behavior in psychiatric patients**



#### IV. Methods

The methods for this CER follow the guidance provided in the Agency for Healthcare Research and Quality (AHRQ) *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* ([www.effectivehealthcare.ahrq.gov/methodsguide.cfm](http://www.effectivehealthcare.ahrq.gov/methodsguide.cfm)) for the Evidence-based Practice Center (EPC) program.<sup>62</sup> Certain methods map to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.<sup>63</sup> All methods and analyses are determined a priori.

During the topic refinement for this topic, we engaged in a public process to develop draft Key Questions for the review. We generated an analytic framework, preliminary KQs, and preliminary inclusion/exclusion criteria in the form of PICOTS and other details about eligible studies. Information provided by the topic nominator helped guide our processes. Initially, a panel of 10 Key Informants (KIs) gave input on the KQs to be examined; these KQs were posted on AHRQ's Web site for public comment ([www.effectivehealthcare.ahrq.gov](http://www.effectivehealthcare.ahrq.gov)) from June 8, 2015, through June 29, 2015, and revised as needed.

We consulted with seven Technical Experts, who helped provide input during the development of our protocol. Their input helped inform decisions such as the sample size threshold for each eligible study and determination of whether and how to limit assessments of risk of bias of individual studies.

#### Criteria for Inclusion/Exclusion of Studies in the Review

The criteria for inclusion and exclusion of studies are designed to identify studies that can answer the KQs and are based on the PICOTS mentioned above and noted in Table 1 below.

Table 1. Eligibility criteria for review of strategies to de-escalate aggressive behavior

PICOTS	Inclusion	Exclusion
Populations	KQs 1 through 3: Adult individuals (ages 18 or older) with an identified psychiatric disorder, including substance use disorders and delirium (but not dementia), or with severe psychiatric symptomatology, who are at risk of or actively exhibiting aggressive behavior toward self, others, or property.	All other populations
Interventions	KQs 1a and 2a: Strategies (early intervention techniques) targeted to reduce the likelihood of aggressive behavior, such as: <ul style="list-style-type: none"><li>• Supportive language and verbal de-escalation</li><li>• Milieu-based changes, such as sensory rooms or staffing changes (including increased staff-to-patient ratios), specific staff training programs (including psychoeducation about collaborating with patients to reduce aggression risk), or peer-based interventions</li></ul>	All other interventions For medication-based interventions, those that are not FDA-approved for any indication

Table 1. Eligibility criteria for review of strategies to de-escalate aggressive behavior (continued)

PICOTS	Inclusion	Exclusion
	<ul style="list-style-type: none"> <li>• Adjustments to the primary psychotropic regimen for the purpose of decreasing agitation or preventing aggression; these approaches (adjustments) may include an increase in an antipsychotic or mood stabilizer that treats the underlying psychiatric disorder)</li> <li>• Any intervention, or combination of interventions, different from seclusion and restraints that is aimed at preventing aggressive behavior (e.g., implementation of a procedure informed by the NASMHPD's Six Core Strategies)</li> </ul> <p>KQs 1b/1c and 2b/2c: Strategies targeted to decrease aggression for those who are actively aggressive, such as:</p> <ul style="list-style-type: none"> <li>• Psychiatric Emergency Response Teams</li> <li>• Medication protocols that employ on- or off-label use of FDA-approved medications to treat aggressive behavior, such as those described in project BETA</li> <li>• Any intervention, or combination of interventions, different from seclusion and restraints that is aimed at decreasing aggressive behavior (e.g., implementation of a procedure informed by NASMHPD's Six Core Strategies)</li> </ul>	
	KQ 3: Same as KQs 1 and 2	
Comparators	<p>KQs 1a and 2a:</p> <ul style="list-style-type: none"> <li>• Other strategies (early intervention techniques), but not seclusion and restraints, targeted to reduce the likelihood of aggressive behavior, as described above for KQs 1a and 2a</li> <li>• Usual care, defined as the standard of care for a particular setting before implementation of an intervention designed to decrease the likelihood of aggression and/or the use of seclusion and restraint</li> </ul> <p>KQs 1b/1c and 2b/2c:</p> <ul style="list-style-type: none"> <li>• Other strategies targeted to decrease aggression for those who are actively aggressive, as described above for KQs 1b/1c and 2b/2c</li> <li>• Seclusion or restraint (for 1b and 2b only):</li> </ul>	<p>All KQs</p> <ul style="list-style-type: none"> <li>• A study with no comparison group</li> <li>• For medication-based strategies, placebo-only comparisons and those comparing different doses or routes of administration</li> </ul>

Table 1. Eligibility criteria for review of strategies to de-escalate aggressive behavior (continued)

PICOTS	Inclusion	Exclusion
	<ul style="list-style-type: none"> <li>- Seclusion (involuntary confinement where individual is physically prevented from leaving)</li> <li>- Restraints, whether physical (e.g., any manual method, physical or mechanical device, material, or equipment that immobilizes or reduces the ability of a patient to move freely) or chemical (e.g., a psychotropic drug or medication when it is used as a restriction to manage the patient's behavior)</li> <li>• Usual care, defined as the standard of care for a particular setting before implementation of an intervention designed to decrease aggression and/or the use of seclusion and restraint</li> </ul> <p>KQ 3: Same as KQs 1 and 2</p>	
Outcomes	<p>KQs 1a, 1b, and 1c:</p> <ul style="list-style-type: none"> <li>• Intermediate outcomes:               <ul style="list-style-type: none"> <li>- Decreased aggression in terms of frequency, severity, or duration (as measured by direct counts or by validated aggression scales)</li> <li>- <u>KQs 1a and 1c only</u>: Reduced use of seclusion or restraints (decreased rate, amount, or duration)</li> <li>- Other secondary outcomes will also be included, including length of time in the emergency department, but to be eligible, studies must report on at least one of the outcomes above</li> </ul> </li> <li>• Final health outcomes: improved quality of life, functioning, or patient experience; improved therapeutic relationship; decreased subsequent aggressive behavior; decreased subsequent use of seclusion or restraints; general resource use or costs</li> </ul> <p>KQs 2a, 2b, and 2c: Patient injury or accidental death, staff injury, staff distress, patient psychological trauma (per self-report or clinical assessment); decreased adherence or engagement with treatment by patient; other side effects of interventions (e.g., medication side effects, such as excessive sedation, acute dystonia, and akathisia)</p> <p>KQ 3: Same as KQs 1 and 2</p>	None

Table 1. Eligibility criteria for review of strategies to de-escalate aggressive behavior (continued)

PICOTS	Inclusion	Exclusion
Timing	All KQs: Imminently or within current episode of care (e.g., inpatient hospitalization, emergency department stay)	All KQs: Outside current episode of care
Settings	All KQs: Acute care settings, including emergency department or hospital (e.g., private or public psychiatric hospitals, general medical hospitals at which discharge occurs within 35 days of beginning treatment)	All KQs <ul style="list-style-type: none"> <li>• Outpatient, community-based, jails, prisons, schools, chronic care or long-term care settings</li> </ul>
Study designs	All KQs <ul style="list-style-type: none"> <li>• Systematic reviews, with or without meta-analyses</li> <li>• Randomized controlled trials</li> <li>• Nonrandomized controlled trials</li> <li>• Cohorts (prospective and retrospective)</li> <li>• Case-control studies</li> <li>• Single group pre/post studies</li> <li>• Interrupted time-series designs</li> </ul>	All KQs <ul style="list-style-type: none"> <li>• Case studies or series</li> <li>• Cross-sectional studies</li> <li>• Studies without a comparison group</li> <li>• Nonsystematic review</li> </ul>
Publications	All KQs: Original research	All KQs: Not original research (e.g., editorials without original data, newspaper articles)
Geographic locations	Developed countries (“very high” human development index per the United Nations Development Programme) <sup>61</sup>	All other countries
Language	English	All other languages

BETA = Best Practices in Evaluation and Treatment of Agitation; FDA = U.S. Food and Drug Administration; KQ = Key Question; NASHMPD = National Association of State Mental Health Program Directors; PICOTS = populations, interventions, comparators, outcomes, timing, and settings.

### Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions

To identify articles relevant to each KQ, we will search MEDLINE® (via PubMed), Embase®, the Cochrane Library, Academic Search Premier, PsycINFO, and CINAHL (Cumulative Index to Nursing and Allied Health Literature) from January 1, 1991, through July 15, 2015, using analogous search terms (Appendix A). We selected this date because this year marks the time that HCFA first released rules to minimize the use of seclusion and restraints in health care facilities.<sup>64</sup> An experienced information scientist (EPC librarian) will run the searches.

Our search will focus on comparative studies of de-escalation strategies (seclusion, restraints, or alternatives to seclusion or restraints) for patients with psychiatric disorders or severe psychiatric symptomatology at risk of, or presenting with, aggressive behavior across various acute health care settings. Search strings will include various Medical Subject Heading (MeSH) terms for psychiatric disorders, acute health care settings, and aggressive behavior. Our inclusion criteria will limit the search to populations 18 years of age and older.

Also, they will include any psychiatric or substance use disorder, as well as delirium. If the study population is limited to patients with dementia, that article will not be eligible. Acute health care settings include general hospitals, psychiatric hospitals, and emergency departments in these hospitals. To capture aggressive behavior, we will use MeSH terms for aggression, violence, psychomotor agitation, hostility, crisis

intervention, physical restraint, patient isolation, and psychotropic medications. We will limit the searches to English and human-only studies.

We will review systematic reviews (SRs) that address any parts of our KQs and dually assess them for quality using a modified AMSTAR (Assessment of Multiple Systematic Reviews) instrument.<sup>65</sup> Criteria for this assessment included methods used for the literature searches, review of the literature, and assessment of the risk of bias of any included studies. If we identify a high-quality systematic review, we will use it in place of the complete de novo search for that part of the KQ, but we will update our own searches based on one year before the end date of the search used for that systematic review. We will include pooled estimates of effect or other relevant results from SRs with meta-analyses that meet our inclusion/exclusion criteria for population, comparisons, and outcomes. Should identified SRs use inclusion/exclusion criteria that differ from ours or SRs without meta-analyses, we will review their reference lists to ensure that we include all relevant studies.

In addition to electronic searches, we will manually search reference lists of pertinent reviews, included trials, and background articles on this topic to identify any relevant citations that our searches might have missed. We will import all citations into an EndNote® X7 electronic database.

We will search for gray literature relevant to this review following guidance from the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* for these steps.<sup>66</sup> Sources of gray literature will include ClinicalTrials.gov, the World Health Organization's International Clinical Trials Registry Platform, Drugs@FDA, the European Medicines Agency, the National Institute of Mental Health Web site, the American Psychological Association Web site, the American Psychiatric Association Web site, the Substance Abuse and Mental Health Services Administration Web site, Scopus, and the Conference Proceedings Citation Index.

The AHRQ Scientific Resource Center will request scientific information packets or information on unpublished studies or data relevant for this systematic review from relevant pharmaceutical manufacturing companies and other stakeholders and organizations related to the use of pharmacologic and nonpharmacologic alternatives to seclusion or restraints.

### **Data Abstraction and Data Management**

We will design, pilot-test, and use a structured data abstraction form to ensure consistency of data abstraction. Trained reviewers will initially abstract data from each study. A senior reviewer will then read each abstracted article and evaluate the completeness and accuracy of the data abstraction. We will resolve discrepancies by consensus or by involving a third, senior reviewer.

We will abstract the following data from included trials and studies: study designs, eligibility criteria, population characteristics (such as age, sex, race, ethnicity), interventions, comparators, additional medications or interventions allowed, outcomes of interest and methods of outcome assessment, sample sizes, attrition, settings, geographic locations, and study funders. We will record intention-to-treat results (i.e., all patients are analyzed as randomized with missing values imputed) if available. For studies eligible for quantitative analyses, if any, we may contact authors if reported data are incomplete or missing.

For SRs meeting all of the inclusion criteria, we will abstract study design and methods, number of studies, and number of patients included in meta-analyses; characteristics of included studies, populations, and interventions; results; and adverse events, if reported. As appropriate, we may update the results of these reviews quantitatively or qualitatively and assess the strength of evidence as described below.

### **Assessment of Methodological Risk of Bias of Individual Studies**

To minimize risk of bias in observational and noncontrolled studies addressing adverse outcomes (a key focus of our report), we plan to require a minimum sample of 100 in nonrandomized studies (consistent with our work in prior CERs<sup>67</sup>). We plan not to assess risk of bias in noncontrolled or single-group pre/post studies because the ability of these study designs to support causal inferences is very limited due to potential confounding from multiple sources that generally do not affect controlled studies as much (e.g., secular, time-based changes in outcomes of interest, selection bias, the influence of concurrent interventions, and attrition-related bias).

To assess the risk of bias of trials and studies, we will use definitions based on AHRQ guidance<sup>68</sup> and as specified below. We will rate the risk of bias for each relevant outcome of a study as low, medium, or high. In general terms, results of a study with low risk of bias will be considered to be valid. Medium risk of bias implies some confidence that the results represent true treatment effect. The study is susceptible to some bias, but the problems are not sufficient to invalidate the results (i.e., no flaw is likely to cause major bias). A study with high risk of bias has significant methodological flaws (e.g., stemming from serious errors in design or analysis) that may invalidate its results.

Ratings of risk of bias are not comparable across study designs. That is, a low-risk-of-bias nonrandomized study does not necessarily equal a low-risk-of-bias randomized controlled trial. We will take the limitations of certain study designs into consideration when we grade the strength of the evidence (explained below).

To determine risk of bias in a standardized way, we will use the Cochrane Risk of Bias tool to appraise randomized controlled trials. For observational studies, we will employ criteria outlined in the RTI Risk of Bias Tool for Observational Studies.<sup>69</sup>

In general terms, a systematic review with low study limitations is considered well done and results are considered valid. A systematic review with medium study limitations is susceptible to some bias but probably not sufficient to invalidate its results. The moderate quality category is likely to be broad, so studies with this rating will vary in their strengths and weaknesses. A rating of high study limitations indicates methodological shortcomings (e.g., literature search in only one electronic database, no dual review of abstracts and full text articles, or the lack of critical appraisal of included studies) that may invalidate the systematic review's results.

Two independent reviewers will assign risk of bias ratings. Disagreements will be resolved by discussion and consensus or by consulting a third, independent party.

In our analyses and syntheses, we will include all eligible studies regardless of risk of bias. For quantitative analyses if any, however, we will use studies with high risk of bias only for sensitivity analyses.

## Data Synthesis

Throughout this review we will synthesize the literature qualitatively. We will stratify study data by whether they are controlled studies (e.g., RCT, cohort studies) vs. non controlled studies (e.g., pre/post, interrupted time series). When data are sufficient for controlled studies (i.e., if we find three or more similar studies for a comparison of interest), we will augment findings with quantitative analyses (i.e., meta-analysis) of the data from those studies (sorting RCTs together, and controlled observational studies together). We will conduct meta-analyses of data for head-to-head comparisons for trials that are fairly homogenous in terms of study populations and outcome assessments. For all analyses, we will use fixed- or random-effects models to estimate summary measures of effect.

More specifically, to determine whether quantitative analyses are appropriate, we will assess the clinical and methodological heterogeneity of the studies under consideration following established guidance.<sup>70</sup> We will do this by qualitatively assessing the PICOTS of the included studies, looking for similarities and differences. If we conduct quantitative syntheses (i.e., meta-analysis), we will assess statistical heterogeneity in effects between studies by calculating the  $\chi^2$ -statistic and the  $I^2$  statistic (the proportion of variation in study estimates attributable to heterogeneity). The importance of the observed value of  $I^2$  depends on the magnitude and direction of effects and on the strength of evidence for heterogeneity (e.g., p-value from the chi-squared test or a confidence interval for  $I^2$ ). If we include any meta-analyses with considerable statistical heterogeneity in this report, we will provide an explanation for doing so, considering the magnitude and direction of effects. We will also examine potential sources of heterogeneity using sensitivity analysis or analysis of subgroups. We plan to stratify analyses and/or perform subgroup analyses when possible and appropriate to examine clinical heterogeneity.

For any quantitative analyses, we will conduct sensitivity analyses including high risk-of-bias studies. Planned stratifications or categories for subgroup analyses include subgroups listed in the analytic framework under KQ 3. When quantitative analyses are not appropriate (e.g., because of heterogeneity, insufficient numbers of similar studies, or insufficiency or variation in outcome reporting), we will synthesize the data qualitatively.

We will follow EPC guidance to assess publication bias.<sup>62</sup> Depending on the evidence available to us, we will attempt quantitative tests of publication bias, such as funnel plot asymmetry, the trim and fill method, or selection modeling.<sup>71</sup>

## Grading the Strength of Evidence for Major Comparisons and Outcomes

We will grade the strength of evidence based on the guidance established for the EPC Program.<sup>69</sup> Developed to grade the overall strength of a body of evidence, this approach incorporates five key domains: study limitations (includes study design and aggregate risk of bias), consistency, directness, precision, and reporting bias. For some scenarios, this approach also considers other optional domains that may be relevant: a dose-response association, plausible confounding that would decrease the observed effect, and strength of association (magnitude of effect). Should new and eligible studies be identified that are relevant to prior eligible systematic review findings, we will quantitatively incorporate those findings to produce an updated meta-analytic result.



Mirroring our decision to not assess the risk of bias of noncontrolled or single-group pre/post studies, we plan also not to grade the strength of evidence based on these study designs. Their lack of usability for drawing causal inferences precludes including them in the process of grading the strength of evidence about the comparative benefits and harms of strategies to prevent or reduce aggressive behavior.

Grades reflect the strength of the body of evidence to answer KQs on the comparative benefits and harms of the interventions in this review. Table 2 defines the four grades of strength of evidence.<sup>69</sup>

**Table 2. Definition of strength of evidence grades**

Grade	Definition
High	We are very confident that the estimate of effect lies close to the <i>true effect</i> for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable (i.e., another study would not change the conclusions).
Moderate	We are moderately confident that the estimate of effect lies close to the <i>true effect</i> for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	We have limited confidence that the estimate of effect lies close to the <i>true effect</i> for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the <i>true effect</i> .
Insufficient	We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

Two trained reviewers will assess each domain for each key outcome; differences will be resolved by consensus. One of the two reviewers will always be a senior researcher with experience in grading strength of evidence.

### Assessing Applicability

We will assess applicability of the evidence following guidance from the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.<sup>72</sup> We will use the PICOTS framework to explore factors that affect applicability. Some factors identified a priori that may limit the applicability of evidence include the following: age of enrolled populations, sex of enrolled populations (e.g., fewer men may be enrolled in some studies), race or ethnicity of enrolled populations, diagnoses of involved sample, and location of and staffing for specific interventions.

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## VI. Definition of Terms

- Hospital-Based Inpatient Psychiatric Services (HBIPS)-2: Joint Commission National Quality Core measure for physical restraint endorsed by the National Quality Forum (2a: overall rate, 2b: children 1 through 12 years; 2c: adolescents 13 through 17 years; 2d: adults 18 through 64 years; 2e: older adults ≥ 65 years)
- HBIPS-3: Joint Commission National Quality Core measure for seclusion endorsed by the National Quality Forum (3a: overall rate, 3b: children 1 through 12 years; 3c: adolescents 13 through 17 years; 3d: adults 18 through 64 years; 3e: older adults ≥ 65 years)

## VII. Summary of Protocol Amendments

If we need to amend this protocol, we will give the date of each amendment, describe the change and give the rationale in this section. Changes will not be incorporated into the protocol. Example table below:

Table 3. Protocol Amendments

Date	Section	Original Protocol	Revised Protocol	Rationale
This should be the effective date of the change in protocol	Specify where the change would be found in the protocol	Describe the language of the original protocol.	Describe the change in protocol.	Justify why the change will improve the report. If necessary, describe why the change does not introduce bias. Do not use justification as “because the AE/TOO/TEP/Peer reviewer told us to” but explain what the change hopes to accomplish.

## VIII. Review of Key Questions

AHRQ posted the key questions on the Effective Health Care website for public comment. The EPC refined and finalized the key questions after review of the public comments, and input from Key Informants and the Technical Expert Panel (TEP). This input is intended to ensure that the key questions are specific and relevant.

## IX. Key Informants

Key Informants are the end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform healthcare decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

## X. Technical Experts

Technical Experts constitute a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and identify particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor do they contribute to the writing of the report. They have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

## XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparation of the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers. The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published three months after the publication of the evidence report.

Potential Peer Reviewers must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Invited Peer

Reviewers may not have any financial conflict of interest greater than \$10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

#### XII. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than \$1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest that cumulatively total greater than \$1,000 will usually disqualify EPC core team investigators.

#### XIII. Role of the Funder

This project was funded under Contract No. xxx-xxx from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The Task Order Officer reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

## APPENDIX A

Table A1. Search strategy and yield in PubMed

	<b>Search String</b>	<b>Results</b>
#1	Search ("Substance-Related Disorders"[Mesh] OR ("Mental Disorders"[MeSH] OR "Mood Disorders"[Mesh] OR "Schizophrenia and Disorders with Psychotic Features"[Mesh] OR Depression[Mesh] OR ("Depressive Disorder, Major"[Mesh]) OR "Anxiety Disorders"[Mesh]) OR "Eating Disorders"[Mesh] OR "Personality Disorders"[Mesh] OR ((severe OR serious OR persistent) mental illness[Text Word]))	<u>1045741</u>
#2	Search ("Aggression"[Mesh] OR "Violence"[Mesh] OR ("Psychomotor Agitation"[Mesh]) OR "Hostility"[Mesh] OR "Crisis Intervention"[Mesh] OR "Restraint, Physical"[Mesh] OR "Patient Isolation"[Mesh] Schema: nomesh	<u>121779</u>
#4	Search #1 AND #2	<u>36548</u>
#5	Search (((("Hospitals, General"[Mesh]) OR "Emergency Service, Hospital"[Mesh] OR ("Hospitals, Psychiatric"[Mesh] OR "Psychiatric Department, Hospital"[Mesh]) OR "Inpatients"[Mesh] OR hospitalization [mesh]))	<u>248843</u>
#6	Search (#4 AND #5)	<u>3460</u>
#7	Search (((("Comparative Effectiveness Research"[Mesh] OR "Comparative Study" [Publication Type] OR "Pragmatic Clinical Trials as Topic"[Mesh]) OR comparison OR comparator OR comparative))	<u>2344453</u>
#8	Search (#6 AND #7)	<u>479</u>
#9	Search ("Crisis Intervention"[Majr] OR "Restraint, Physical"[Majr] OR "Patient Isolation"[Majr])	<u>8464</u>
#10	Search (#1 AND #5 AND #9)	<u>603</u>
#11	Search (#8 OR #10)	<u>1008</u>
#12	Search "Antipsychotic Agents"[MeSH Terms] OR "Antipsychotic Agents"[nm]) OR "Valproic Acid"[Mesh] OR "Droperidol"[Mesh] OR "Promethazine"[Mesh] OR "Trazodone"[Mesh] OR "Amitriptyline"[Mesh] OR "Chlormethiazole"[Mesh] OR "Citalopram"[Mesh] OR "Chlorpromazine"[Mesh] OR "topiramate" [Supplementary Concept] OR "Diphenhydramine"[Mesh] OR "Carbamazepine"[Mesh] OR "Pindolol"[Mesh] OR "Lithium Carbonate"[Mesh] OR "Hydroxyzine"[Mesh] OR "Nadolol"[Mesh] OR "Sertraline"[Mesh] OR "Diazepam"[Mesh] OR "lurasidone" [Supplementary Concept] OR "Metoprolol"[Mesh] OR "Lorazepam"[Mesh] OR "iloperidone" [Supplementary Concept]	<u>127479</u>
#13	Search "Restraint, Physical"[Mesh] OR "Patient Isolation"[Mesh])	<u>14797</u>
#14	Search (#12 AND #13)	<u>334</u>
#15	Search (#1 AND #5 AND #14)	<u>50</u>
#37	Search "Tranquilizing Agents/administration and dosage"[MAJR]	<u>3600</u>
#38	Search (#12 AND #37)	<u>2700</u>
#39	Search (#1 AND #5 AND #38)	<u>240</u>
#40	Search (#15 OR #39)	<u>288</u>
#41	Search (#7 AND #40)	<u>87</u>
#42	Search (#11 OR #41)	<u>1077</u>
#43	Search (#11 OR #41) Filters: Humans	<u>1075</u>
#44	Search (#11 OR #41) Filters: Humans; English	<u>902</u>
#45	Search (#11 OR #41) Filters: Publication date from 1980/01/01; Humans; English	<u>811</u>
#46	Search (#1 AND #2 AND #5 AND #37) Filters: Publication date from 1980/01/01; Humans; English	<u>19</u>
#47	Search (#1 AND #2 AND #5 AND #37)	<u>22</u>
#50	Search (#45 OR #47) Filters: Publication date from 1980/01/01; Humans; English	<u>825</u>
#51	Search (#45 OR #47)	<u>828</u>

Adds Using MAJOR headings

	<b>Search String</b>	<b>Results</b>
#1	Search "Hospitals, Psychiatric"[MAJR] AND ("Patient Isolation/utilization"[MAJR] OR "Restraint, Physical/utilization"[MAJR])	<u>42</u>
#2	Search "Hospitals, Psychiatric"[MAJR] AND ("Patient Isolation"[MAJR] AND "Restraint, Physical"[MAJR])	<u>54</u>
#3	Search (("Psychiatric Department, Hospital"[MAJR] AND ("Patient Isolation/utilization"[MAJR] OR "Restraint, Physical/utilization"[MAJR])))	<u>16</u>
#4	Search (#1 OR #2 OR #3)	<u>86</u>
#5	Search (#1 OR #2 OR #3) Filters: Humans	<u>86</u>
#6	Search (#1 OR #2 OR #3) Filters: Humans; English	<u>75</u>
#7	Search (#1 OR #2 OR #3) Filters: Publication date from 1980/01/01; Humans; English	<u>75</u>
#8	Select 75 document(s)	<u>75</u>