I. Background and Objectives for the Systematic Review

Background

Definition of Long-term Care:

LTC refers to myriad services designed to provide assistance over prolonged periods to compensate for loss of function due to chronic illness or physical or mental disability.\(^1\) LTC varies in frequency and intensity according to the needs of the recipients, and it includes both hands-on, direct care as well as general supervisory assistance. LTC supports older adults in two distinct realms: activities of daily living (ADLs) and instrumental activities of daily living (IADLs). ADLs include such basic functions as eating, bathing, dressing, getting into and out of bed or a chair, and using the toilet. IADLs are additional tasks necessary to maintain independence, such as preparing meals, managing medications, shopping for groceries, and using transportation.

LTC is distinct from acute or episodic medical interventions because care must be integrated into an individual’s daily life over an extended time period. LTC also stands apart from so-called post-acute care, which occurs immediately after a hospitalization. LTC affects not only the direct recipients, but also their family members, who are often the primary source of support for older adults with functional limitations.\(^2\)

Long-term Care Settings and Services:

LTC can be delivered in institutional settings like nursing homes, or in the community in the form of HCBS.

HCBS refers to services of variable frequency and intensity provided in a wide array of noninstitutional settings, from recipients’ own homes to various congregate living arrangements. Care provided through HCBS may be pieced together from multiple agencies and independent providers with or without overall coordination or management. Both the nomenclature and the nature and scope of services vary tremendously between settings. For example, the continuum of facilities and services included under assisted living (AL), a particular category of HCBS, blurs the boundaries between institutional and noninstitutional care. In general, AL is provided in independent apartments for seniors, which offer substantial privacy and control for residents; but some AL (especially for those with severe cognitive impairments), is provided in more regimented environments. Even with the rest of the population served, the level and intensity of supportive services varies widely. Conversely, some models of congregate group housing seem closer to institutional settings. In light of these complexities, HCBS must be clearly defined and conceptualized.

Sample list of Home and Community-based Services:

- Care coordination or case management
- In-home services (provided in recipients’ own homes)
  - Personal care assistant service
  - Personal attendant service
- Homemaker agency and personal care agency services
- Home hospice services
- Home delivered meals
- Home reconfiguration or renovation
- Medical services
- Transportation
- Cash payments or allowances managed by the consumer or a consumer representative to pay for above services

Services provided in congregate living settings that are expected to be the recipient’s home, such as assisted living, adult foster homes, small group homes, and residential care facilities:
- Cooking, housekeeping, mobility assistance, which are all services provided by personal care assistants and personal attendants or home health aides under HCBS (could be consolidated as restaurant service as well as in-home services in the resident’s unit)
- Personal care (could include medication administration, medication) management
- Activity program
- General oversight and safety supervision
- Wellness assistance and health monitoring
- Palliative care

Services provided outside the recipient’s home (regardless of whether it is a private home or a group residential setting):
- Adult day care
- Day health care
- Senior center programming

Compared to HCBS, NHs are relatively easy to define. Nursing homes are institutional facilities licensed by the state that offer 24-hour room and board, supervision and nursing care. However, NHs have multiple functions and serve distinct populations tied to specific funding streams. For example, NHs serve not only long-stay residents (the population of interest to this review), but also short-stay residents who receive rehabilitation or post-hospital recuperation. A list of services in nursing homes might include:

- Personal care, ADL services
- Medication management and administration
- Nursing management, restorative nursing
- Palliative care
- Meals
- Rehabilitation
- Activities
- Transportation
- General care coordination, care planning, oversight

Comparing HCBS to NH:
Apples-to-apples comparisons and meaningful evaluations of outcomes between HCBS and NHs are challenging. Meaningful comparisons must include services of roughly
equivalent type, frequency, and intensity. Comparisons of HCBS and NHs are complicated by heterogeneity.

Heterogeneity in Long-term Care Recipients
LTC serves older adults with varying degrees of physical and mental disability and/or chronic illness, as well as younger individuals with impairments that create a need for assistance with ADLs and IADLs. Therefore, LTC recipients include those with a disability acquired as a concomitant of aging and those with long-standing or even congenital disability who may have entered LTC earlier in life and are aging within the system. Ultimately, LTC recipients require a wide range of assistance with tasks of daily living. Any comparisons of NH care and HCBS will require an understanding of actual comparisons made by investigators—i.e., the characteristics of those served and the service mix in both the NH and the HCBS. In general, HCBS clients should be compared to long-stay NH residents. Even still, measurement issues further confound the effort to compare case mixes between institutions and community care. For example, researchers may use IADLs for community samples but would not see them as applicable to nursing home residents.

Heterogeneity in Long-term Care Settings and Services
LTC is provided in a range of settings (physical and social environments in which care is provided), and these settings are integral to LTC delivery. The appropriateness of a particular setting for an LTC recipient is based on a complex interplay between the characteristics of the individual, the settings, and the services.

Further, the type, frequency, and intensity of LTC services vary across settings and within settings. HCBS includes a wide variety of settings and services. A particular problem is classifying AL, which, although institutional, is generally more restrictive with fewer services than NH.

Assessing the Cost of Care
Assessing costs in the context of LTC requires attention to expenses associated with several factors, including housing; specific services delivered; health care utilization (including acute care services such as hospitals, emergency departments); and, finally, costs incurred by recipients and their families. Meaningful cost comparisons between HCBS and institutional care must determine and specify the exact costs being counted. For example, NH care includes room and board while HCBS care does not. Meanwhile, some cost analyses of HCBS include all public subsidies received by HCBS clients (e.g., rent, transportation, and food stamps), arguing that these are not accrued by NH residents.

Objective of the Review
We will compare long-term care (LTC) for older adults delivered in institutional settings such as nursing homes (NH) to care delivered in home and community-based settings (HCBS). We will analyze the benefits and harms of providing care in these settings and compare the costs of providing these services across the two settings taking into account both the direct costs of care as well as costs such as resource utilization (i.e., hospital use) and family burden. We will consider costs separately from the question of effectiveness; this review will not look at cost-effectiveness. The need for LTC exists across age groups; however, this review will focus exclusively on adults aged 60 and older who use long-term care.
Relevance of the Review to Consumers, Researchers and Policy Makers

Older people and their families as well as policymakers have an immediate interest in determining which type of care is most suitable for whom. Issues related to service delivery and financing mechanisms are central to LTC policy, and policymakers grapple with the scope, mix, quality, and financing of LTC services. Current financial retrenchment and budgetary pressures intensify the need to identify effective means of delivering LTC services while minimizing costs. Policymakers may be concerned about payment costs, but other costs must also be considered, including family care burden and induced use of other services.

For the growing number of older adults who need long-term care, identifying the setting or program that accounts for their preferences while best serving their needs is a critical priority. The view of HCBS has changed over time. Early demonstration projects (from the mid 1970s through about 1985) on the effectiveness and costs of expanding LTC to include HCBS generated a large empirical literature as well as many reviews. They were driven by a “substitution” model, which viewed HCBS as an alternative (hopefully a cheaper alternative) to the NH. But by the mid 1990s, there emerged a great deal of innovation and a shift toward newer models of organizing, financing, and delivering care, along with active use of Medicaid waivers that allowed states to use money previously targeted for NHs to support HCBS. These changes have not been adequately reviewed in the literature. A clear synthesis of the latest evidence will help inform the policy debate.

II. The Key Questions

We developed the key questions after a topic refinement process that included a preliminary review of the literature and consultation with key informant panel of LTC experts and stakeholders. Key informants affirmed that differences in case mix across settings must be considered when evaluating studies on LTC. Discussion with key informants also helped us define the settings and services covered under HCBS.

Based on key informant input, we made the following changes:

- We identified HCBS settings to include: recipient’s own home, congregate living arrangements such as room and board, adult foster care and assisted living, and non-residential settings such as adult day care.
- We excluded from our purview short-stay NH residents and those receiving Medicare home health services.

The draft key questions were posted for public comment on the AHRQ Effective Health Care Program website for additional feedback from October 10, 2011 to November 03, 2011. We also sought input from a technical panel of experts (TEP) convened to provide methodological and content expertise to the review. In response to input from the public and the TEP, we made the following specific changes.

- We revised the age limit for inclusion from 65 years to 60 years
- We added specific sub-questions (1.a and 1.b) to address the issue of case-mix differences across settings
The final key questions are:

**Question 1**

What are the benefits and harms of long-term care provided through Home and Community-based Services (HCBS) compared to institutions such as nursing homes (NH) for older adults aged 60 and over who need long-term care (LTC)?

a. To what extent do HCBS and NHs serve similar populations?

b. How do the outcomes of the services differ when tested on similar populations?

c. What are the harms to older adults as a result of HCBS and NH?

**Question 2**

What are the costs (at the societal and personal level) of HCBS and NH (per recipient and in the aggregate) for adults over age 60? Costs may include direct costs of care as well as costs such as resource utilization and family burden.

The definitions of population, intervention/comparator, outcomes, setting and time-frame are:

**Population(s)**
- Older adults (age>60) needing LTC, with adjustment for the Program of All-Inclusive Care for the Elderly (PACE) where eligibility begins at 55.

Older adults who need LTC are heterogeneous groups with varying degrees of physical and mental disability and/or of chronic illness. They require different levels of assistance with tasks of daily living. Moreover, LTC recipients include those who acquire a disability as a concomitant of aging as well as those with long-standing disability who are now aging within the LTC system. A major sub-group of interest is older adults who have dementia or mental illness. Patient characteristics of interest that might modify outcomes include:

- Age
- Race
- Gender
- Functional status
- Clinical status
- Cognition
- Rural/urban
- Morbidities
- Mental illness
Interventions

- Home and Community-based Services. Assisted living services and facilities will be included as one form of HCBS.
  - Care coordination or case management
  - In-home services (provided in recipients’ own homes)
    - Personal care assistant service
    - Personal attendant service
    - Homemaker agency and personal care agency services
    - Home hospice services
    - Home delivered meals
    - Home reconfiguration or renovation
    - Transportation
    - Cash payments or allowances managed by the consumer or a consumer representative to pay for above services.
  - Services provided in congregate living settings such as assisted living, adult foster homes, small group homes, residential care facilities, which are expected to be the resident’s home.
    - Cooking, housekeeping, mobility assistance, which are all services provided by personal care assistants and personal attendants or home health aides under HCBS (could be consolidated as restaurant service as well as in-home services in the resident’s unit)
    - Personal care (could include medication administration, medication management
    - Activity program
    - General oversight and safety supervision
    - Wellness assistance and health monitoring
    - Palliative care
  - Services provided outside the recipient’s home (regardless of whether it is a private home or a group residential setting)
    - Adult day care
    - Day health care
    - Senior center programming

Each comparison must specifically define what is included in the package of services. Because HCBS requires that someone provide room and board whereas NH and other institutional care forms provide these as part of their core services, we need to accurately identify what each type of care includes.

Comparators

- Nursing home care (long-term care, not short-term stays)

Services provided in nursing homes might include:
  - Personal care, ADL services
  - Medication management and administration
  - Nursing management, restorative nursing
  - Palliative care
Post-acute care, which addresses care immediately after a hospitalization, is excluded.

Outcomes

- Physical function
- Cognition
- Social function
- Pain
- Mental health outcomes (e.g., depression and anxiety)
- Quality-of-life outcomes (including quality of life related to general health)
- Outcomes related to family caregivers (e.g., strain on family caregivers)
- Death, place of death
- Frequency of utilization of acute care services (e.g., hospitals, emergency departments)
- Satisfaction
- Individual and aggregate costs

LTC costs may include those related to housing, services provided, health care utilization including acute care services such as ERs and hospitals, and expenses borne by individuals and their families.

Reported harms are safety, inadequate preventive care, unnecessary hospitalizations, and concerns about abuse or neglect.

Timing

- We are looking at both cross-sectional studies and longitudinal designs. The latter can cover varying periods ranging from 6 months to many years (some effects are only evident after several years).
III. Analytic Framework

Figure 1. Analytical Framework

[Diagram showing Analytical Framework for Long-term Care for Older Adults: A Comparative Effectiveness Review of Institutional Versus Home and Community-Based Care]

- Nursing Home Care
- Home and Community-Based Care

Outcomes
- Physical function
- Social function
- Cognition
- Pain
- Death, Place of Death
- Mental health outcomes (depression, anxiety)
- Satisfaction
- Quality-of-life outcomes (including health-related quality of life)
- Frequency of utilization of acute care services (e.g., hospitalizations and ER visits and subsequent LTC)
- Outcomes related to family care givers (e.g., strain on family caregivers, health effects)

KQ 1.a
KQ 1.b
KQ 1.c
KQ 2

Safety
Inadequate preventive care
Unnecessary hospitalizations
Abuse
Neglect

Elderly
(Age>60)

Age
Race/ethnicity
Gender
Functional status
Clinical status
Cognition
Rural/Urban
Morbidity
Mental illness
Payer (Medicare, Medicaid or self)
Prior service use
Disability history

Individual and Aggregate Costs; Costs include the direct cost of care and costs such as resource utilization (e.g., hospitalizations and ER visits and subsequent LTC) and burden on family members
IV. Methods

A. Criteria for Inclusion/Exclusion of Studies in the Review

Inclusion Criteria

- Randomized controlled trials (RCTs) and observational studies.
- Studies published in English.
- International studies from countries with comparable health systems (e.g., Canada, Australia, Britain, Norway, Sweden and other European Countries) will be included.
- Study population is older adults (age>60). (We will include recipients of Program of All-Inclusive care for the elderly (PACE) where eligibility begins at 55.)
- Studies that directly compare outcomes of care between NH and HCBS. We will also use cross-sectional studies to compare populations served.
- Studies from 1995-current. We limit studies by date because early studies on LTC (from 1980s onward) have been extensively reviewed whereas more recent studies have not.

Exclusion criteria

- Studies on post-acute care or Medicare home health care population.
- Non-English language studies.

Rationale: Our discussions with the technical panel of experts indicate that studies most relevant to current landscape of long-term care in the United States are published in English. Therefore, the restriction on language would not affect the findings of the review.

- Studies that do not have a direct comparison between NH and HCBS (e.g., studies that compare one type of HCBS to another).

B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions. Based on preliminary review of the literature and input from experts, we anticipate identifying few or perhaps no RCTs that directly compare HCBS and NH settings and services. Therefore, observational studies and grey literature in the form of program evaluations and reports to state and federal funding agencies are critical sources of evidence for the review.
We will search MEDLINE (via OVID) and Age Line\(^1\) and grey literature sources. The preliminary search strategy is listed in Appendix A. Bibliographic database searches will be supplemented with a backward and forward citation search of highly relevant documents and hand searching. We will update the literature search while the draft report is under public/peer review.

Two independent reviewers will screen titles/abstracts using the inclusion/exclusion criteria listed above. Articles included by either reviewer will undergo full-text screening, after which two reviewers must agree on a final inclusion/exclusion decision. Disagreements will be resolved by discussion or, when needed, by consultation with a third reviewer. Articles meeting eligibility criteria will be included for data abstraction. We will follow the same screening procedure for the literature update.

C. Data Abstraction and Data Management. We will download search results into EndNote\(^0\) reference-management system. Data from included studies will be abstracted directly into evidence tables by one reviewer and validated by a second reviewer. Disagreements will be resolved by consensus or, when needed, by consultation with a third reviewer.

We will abstract data on study design (cross-sectional or longitudinal), location (U.S. or International), eligibility criteria, characteristics of study participants, descriptors to assess details of the intervention (setting, services provided), outcomes reported, and length of followup. We will abstract data on characteristics of population served from cross-sectional studies and studies that report case-mix. Data elements will also include descriptors to assess methodological quality and study applicability.

D. Assessment of Methodological Quality of Individual Studies. We will assess methodological quality of individual studies for each key question using criteria specific to study design according to current AHRQ guidance\(^7\). The primary and secondary abstractor/evaluator will independently assess the risk of bias of each eligible study using tools specific to study design. The full team will meet to reconcile and discuss any differences of individual component ratings and assign the overall quality rating.

Since we anticipate differences in case-mix across settings, selection bias will be a critical domain in assessing overall quality. Studies that account for case-mix differences using techniques such as multivariate analysis, propensity score matching, or instrumental variables, will be considered higher quality. In addition to selection bias, we will evaluate completeness of intervention specification, use of equivalent outcome measures across experimental and control groups, and differential loss to follow up. Specific questions to address the above criteria will be adapted from the RTI item bank for risk of bias in observational studies.\(^8\) Overall risk of bias will be assessed as high, moderate, low, or unclear based on individual component ratings.

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\(^1\) AgeLine database is an interdisciplinary index of the literature on aging with exclusive focus on older adults (>50) and aging related issues.

Source: [www.effectivehealthcare.ahrq.gov](http://www.effectivehealthcare.ahrq.gov)

Published Online: December 20, 2011
As mentioned, we anticipate that few (if any) randomized controlled trials will meet eligibility criteria. RCTs that meet inclusion criteria will be assessed according to recommendations of the EPC Methods guide for Comparative Effectiveness Reviews.\(^7\) Specific applicable criteria are: adequacy of randomization; the comparability of groups at baseline; use of specific analytical methods to control for baseline differences; intervention specification; the completeness of followup; and use of equivalent outcome measures across the study arms. We will assume a low risk of bias when RCTs meet all the quality criteria; a moderate risk of bias if at least one of the quality criteria was not met; and a high risk of bias if two or more quality criteria were not met. We will assign an unknown risk of bias for the studies with poorly reported quality criteria.

E. Data Synthesis. We will design evidence summary tables relevant to each key question. Evidence tables will include data fields in the following categories: study design; casemix; intervention/comparator; outcomes; risk of bias and applicability. Specific data fields are noted in the data management section. The evidence tables will be pilot tested by two independent investigators using a randomly selected set of articles. The tables will be revised if necessary to ensure consistency and clarity of presentation.

Preliminary analysis of the literature and discussions with TEP panel indicate that quantitative synthesis of the literature may not be feasible because of heterogeneity in studies. Therefore, we will synthesize results qualitatively to arrive at conclusions regarding effectiveness. We will compare characteristics of populations served across settings using data from cross-sectional studies and studies that report casemix. We will compare across settings characteristics of those served in the domains of physical function, cognition, mental health/affect, and comorbidities. We will qualitatively synthesize results from individual studies to evaluate the extent to which HCBS and NH serve similar populations. Throughout the analysis, we will consider AL to be a separate category within HCBS.

To compare outcomes of care across settings, we will first categorize studies by the outcome domain investigated. We will compare results across settings for specific outcome domains. (e.g., physical function, cognitive function, mental health/affect, utilization of acute care services, costs, and harms). We will qualitatively synthesize the results to evaluate the differences in trajectories of older adults with specific characteristics as a result of care provided in NH or HCBS settings.

We will analyze international studies separately because differences in organization of health care system, models of care and reimbursement policies between countries have the potential to limit applicability. We will consider the impact of such differences for each individual study and evaluate the applicability of study results to long-term care in the United States. We will not be evaluating any other sub-groups for sub-analysis.
F. Grading the Evidence for Each Key Question. We will assess the strength of evidence for each key question using the approach described in the EPC methods manual. In brief, the EPC approach requires assessment of four domains:

- Risk of bias (internal validity)
- Consistency (similarity of effect sizes of included studies)
- Directness (single direct link between intervention and outcome)
- Precision (degree of certainty surrounding an effect estimate)

Based on initial review of the literature, we expect risk of bias to be the most important domain in grading the strength of evidence. We will evaluate individual domains listed above qualitatively and assess a summary rating of “high,” “moderate,” or “low” strength of evidence. We will assign a summary rating of “insufficient” when evidence is either unavailable or does not permit a conclusion. However, we will report the study results and the rationale for insufficient grade.

These ratings will be interpreted as follows:

1. High: High confidence that the evidence reflects the true effect; further research is very unlikely to change the confidence in the estimate of effect.

2. Moderate: Moderate confidence that the evidence reflects the true effect; further research may change our confidence in the estimate of effect and may change the estimate.

3. Low: Low confidence that the evidence reflects the true effect; further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.

   Insufficient: Evidence either is unavailable or does not permit a conclusion.

G. Assessing Applicability-To assess applicability of individual studies, we will assess the eligibility requirements for enrollment, services delivered and the delivery mechanisms and the sources of finance.

V. References


4. Kane RA, Kane RL. Long-Term Care: Principles, Programs, and Policies. New York:


VI. Definition of Terms

None.

VII. Summary of Protocol Amendments

In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale.

VIII. Review of Key Questions

For all EPC reviews, key questions were reviewed and refined as needed by the EPC with input from Key Informants and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed. In addition, for Comparative Effectiveness reviews, the key questions were posted for public comment and finalized by the EPC after review of the comments.

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 comprise a multi-disciplinary group of clinical, content, and methodologic experts who provide input in defining populations, interventions, comparisons, or outcomes as well as identifying particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design and/or 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 contribute to the writing of the report and have not reviewed the report, except as given the opportunity to do so through the 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 methodologic expertise. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. Peer reviewers do not participate in writing or editing of the final report or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for CERs and Technical briefs, be published three months after the publication of the Evidence report.

Potential 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.
Appendix A: Search Strategy

1  "long-term care".ti,ab. (11924)
2  "day care".ti,ab. (5292)
3  "assisted living".ti,ab. (1019)
4  "adult day health center".ti,ab. (6)
5  "adult day health care".ti,ab. (47)
6  "adult foster care".ti,ab. (13)
7  "independent living".ti,ab. (1383)
8  "board and care".ti,ab. (98)
9  "home health care".ti,ab. (1899)
10 "group residential care".ti,ab. (1)
11 "residential care".ti,ab. (1562)
12 "home and community based care".ti,ab. (66)
13 "home and community based services".ti,ab. (184)
14 "personal care services".ti,ab. (52)
15 "aging in place".ti,ab. (117)
16 "continuing care retirement communit$".ti,ab. (143)
17 "group residential care".ti,ab. (1)
18 or/1-17 (22839)
19 exp nursing homes/ (29644)
20 institutionalization/ (4485)
21 nursing home$.ti,ab. (18990)
22 "institutional care".ti,ab. (1219)
23 (nursing adj home$).tw. (18990)
24 (residential adj (aged or elderly or geriatric)).tw. (242)
25 or/19-24 (39894)
26 18 and 25 (5814)
27 Randomized controlled trials as topic/ (77322)
28 randomized controlled trial/ (319749)
29 random allocation/ (73347)
30 double blind method/ (113493)
31 single blind method/ (15658)
32 clinical trial/ (469154)
33 clinical trial, phase i.pt. (11784)
34 clinical trial, phase ii.pt. (18612)
35 clinical trial, phase iii.pt. (6631)
36 clinical trial, phase iv.pt. (654)
37 controlled clinical trial.pt. (83741)
38 randomized controlled trial.pt. (319749)
39 multicenter study.pt. (138409)
40 clinical trial.pt. (469154)
41 exp clinical trials as topic/ (250981)
42 or/27-41 (891168)
43 epidemiological studies/ (5210)
exp case control studies/ (531568)
exp cohort studies/ (1142375)
case control.tw. (58287)
(cohort adj (study or studies)).tw. (56874)
cohort analy$.tw. (2606)
cohort analy$.tw. (2606)
(follow up adj (study or studies)).tw. (32735)
(observational adj (study or studies)).tw. (28309)
longitudinal.tw. (106963)
retrospective.tw. (202746)
cross sectional.tw. (116611)
cross-sectional studies/ (133369)
or/43-55 (1524081)
26 and 42 (460)
26 and 56 (1065)
limit 57 to (english language and yr="1995-Current") (408)
limit 58 to (english language and yr="1995-Current") (876)
(case reports or comment or editorial or historical article or letter or news or newspaper article or"review").pt. (4469446)
59 not 61 (372)
60 not 61 (847)