VETERANS HEALTH ADMINISTRATION
OFFICE OF PATIENT CARE SERVICES
TECHNOLOGY ASSESSMENT PROGRAM

BRIEF OVERVIEW:

Hypothermia after Cardiac Arrest

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TECHNOLOGY ASSESSMENT PROGRAM

An Effective Resource for Evidence-based Managers

VA's Technology Assessment Program (TAP) is a national program within the Office of Patient Care Services dedicated to advancing evidence-based decision making in VA. TAP responds to the information needs of senior VA policy makers by carrying out systematic reviews of the medical literature on health care technologies to determine "what works" in health care. "Technologies" may be devices, drugs, procedures, and organizational and supportive systems used in health care. TAP reports can be used to support better resource management.

TAP has two categories of products directed toward filling urgent information needs of its VA clients. TAP assigns a category to each new request based largely on the availability of studies from results of initial searches of peer-reviewed literature databases:

- The ***Short report*** is a self-contained, rapidly-produced qualitative systematic review between 5 and 20 pages in length. It provides sufficient background information and clinical context to its subject to be accessible to a wide audience, including non-clinician managers.

- The ***Brief overview*** originated as an internal memo to VA clients with both well-defined and urgent information needs. It usually comprises 2 to 10 pages and assumes sufficient existing knowledge regarding clinical context and technology issues by its readers to omit these components. It often requires some additional reading of documents (provided with the overview for the client) to obtain a full and comprehensive picture of the state of knowledge on the topic.

All TAP products are reviewed internally by TAP's physician advisor and key experts in VA. Additional comments and information on this report can be sent to:

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No contributors to this review report conflicts of interest.

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A SUMMARY FOR HTA REPORTS

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This summary form is intended as an aid for those who want to record the extent to which an HTA report meets the 17 questions presented in the checklist. It is NOT intended as a scorecard to rate the standard of HTA reports – reports may be valid and useful without meeting all of the criteria that have been listed.

Brief Overview:
Hypothermia after cardiac arrest

April 2010

Item	Yes	Partly	No
Preliminary			
1. Appropriate contact details for further information?	√		
2. Authors identified?	√		
3. Statement regarding conflict of interest?			√
4. Statement on whether report externally reviewed?			√
5. Short summary in non-technical language?			√
Why?			
6. Reference to the question that is addressed and context of the assessment?	√		
7. Scope of the assessment specified?	√		
8. Description of the health technology?	√		
How?			
9. Details on sources of information?	√		
10. Information on selection of material for assessment?	√		
11. Information on basis for interpretation of selected data?	√		
What?			
12. Results of assessment clearly presented?	√		
13. Interpretation of assessment results included?	√		
What Then?			
14. Findings of the assessment discussed?	√		
15. Medico-legal implications considered?			√
16. Conclusions from assessment clearly stated?	√		
17. Suggestions for further actions?	√		

BRIEF OVERVIEW: HYPOTHERMIA AFTER CARDIAC ARREST

ABBREVIATIONS IN THIS REVIEW

AAN, American Academy of Neurology

ALS, advanced life support

AMI, acute myocardial infarction

APACHE, acute physiology and chronic health evaluation

CABG, coronary artery bypass graft

CEDIT, Comité d'Evaluation et de Diffusion des Innovations Technologiques (France)

CCT, controlled clinical trial

CI, 95% confidence interval

CPC, cerebral performance category

CVA, cerebro-vascular accident

ED, emergency department

ERC, European Resuscitation Council

GP, general practitioner

GCS, Glasgow Coma Score

HACA, Hypothermia After cardiac Arrest

HF, hemofiltration

HR, hazard ratio

HRV, heart rate variability

ICU, intensive care unit

IHCA, in-hospital cardiac arrest

ILCOR, International Liaison Committee on Resuscitation

IQR, inter-quartile range

LR, likelihood ratio

MI, myocardial infarction

NNT, number needed to treat

NS, not statistically significant

OHCA, out of hospital cardiac arrest

OR, odds ratio

PCI, percutaneous coronary intervention

Q-EEG, quantitative electroencephalography

RCT, randomized controlled trial

ROSC, return of spontaneous circulation

RR, relative risk

RRS, rapid response systems

SD, standard deviation

SEP, somato-sensory evoked potential

TAAG, Technology Assessment Advisory Group (VHA Office of Patient Care Services)

TH, therapeutic hypothermia

TPA, rTPA, (recombinant) tissue plasminogen activator

VF/VT, ventricular fibrillation/tachycardia

QALY, quality-adjusted life year

BRIEF OVERVIEW: HYPOTHERMIA AFTER CARDIAC ARREST

INTRODUCTION

"Cardiac arrest is an important public health problem. The incidence of out-of-hospital cardiac arrest (OHCA) in North America is between 0.53 and 0.91 per 1000 population, and only about 8% of these patients survive. Therapeutic hypothermia involves cooling comatose patients to a temperature of 32-34°C for a period of 12-24h after they are successfully resuscitated from cardiac arrest. This therapy has been shown to improve survival in patients who have return of spontaneous circulation but remain comatose after OHCA. A meta-analysis using individual patient data (Holzer, 2005) from 3 studies demonstrated that the number needed to treat was only 6 patients to allow one additional person to survive to hospital discharge with good neurologic function. This study included patients with all cardiac arrest rhythms, but the vast majority (>91%) had ventricular fibrillation or pulseless ventricular tachycardia." (Bigham, 2010).

"Post-resuscitation care of comatose survivors of cardiac arrest using induced hypothermia (IH) is recommended by the American Heart Association (AHA) and the International Liaison Committee on Resuscitation (ILCOR) to improve neurological outcomes but it has been performed primarily later in the course of care. Recently, it has been shown that pre-hospital cooling is feasible, safe, and effective in lowering patient temperature." Suffoletto (2008).

"…barriers that clinicians face in order to implement therapeutic hypothermia promptly and efficiently…may fear complications and unforeseen side effects of this relatively new therapy. The lack of equipment for effective body cooling, lack of awareness…" Acosta (2008).

"Hypothermia is well known to provide neuroprotection following various brain insults in experimental animals. Two recently completed clinical trials of whole body hypothermia in out-of-hospital cardiac arrest patients demonstrated significantly improved survival rates and neurologic outcomes. These results provide new excitement and encouragement for clinical application of hypothermia in cerebrovascular disease. However, the intensive care challenges and adverse events (e.g. prolonged times to target temperatures, shivering and sedation, pneumonia) during the management of hypothermia, dampen enthusiasm for widespread application especially in elderly stroke patients…new technology, the ChillerPad™ and ChillerStrip™ Systems developed by Seacoast Technologies, Inc. (Portsmouth NH, USA). The latter device has received FDA approval…" Wagner (2005).

"Despite compelling data supporting it use, hypothermia has yet to be broadly incorporated into physician practice...Among reasons for non-use...were not enough data …lack of incorporation of hypothermia into advanced cardiovascular support (ACLS) protocols, ...and cooling methods were technically too difficult or too slow." Abella (2005).

"Sudden cardiac arrest is not uncommon as a complication of coronary heart disease (ischemic heart disease)…Most cases of cardiac arrest occur out of hospital…Treatment outcomes in this group have not improved substantially in the past 20 years. Only 4% of those affected are discharged alive from the hospital following resuscitation and treatment. The outcome of treatment depends partly on the time that has elapsed between cardiac arrest and the reestablishment of stable circulation. Most patients who are resuscitated from cardiac arrest are unconscious and require care at an intensive care unit. Lowering the body temperature (induced hypothermia) after resuscitation from cardiac arrest is a treatment method intended to limit the damage, mainly to the brain, that occurs when blood circulation ceases. Body temperature is lowered to 32-34

degrees, which usually requires sedation of the patient, administration of muscle relaxants, and the subsequent use of ventilator treatment…

"The potential target group for therapeutic hypothermia includes people who are unconscious after resuscitation from cardiac arrest and whose condition would suggest a risk for tissue damage due to oxygen deficiency. Most patients would be patients with coronary heart disease. Criteria have not been established for selecting patients for therapeutic hypothermia, so the size of the potential target group for this treatment method cannot be estimated..." SBU (2006).

BACKGROUND

VHA's TAAG asked TAP for a review of the literature as support for use of hypothermia after cardiac arrest, initially in 2008 and again in 2010. TAP approached its charge through available systematic reviews, guidelines or technology assessments based on such reviews, and economic evaluations using high quality primary studies or reviews as sources of effectiveness data. This document will refer collectively to these synthesis publication types as "reviews". We then updated review searches to the preset to confirm the presence or absence of subsequently review-eligible studies that would change review conclusions.

METHODS

Analytic framework: epidemiologic study cycle

The progression of epidemiologic studies, or the epidemiologic study cycle, confirming the existence and strength of an observed association between exposure and disease (or intervention and outcome) is both well-documented and the foundation for the systematic review framework outlined below (Ibrahim, 1985; Mausner and Kramer, 1985; Lilienfeld and Stolley, 1994; Muir Gray, 1997): it begins with observational, hypothesis-generating studies such as single case or case series reports, then on to cross-sectional (also known as survey, correlational, or ecological) studies, which ascertain exposure and disease at the same point in time, then progresses through analytic, hypothesis-testing studies (case-control or cohort, from which relative risk or estimates can be calculated), and culminates in the randomized controlled trial confirming causality.

Analytic framework: systematic reviews

Cook (1997) and Mulrow (1997) define systematic reviews: "*Systematic reviews are scientific investigations in themselves, with pre-planned methods and an assembly of original studies as their "subjects". They synthesize the results of multiple primary investigations by using strategies that limit bias and random error…"*

The same authors further specify characteristics of systematic reviews and contrast them with traditional narrative reviews: the latter synthesize articles without reporting methods of selection or quality assessment criteria and thus do not qualify as reproducible science.

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Systematic reviews:

- Ask a focused clinical question;
- Conduct a comprehensive search for relevant studies using an explicit search strategy;
- Uniformly apply criteria for inclusion and exclusion of studies;

- Rigorously and critically appraise included studies;
- Provide detailed analyses of the strengths and limitations of included studies.

Systematic reviews can be quantitative (i.e., meta-analytic, applying statistical methods to summarize study results) or qualitative; in either case the inferences or conclusions of the review must follow logically from the evidence presented. The rigor of this approach is illustrated by the place of systematic reviews in evidence grading schemes (Cook, 1995; Guyatt 1995), where they receive the highest level designation.

Analytic framework: registries in technology assessment
Large health care databases, data sets, or registries, while not necessarily intended for research use, can make useful contributions to technology assessment (Antczak-Bouckoms, 1991) and have numerous advantages over other information sources: non-intrusive data collection, large population coverage and sample size, low cost, easy long-term follow-up, and no reliance on individual recall (Blais, 1991). As observational studies, registry analyses equate to cross-sectional studies and provide only suggestive inference for causation.

Search strategy
TAP searched Medline via PubMed and Dialog, Embase, and Cochrane databases from 1990 to April, 2010. Search terms were: hypothermia, cardiac arrest, and resuscitation; all searches were restricted to adult human patients and English language publications. TAP also included search terms to identify existing reviews, economic analyses, and technology assessments, i.e., syntheses of the literature that would enhance TAP's ability to quickly meet the information needs of OPCS. Hand searching reference lists of articles initially retrieved allowed TAP to identify and retrieve additional full-text publications.

Finally, the databases of the International Network of Agencies for Health Technology Assessment (INAHTA; www.inahta.org) were searched, and an electronic query addressed to TAP's colleague INAHTA members requested information on completed or in-progress reviews and technology assessments. One reviewer (KF) read and abstracted all retrievals.

Included
- Systematic reviews;
- Technology assessments;
- Cost-effectiveness or-utility analyses;
- Other studies clearly based on systematic reviews were included;
- Subsequently published papers eligible for the reviews;
- Since implementation of hypothermia may be problematic (Holzer, 2005; Appendix Table 1), TAP include implementation studies reporting survival or neurologic outcomes.

Excluded
- Non-English language articles;
- Studies in pediatric populations or applications other than cardiac arrest;
- Pre-clinical studies;
- Single case reports;
- Case series;
- Narrative reviews and other publications lacking primary clinical data and/or explicit methods descriptions.
- Previous version or duplicate publications;
- Unintelligible reports;
- "Quasi-systematic" reviews, i.e., those indexed or titled as systematic but which on close examination do not meet criteria or are inadequately reported to judge; quasi systematic

reviews often attend to some details of truly systematic methods but miss their essential spirit of critical analysis;

- Primary studies included in available systematic reviews or assessments, except for core studies covered by both Arrich (2009) and Williams (2007), which are abstracted for reference in Appendix Table 1.

RESULTS

Appendix Table 1 abstracts available reviews; Table 2 abstracts subsequently published review-eligible primary studies not available to Table 1 reviewers. Table 3 abstracts before-and-after implementation studies. Table 4 lists in-progress studies, which provide a list of hypothermia issues in continuing need of resolution as discussed below. Table 5 (page 25) lists specific reasons for exclusion.

CONCLUSIONS AND DISCUSSION

The RCT and meta-analytic evidence supporting hypothermia for comatose survivors of resuscitation from ventricular fibrillation cardiac arrest is characterized by some writers as "compelling". Others (SBU, 2006; CEDIT, 2004; ANZHSN, 2005; all in Table 1) are more circumspect, citing heterogeneity among trials, relatively small numbers, technical or organizational impediments to wide implementation, and the need for continuing research.

While agreeing on the relatively small body of eligible research and need for more studies to close knowledge gaps, the most recent high-quality review [Arrich (Cochrane; 2009) in Appendix Table 1] finds available evidence consistent for positive effects of hypothermia on survival and neurologic outcome. In this context, we note the addition of hypothermia to complex interventions for improvement of resuscitation protocols (Appendix Table 4) and the corresponding difficulties of isolating its effects from those of other interventions.

Of particular note, studies covered here provide evidence that simple "low-tech" methods (cold IV fluids, blankets, ice packs) for inducing hypothermia are effective: Arrich (2009) pooled comparable studies using standard cooling, and the single inadequate-quality trial comparing outcomes with simple methods directly to one device (Heard, 2010; Appendix Table 2.) found no significant differences.

IMPLICATIONS FOR RESEARCH

Appendix Table 3 lists aspects of hypothermia still under active research:

- Patient selection;
- Optimal methods for inducing hypothermia.
- Longer-term effectiveness and cost-effectiveness.

As noted above, the numbers of patients enrolled in individual hypothermia trials (and aggregated for meta-analyses) remain small relative to other established therapies. For example, rTPA had been tested in close to 3000 patients within one decade of FDA approval for acute stroke (Hacke, 2004) versus less than 500 for hypothermia (Arrich, 2009; Table 1). Larger numbers allow sub-group analyses, detection of uncommon adverse events, and refinement of patient selection; these advantages are not yet possible for hypothermia in cardiac arrest. Finally, results from the most recent studies (Appendix Table 2) are neither completely consistent nor uniformly statistically significant.

Other unresolved research issues are listed above and in the Appendix tables: they include organizational and technical impediments to broad diffusion, familiar from similar issues for rTPA in stroke and critical to national-level implementation (e.g., TAP overview of acute stroke management, 2004). To borrow from acute stroke: we know that rTPA "works" for well-defined acute stroke patients, but it continues to be under-used due to organizational and institutional barriers, and the simple time constraints imposed by disease, making the HTA agencies assessing on behalf of national healthcare systems and in positions to contribute to research agendas more cautious than professional associations. Hypothermia "works" for VF/VT cardiac arrest, but issues still unresolved by definitive research give pause before national-level implementation.

APPENDIX

Table 1. Reviews, technology assessments, and policy recommendations

Reference	Purpose/details	Results/Comments
Core reviews: Cochrane and EPC		
Arrich (Cochrane; 2009);	Effectiveness of therapeutic hypothermia in patients after cardiac arrest: • Multiple databases, 1971-2007; • RCTs or quasi-RCTs assessing effectiveness (any method of cooling applied within 6 hrs of cardiac arrest) in adults; • Neurologic outcomes during hospital stay by CPC values or categories; • No language restrictions; • Meta-analysis with subgroup analyses from data (for cause and location of cardiac arrest and primary ECG rhythm); • Assessment of publication bias	**4 trials, 1 abstract (481 patients); 5 studies:** • 3/5 studies of good quality; • No studies reported long-term survival, dependency, QoL, or cost-effectiveness; • 3 comparable studies on conventional cooling methods (extracorporeal ice packs, water immersion; intravascular catheters or fluids) provided individual patient data on reviewers' request: hypothermia group more likely to reach best CPC values of 1 or 2 (5-point scale where 5 = brain death) during hospital stay (RR from individual patient data, 1.55; CI, 1.22-1.96); • Hypothermia group more likely to reach hospital discharge. (RR individual patient data, 1.35; CI, 1.22-1.96); • Ns differences in adverse events across all studies. **Conclusions:** *"Conventional cooling methods to induce mild hypothermia seem to improve survival and neurologic outcome after cardiac arrest. Despite the small number of included trials and patients, our review supports the current best practice as recommended by the International Resuscitation Guidelines."* **Implications for research:** *"Future research should be done with standardized temperature monitoring (esophageal or bladder) in order to be able to compare between groups and between studies at a later stage. Effective measures need to be advanced to cool the patient to the target temperature within a short period, which should decrease heterogeneity within the study population. For studies with a focus on out-of-hospital cooling, practical methods need to be evaluated. To further investigate the effect of cooling on subgroups, like patients with a non-VF/VT as primary cardiac rhythm, or patients with in-hospital cardiac arrest, methodologically sound studies are needed. There is a knowledge gap concerning an optimal cooling protocol…."*
Williams (EPC;2007)	Efficacy and safety of induced hypothermia: • Medline only, dates not reported; • RCTs, CCTs, retrospective studies in English; • Death or disability in adults post-cardiac arrest; • Quality assessment by modified Jaddad scale; • Cochrane software for meta-analysis (2 highest quality comparable studies).	**8 studies (578 patients):** • 4RCTs; 2CCTs (historical controls);2 retrospective series; • Pooled results of 2 comparable RCTs: all RRs favored hypothermia. **Conclusions:** *"The evidence demonstrates that induction of therapeutic hypothermia (32-33° C) after cardiac arrest is associated with a reduction in mortality and the poor outcome of death or disability. Most of the studies to evaluate the efficacy and safety of induced hypothermia post-cardiac arrest were conducted in unconscious patients with the return of spontaneous circulation. The initial cardiac rhythms of patients included in the trials were ventricular fibrillation/tachycardia (VF/VT) and asystole/pulseless electrical activity. The largest study (HACA, 2002) was a good quality RCT that demonstrated statistically significant reductions in mortality and the poor outcome of death or disability in patients post-cardiac arrest with initial VF/VT. A retrospective study also showed a statistically significant reduction in death or disability. All the other studies demonstrated improved outcomes although the results were not statistically significant."*

Reference	Purpose/details	Results/Comments
Reference studies included by Williams and Arrich (previous page)		
Holzer (2005); Cochrane review (as Mullner, 2003)	Systematic review with individual patient data meta-analysis; • Randomized and quasi-randomized trials; • Adults successfully resuscitated; • Hypothermia (any target temperature < 35 degrees C) applied within 6 hrs of arrival at ED and neurologic outcome compared; • Multiple databases, 1990-2002 • Excluded: studies without control groups or with historical controls • Trial authors supplied individual patient data.	3 RCTs; • More patients in hypothermia group were discharged with favorable neurologic recovery (RR, 1.68; CI, 1,29-2.97); • CI for NNT to allow one additional favorable outcome, 4-13; • One study followed patients to 6 months or death: being alive at 6 months with favorable neurologic recovery was more likely in hypothermia group (RR, 1.44; CI, 1.11-1.76). **Conclusions: "***Mild therapeutic hypothermia improves short-term neurologic recovery and survival in patients resuscitated from cardiac arrest of presumed cardiac origin. Its long-term effectiveness and feasibility at an organizational level need further research."*
Hypothermia after cardiac arrest study group (HACA; 2002)	Does mild systemic hypothermia increase the rate of neurologic recovery after resuscitation from cardiac arrest due to ventricular fibrillation?	Multi-center RCT (Europe and Australia) with blinded assessment of outcome: • Patients resuscitated after cardiac arrest due to ventricular fibrillation randomly assigned to • Therapeutic hypothermia by external cooling device (target temperature in the bladder, 32-34°C: (n = 136)); or to standard treatment with normothermia (n = 137); • 55% of hypothermia group had favorable neurologic recovery Vs. 39% of normothermia group (RR, 1.4; CI, 1.08-1.81); • Mortality at 6 months: 41% in hypothermia group Vs 55% in normothermia group (RR, 0.75; CI, 0.58-0.95); • Complication rate did not differ significantly between the groups. **Conclusions:** *"In patients who have been successfully resuscitated after cardiac arrest due to ventricular fibrillation, therapeutic mild hypothermia increased the rate of favorable neurologic outcome and reduced mortality."*
Bernard (2002)	Effects of hypothermia versus normothermia in patients who remained unconscious after resuscitation from out-or-hospital cardiac arrest	RCT conducted in Melbourne Australia, 1996-1999: • Patient selection: ventricular fibrillation on ambulance arrival; successful ROSC followed by persistent coma; transfer to one of four participating EDs; • Exclusions: age < 18 for males; age < 50 for females; cardiogenic shock (systolic BP<90mm Hg despite epinephrine); possible cause of coma other than cardiac arrest (drug overdose, head trauma, CVA); intensive care bed not available at a participating institution. • Patients randomized according to odd- or even-numbered day of month: suboptimal randomization process and adjustment for baseline differences between groups; • Patients assigned to hypothermia: begun by paramedics in the field by removing clothing plus cold packs to head and torso; • Following ED arrival: patients received routine assessment and treatment, including mechanical ventilation and correction of cardiovascular instability; • Patients ready for discharge were evaluated by specialist in rehab medicine blinded to treatment group. **Results:** 84 patients eligible for enrollment over 33 months; data on 7 patients excluded from analyses (transferred to

Reference	Purpose/details	Results/Comments
		nonparticipating ICU or refused consent); • 77 patients randomized (43 hypothermia, 34 normothermia); • 21 of 43 hypothermia patients (49%) survived with good outcome (discharged home or to rehab facility); Vs 9 of 34 normothermia patients (26%; P = 0.046); • After adjustment for baseline differences in age and time from collapse to ROSC: OR for good outcome with hypothermia vs normothermia, 5.25 (CI, 1.47-18.76; P = 0.011); • Hypothermia was associated with a lower cardiac index, higher systemic vascular resistance, and hyperglycemia; • There was no difference in the frequency of adverse events. **Conclusions:** *"Our preliminary observations suggest that treatment with hypothermia appears to improve outcomes in patients with coma after resuscitation from out-of-hospital cardiac arrest"*
Other relevant reviews		
Merchant (2009)	Model for cost-effectiveness: • Monte Carlo simulation with sensitivity analyses using outcomes from HACA (2002, above); • Patients with witnessed VF OHCA	**Model:** • Patients receiving hypothermia gained average 0.66 QALY Vs. conventional care, at incremental cost of $31,254; • Incremental cost-effectiveness ratio, $47,168/QALY; • Sensitivity analyses: poor neurological outcome post-cooling, costs of hospital/long-term care were most influential variables. **Conclusions:** *"In cardiac arrest survivors who meet HACA criteria, therapeutic hypothermia with a cooling blanket improves clinical outcomes with cost-effectiveness that is comparable to many economically acceptable health care interventions in the United States."*
Cheung (2006)	Systematic review: • Multiple databases, 1966-2005; • RCTs: adult patients with primary cardiac arrest who remained comatose after ROSC; randomized to mild induced hypothermia (32-34° C) or normothermia within 24 hrs of presentation and reporting discharge neurologic outcome, mortality, or significant treatment-related adverse effects; • No language/publication restrictions.	4 studies involving 436 patients (232 hypothermic) pooled: • Mild hypothermia decreased in-hospital mortality (RR, 0.75; CI, 0.62-0.92) and reduced poor neurologic outcome (RR, .74; CI, 0.62-0.84; NNT,7 to save one life, 5 to improve neurologic outcome); • No evidence of treatment-limiting side effects. **Conclusions:** *"Therapeutically induced mild hypothermia decreases in-hospital mortality and improves neurologic outcome in comatose cardiac arrest survivors. The possibility of treatment-limiting side effects cannot be excluded."*
SBU (2006)	• Early assessment of new health technology: Does treatment that lowers body temperature by 3-5 degrees after resuscitation from cardiac arrest increase the chance for	**2 RCTs:** • One high quality RCT found an association between hypothermia and improved outcome; • The other low quality RCT: intervention group patients could be discharged to a lower level of care than controls. **Ethical concerns:**

Reference	Purpose/details	Results/Comments
	survival or decrease the risk for permanent functional impairment? • Included: RCTs reporting survival and neurological function	• The method has not been adequately assessed; • It is unknown if benefits from resources devoted to this therapy can be appropriately weighted against alternate uses of the resources. **Economic concerns:** • During hypothermia the patient is placed on a ventilator and requires 1-2 extra days of intensive care; • Cost-effectiveness cannot be calculated since treatment effects are uncertain. **Conclusions:** *"The scientific evidence is insufficient to show that treatment with induced hypothermia after resuscitation from cardiac arrest improves survival or lowers the risk for permanent functional impairment. Although the scientific evidence is too weak to support reliable conclusions, the method appears to be promising and potentially may be of clinical importance. However, it is essential to continue testing this method in Sweden under scientifically acceptable conditions so that its benefits, risks, and cost effectiveness can be assessed. Until adequate scientific evidence is available, therapeutic hypothermia should be used only within the framework of well-designed, prospective, and controlled trials."*
ANZHSN (2005)	Horizon scanning prioritizing summary: methods not fully reported	• Received Therapeutic Goods Administration approval in 2005, but not yet available for purchase in Australia. • Studies (levels I-IV evidence) have demonstrated that moderate hypothermia appears to improve neurological outcomes in cardiac patients. • Mild hypothermia (level I evidence) induced by external cooling demonstrates favorable short term neurologic recovery and survival in comatose patients resuscitated from cardiac arrest. • ILOCR recognized value of hypothermia in the immediate treatment of comatose survivors of ventricular fibrillation cardiac arrest and recommended that hypothermia be induced in unconscious adults with spontaneous circulation who have experienced an out of hospital cardiac arrest: 32-34^0 C when initial rhythm is ventricular fibrillation. **2 feasibility and safety studies**: • 39 patients total; • 4 patients died; 2 cases of sepsis; 2 patients in persistent vegetative state;18 patients with good neurologic recovery. **Conclusions:** *"There is currently insufficient evidence to assess the effectiveness of hypothermia induction with CoolGard™.. However, there is recognition of the benefits of hypothermia for improving neurological outcomes."* **Recommendation:** *"In the absence of randomized studies assessing its safety and effectiveness and comparing it to external surface cooling, it is recommended that this technology be monitored."*
CEDIT (2004)	Rapid assessment procedure (preliminary investigation of effectiveness): CoolGard™ internal cooling device for acute myocardial infarction	• CoolGard 3000™ is the only device available in France: 7-8 units had been purchased or made available but were not used extensively. • Purpose: to induce hypothermia concurrently with coronary reperfusion; • From the little data available in the literature, the best use appears to be anterior wall infarction; • Central unit approx 30,000 Euros; single use consumable supplies, 890 Euros/patient. **Conclusions:** *"CEDIT cannot, based on the data already published, recommend the use of the CoolGard 3000™ internal*

Reference	Purpose/details	Results/Comments
		cooling system to induce hypothermia for the early treatment of myocardial infarction. It should be noted that this opinion does not concern the already recognized indication, i.e., cardiac arrest subsequent to ventricular fibrillation, for which a national assessment comparing internal cooling to external cooling is planned."
Winters (2007)	Impact of RRS (specialized teams of caregivers who identify and treat patients with early signs of clinical deterioration on general medical wards) on hospital mortality and cardiac arrest rates: • Multiple databases, 1990-2005; • English-language observational and randomized trials of RRS in adults.	8 relevant studies met inclusion criteria: 5 used historical controls; one, concurrent controls; and two used cluster-randomized designs: • Pooled (two randomized studies RR for hospital mortality, RRS vs controls, 0.76(CI, 0.39-1.48); five observational studies, 0.87(CI, 0.73-1.04); • RR for cardiac arrest, 0.94 (CI, 0.79-1.13) in single randomized study; and 0.70 (CI, 0.56-0.92) in four observational studies. **Conclusions:** *"We found weak evidence that rapid response systems are associated with a reduction in hospital mortality and cardiac arrest rates, but limitations in the quality of the original studies, the wide confidence intervals, and the presence of heterogeneity limited our ability to conclude that rapid response systems are effective interventions. Large randomized controlled trials are needed to clarify the efficacy of rapid response systems."*
Aung (2005)	To determine the effectiveness of vasopressin in treating cardiac arrest: • RCTs with human subjects and reporting morbidity /mortality outcomes, 1966-2004.	5 RCTs, 4 in English, 1 Chinese, enrolling 1519 patients: • 3 trials OHCA, 2 in-hospital; • 3 high quality, two low; • No statistically significant differences between vasopressin and epinephrine groups in failure of return of spontaneous circulation (RR, 0.81; CI, 0,85-1.12); death before hospital admission (RR, 0.72; CI, 0.38-1.39); death within 24 hrs (RR, 0.74; CI, 0.38-1.43); death before discharge (RR, 0.96; CI, 0.94-1.07); or combination of number of deaths and neurologically impaired survivors (RR, 1.00;CI, 0.94-1.07). • Subgroup analysis base on initial rhythm showed NS difference between vasopressin and epinephrine in any of 3 subgroups: ventricular fibrillation or ventricular tachycardia (RR, 0.97; CI, 0.79-1.19); pulseless electrical activity (RR, 1.02; CI, 0.95-1.10); or asystole (RR, 0.97; CI, 0.94-1.00) **Conclusions:** *"There is no clear advantage of vasopressin over epinephrine in the treatment of cardiac arrest. Guidelines for Advanced Cardiac Life Support should not recommend vasopressin in resuscitation protocols until more solid human data on its superiority are available."*
Booth (2004)	Role of clinical examination in predicting poor outcome in post-cardiac arrest coma: • Multiple databases, 1966-2003; • English-language studies assessing precision and accuracy of clinical exam for post-cardiac arrest coma in adults	11 studies involving 1914 patients: • 5 clinical signs strongly predict death or poor neurological outcome: absent corneal reflexes at 24 hrs (LR, 12.9; CI, 20.-68.7; absent papillary response at 24 hrs (LR, 10.2; CI, 1.8-48.6); absent withdrawal response to pain at 24 hrs (LR, 4.7; CI, 2.2-9.8); no motor response at 24 hrs (LR, 4.9; CI, 1.6-13.0); and no motor response at 72 hrs (LR, 9.2; CI, 2.1-49.4); • Random effects estimate of pretest probability of poor outcome was 77% (CI, 72%-80%); • Highest LR increases pretest probability of 77% to posttest probability of 97% (CI, 87%-100%); • No clinical finding had LRs that strongly predicted good neurological outcome. **Conclusions:** *"Simple physical examination maneuvers strongly predict death or poor outcome in comatose survivors of cardiac arrest. The most useful signs occur at 24 hours after cardiac arrest, and earlier prognosis should not be made by clinical examination alone. These data provide prognostic information, rather than treatment recommendations, which must be made on an individual basis incorporating many other variables."*

Reference	Purpose/details	Results/Comments
Law (2002)	Risk of death after MI in absence of treatment: • Medline, index Medicus; • Studies with FU completed by 1980 and reporting mortality by first or subsequent MI	**23 studies (14211 patients followed after MI):** • 13281 first MI: 3680 identified at time of first MI; • 23% died before reaching hospital; anther 13% during admission; both rates increasing with age.
Policy recommendations		
Nolan (2003)	Narrative review/advisory statement; methods incompletely reported	ILCOR recommendations: *"On the basis of published evidence to date..:* • *"Unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest should be cooled to 32^{0}C for 12 to 24 hours when the initial rhythm was ventricular fibrillation (VF).* • *"Such cooling may be beneficial for other rhythms or in-hospital cardiac arrest."*

Table 2. Subsequently published studies eligible for Table 1 reviews

Reference	Design/methods	Setting	Results/comments
Heard (2010)	Multi-center RCT: • "Arctic Sun" computer controlled high surface area device Vs blankets and ice packs; • Hemo-dynamically stable comatose survivors of OHCA; • Primary outcomes: time to target temperature and 3-month survival; • Randomization by centralized telephone system using fixed-block scheme 1:1 for all centers; • No blinding; • Sample size calculation not reported.	6 US academic medical centers	**64 patients:** • 30 standard cooling, 34 device; • Similar baseline characteristics; • 71% of device group reached target temperature< 4 hrs; 50% standard group; CI for difference, -3.4%-44.6%; NS); • Hypothermia maintenance terminated early for one patient/group: arrhythmia and hypotension (1), family request (1); • NS differences for survival or survival with good neurologic outcome. **Conclusions:** ***"****While the proportion of subjects reaching target temperature within 4h was not significantly different, the Arctic Sun cooled patients to a temperature of 34°C more rapidly than standard cooling blankets."*
Hinchey (2010)	Before-and-after case series: • 3 phase after baseline sequential implementation of 2005 AHA cardiac arrest guidelines: compression to ventilation ratio; avoidance of hyperventilation; minimally interrupted compressions; post-resuscitation hypothermia by cold packs.	Wake County, NC	**1365 patients:** • Similar demographics, clinical and EMS characteristics across all phases; • Overall and witnessed VF/VT survival improved throughout all phases; • Absolute survival increase baseline to full implementation,7.3% (CI, 3.7-10.9); witnessed VF/VT, 27.0% (13.6-40.4); • Additional 25 lives saved annually in population of 840,000. **Conclusions:** *"In the context of a community-wide focus on resuscitation, the sequential implementation of 2005 AHA guidelines for compressions, ventilations, and induced hypothermia significantly improved survival after cardiac arrest. Further study is required to clarify the relative contribution of each intervention to improved survival outcomes."*
Lund-Kordahl (2010)	Before-and-after case series:	Norwegian academic medical center	**1320 patients received ALS for OHCA:**

Reference	Design/methods	Setting	Results/comments
	• Sequential improvements (chest compressions, standardized post-resuscitation/rehab care, hypothermia) to guideline-driven processes), 1996-2005; • All OHCAs in Oslo during study periods.		• NS differences in patient demographics among 3 time period groups; • VF/VT arrests declined with time: (40% vs 33%; p= 0.039), fewer arrests were witnessed (80% vs 72%; p = 0.022), and response intervals increased (7±min Vs 9±4; p<0.001); • Overall survival increased: 7% vs 13%, p = 0.002; witnessed VF/VT arrest, 15% vs 35% (p = 0.001). **Conclusions:** *"Survival after OHCA was increased after improving weak links in our local Chain of Survival."*
Bro-Jeppesen (2009)	Case series: • Consecutive comatose adult survivors of OHCA, 2002-2006; • Before-and-after hypothermia by surface cooling implemented 6/04; • Selection: GCS <9; VF/VT; no contra-indications; • Other care according to European guidelines; • 6 month FU by interview	Danish academic medical center	**79 ICU admissions during intervention period; 77 control period:** • NS differences: demographics or comorbid conditions; • Non shock-able rhythms:27 intervention, 21 control; 6-month survival, 26%, 10%, respectively; • 66% VF/VT intervention, 73% control; • CPC significantly better during intervention period: at ICU discharge and at hospital discharge; • Good outcome (CPC 1 -2): intervention, 97%; control, 73%; p =.003; • Logistic regression adjusted for age sex, time to ROSC: treatment during intervention period significantly related to good outcome at hospital discharge: OR, 17; CI, 1.9-155; p = 0.01; • NS differences for survival of patents with VF/VT between periods; • Multivariate analyses for independent predictors of survival: hypothermia, HR 0.15 (CI, 0.04-0.59; p = 0.007); bystander CPR, HR, 0.19 (0.06-0.54; p = 0.0020) for survival during intervention period. **Conclusions:** *"CPC at discharge from hospital was significantly improved following implementation of hypothermia to comatose patients resuscitated from OHCA with VF/VT. However, significant improvement in survival, cognitive status or QoL could not be detected for long-term FU."*
Don (2009)	Case series: • Before-and-after hypothermia protocol (ice packs or blankets0 implementation: • Survival and neurologic outcomes in patients resuscitated from VF/BVT or asystole OHCA	Seattle	**491 patients:** • Of 72 who did not achieve target temperature, 40 (20%) died in ED or shortly after; • 7% of those without target temperature regained consciousness, 2% had contraindication, 6% had temperature increase or did not have hypothermia protocol; • Pro-hypothermia period: 287 patients; **Pre-post differences:** • Mean esophageal temperature (35.2°C vs 34.1); • Survival to discharge: with hypothermia OR 1.88; CI, 1.03-3.45; non VF/VT arrest (OR, 1.71; CI, 0.85-3.46); • Favorable neurologic outcome: OR, 2.62; CI, 1.2-6.27), but not observed in patients with asystole. **Conclusions:** *"The therapeutic hypothermia period was associated with a significant improvement in neurologic outcomes in patients whose initial rhythm was ventricular fibrillation, but not in patients with other rhythms."*

Reference	Design/methods	Setting	Results/comments
Nielson (2009)	Registry/cross-sectional: • OHCA patients admitted to ICUs for hypothermia, Oct 2004-Oct 2008; • 6-12 month outcomes	European Hypothermia Network: Sweden, Norway Luxembourg, Denmark, Iceland	**986 patients registered/ long-term outcomes for 975:** • Median time, arrest to hypothermia: 90 min (IQR, 160-165); • Time to target temperature: 260 min (178-400); • 50% received angiography, 33% PCI; • Predictors of poor outcome: low GCS at admission; unwitnessed arrest; asystole; • Time to initiate hypothermia NS; • 4% had bleeding requiring transfusion, risk significantly higher if angiography or PCI performed (2.8% vs 6.2%; P = 0.02). **Conclusions:** *"Half of the patients survived, with > 90% having good neurological function at long-term follow-up. Factors related to timing of TH had no apparent association to outcome. The incidence of bleeding was increased if angiography/PCI was performed."*
Schefold (2009)	Case series with historical controls: • Before-an-after hypothermia protocol implementation; • Survival, neurologic outcome, bleeding complications; • Comatose patients receiving TH and PCI after OHCA, Dec 2006-Dec 2006.	Germany	**31 hypothermia patients, 31 controls:** • Peak creatine kinase-MB in hypothermia group: 118U/L (94-248); controls, 131 (98-257); P = 0.51 • 19 hypothermia patients discharged with favorable neurological outcome; 6 controls (P= 0.002); • Hemoglobin values and platelet counts declined in both groups during first 49 hrs (all P< 0.001); • NS differences for bleeding complications or transfusion requirements. **Conclusions:** *"A major improvement in neurological outcome was observed with hypothermia. Our results indicate that the combination of reperfusion strategies and the application of hypothermia do not carry an excessive risk of bleeding complications."*
Tiainen (2009)	• Subset analysis of RCT (HACA, 2002; above); • Arrhythmias and rate variability during and after hypothermia; • Random assignment to hypothermia (external device) or normothermia after VF OHCA; • 6-month outcomes.	Finnish academic medical center	**75 patients randomized:** • Premature ventricular beats increased in hypothermia group early with no difference in VF/VT episodes; • HRV values significantly higher during hypothermia (P<0.01) by NS by two weeks; • Multivariate analyses: only shorter delay to ROSC and SD of individual normal-normal intervals > 100 msec. at 28-48 hrs predicted good outcome. **Conclusions:** *"The use of therapeutic hypothermia of 33°C for 24 hours after CA was not associated with an increase in clinically significant arrhythmias. Preserved 24 to 48-hr HRV may be a predictor of favorable outcome in patients with CA treated with HT."*
Storm (2008)	Case series with historical controls:	Academic medical center, Germany	**52 hypothermia patients; 74 historical controls:** • NS demographic, initial rhythm or epinephrine dose differences;

Reference	Design/methods	Setting	Results/comments
	• 2006-7 admissions to ICU after OHCA; • Hypothermia by ILCOR guidelines: saline plus surface cooling to 33°C with prn midazolam and pancuronium; • Regression and Kaplan-Meier analyses for survival, APACHE, CPC, ICU stay, time on ventilator.		• APACHE score significantly lower in controls; • NS ICU stay difference for all alive or dead patients; among survivors, ICU stay significantly lower in hypothermia group [median 14 days (IQR 8-26) Vs 21 (IQR 15-30; p = 0.017)]; • NS difference in ICU stay for patients who died there: median 9 days (IQR 6-22) Vs 7 (5-10); • ICU stay and time on ventilator prolonged in CPC 3 or 4 Vs 1 or 2 (P= 0.003). • Better probability of one-yr survival in hypothermia group (P = 0.013). **Conclusions:** *"Patients treated with therapeutic hypothermia showed both an impressive improvement in neurological outcome and 1-year survival. Hypothermia did not prolong ICU stay or time on ventilation; rather these parameters were reduced. Although we did not directly calculate the ICU treatment costs, we believe that this could be an additional argument for the application of hypothermia in patients after cardiac arrest."*
Arrich (2007)	Registry analysis	ERC: 19 sites within Europe	Data on 650 patients entered in registry, March 2003-June 2005: • Cardiac arrest with successful ROSC; • 462(79%) received therapeutic hypothermia: 347(59%) cooled with an endovascular device; 114(19%) with other methods(ice packets, cooling blankets, cold fluids); • Median cooling rate, 1.1^{0}C.hr; • Of all hypothermia patients, 15 (3%) had episode of hemorrhage, 28 (6%) had at least one episode of arrhythmia within 7 days after cooling; • There were no fatalities as a result of cooling. **Conclusions:** *"Therapeutic hypothermia is feasible and can be used safely and effectively outside a randomized clinical trial. The rate of adverse events was lower and the cooling rate was faster than in clinical trials published"*

Table 3. Implementation studies

Reference	Design/purpose/details	Results/Comments
Before-and-after		
Hinchey (2010)	See Table 2	
Lund-Kordahl (2010)	Effectiveness of therapeutic hypothermia in patients after cardiac arrest: • multiple databases, 1971-2007; • RCTs or quasi-RCTs assessing effectiveness (any method of cooling applied within 6 hrs of cardiac arrest) in adults; • Neurologic outcomes during hospital stay by CPC values or categories; • No language restrictions; • Meta-analysis with subgroup analyses from data (for cause and location of cardiac arrest and primary ECG rhythm); • Assessment of publication bias.	**4 trials, 1 abstract (481 patients); 5 studies:** • 3/5 studies of good quality; • No studies reported long-term survival, dependency, QoL, or cost-effectiveness; • 3 comparable studies on conventional cooling methods (extracorporeal ice packs, water immersion; intravascular catheters or fluids) provided individual patient data on reviewers' request: hypothermia group more likely to reach best CPC values of 1 or 2 (5-point scale where 5 = brain death) during hospital stay (RR from individual patient data, 1.55; CI, 1.22-1.96); • Hypothermia group more likely to reach hospital discharge. (RR individual patient data, 1.35; CI, 1.22-1.96); • Ns differences in adverse events across all studies. **Conclusions:** *"Conventional cooling methods to induce mild hypothermia seem to improve survival and neurologic outcome after cardiac arrest. Despite the small number of included trials and patients, our review supports the current best practice as recommended by the International Resuscitation Guidelines."* **Implications for research:** *"Future research should be done with standardized temperature monitoring (esophageal or bladder) in order to be able to compare between groups and between studies at a later stage. Effective measures need to be advanced to cool the patient to the target temperature within a short period, which should decrease heterogeneity within the study population. For studies with a focus on out-of-hospital cooling, practical methods need to be evaluated. To further investigate the effect of cooling on subgroups, like patients with a non-VF/VT as primary cardiac rhythm, or patients with in-hospital cardiac arrest, methodologically sound studies are needed. There is a knowledge gap concerning an optimal cooling protocol…."*
Bro-Jeppesen (2009)	See Table 2	
Don (2009)	See Table 2	
Rittenberger (2008)	US academic medical center, 2005-2007: • Linked process interventions to increase hypothermia use: "kit" with order sheet and simple hypothermia equipment (saline, cooling blankets); feedback to individual clinicians; on-call consultants; education for ED and ICU staff and trainees; • Indications for hypothermia: receiving defibrillation of chest compressions for pulseless arrhythmia; intubated; inability to	**241/394 patients met inclusion criteria:** • 135 OHCA (significantly fewer VF/VT arrests in 2006 (30%) than in 2005(55%) or 2007 (49%);106 IHCA (NS differences); • Use of hypothermia and cardiac catheterization significantly increased with time for OHCA but implantable device placement did not; NS for IHCA group; • Good outcomes: OHCA, 21%; IHCA, 8%; • Patients with OHCA and ventricular dysrhythmia more likely to experience good outcome with hypothermia than without it (57% vs 8%; p = .005). **Conclusions:** *"A series of system enhancements improved neurologic outcomes after cardiac arrest in a large, academic tertiary care facility despite a large number of critical care settings. These enhancements were also associated with an increase in the use of hypothermia and cardiac catheterization for OHCA patients and increased use of hypothermia in IHCA. Optimal care for cardiac arrest patients required a multidisciplinary effort that included hospital administrators and clinicians in*

Reference	Design/purpose/details	Results/Comments
	follow verbal commands; • Contraindications: active bleeding intracranial hemorrhage, early withdrawal of care/comfort measures only; traumatic injury; planned surgery; first GCS obscured by sedative or paralytic agent.	*emergency medicine, cardiology, critical care, and rehabilitation."*
Storm (2008)	See Table 2	
Policy statement		
Nolan (2003)	Narrative review/advisory statement; methods incompletely reported	ILCOR recommendations: *"On the basis of published evidence to date..:* • *"Unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest should be cooled to 32^{0}C for 12 to 24 hours when the initial rhythm was ventricular fibrillation (VF).* • *"Such cooling may be beneficial for other rhythms or in-hospital cardiac arrest."*

Table 4. Ongoing studies of hypothermia for cardiac arrest Listed by NIH at www.clinicaltrials.gov (accessed 4/15/10)

Not listed: completed, withdrawn, not yet recruiting, or pediatric trials

Purpose/phase or design	Location	Projected completion (if noted)
Remifentanil and propanolol Vs fentanyl and midazolam during hypothermia/RCT	Norway	Dec 2009
6 month FU for neurologic outcome: hypothermia after ROSC/csase-control	Germany	June 2010
Pre-hospital cooling/case-control	Czech Republic	Aug 2009
Hypothermia after cardiac arrest/cohort	US	Dec 2010
Mild hypothermia following OHCA/RCT	Seattle	Nov 2011
Hypothermia after cardiac arrest/registry	Japan	March 2010
Hypothermia (internal and external) Vs standard ICU management	Singapore	Sept 2010
Intra-arrest (before ROSC) hypothermia/RCT	Grenoble	Feb 2011
Safety and feasibility of endovascular cooling device	Taiwan	
LRS ThermoSuit™ system (IV magnesium sulfate)	Vienna	
LRS ThermoSuit™ system (IV magnesium sulfate)	Canada	
Vigileo (pulse-contour analysis Vs Vigilance (continuous cardiac output devices); observational	Switzerland	
Mortality and neurologic outcomes after in-hospital cardiac arrest; RTC	Germany	April 2010
Hypothermia as soon as possible in the field by rapid saline infusion	US	November 2011
Clinical and economic RTC: external Vs internal cooling	France	November 2009

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Table 5. Excluded studies

See Methods section (pages 2-4) for full inclusion and exclusion criteria

Citation	Reason for exclusion
Bigham, 2010a	Utilization survey: no clinical outcomes
Binks (2010)	
Rossetti (2010)	Validation of predictive factors not outcomes of hypothermia
Toma (2010)	Interview study: no clinical outcomes
Bernard 920090	Natrrative review
Bianchin (2009)	Utilization survey: no clinical outcomes
Garza (2009)	Intervention did not include hypothermia
Friberg (2009)	Narrative review
Janata (2009)	
Kämäräinen (2009)	Efficiency of cooling, not clinical outcome
Koreny (2009)	Intermediate/non-neurologic outcome for non-cardiac application
Sagalyn (2009)	Quasi-systematic
Søreide (2009)	Narrative review
Spaite (2009)	Interventions not analyzed
Brooks (2008)	Narrative review
Bergman (2008)	Single case
Majersik (2008)	Not based on systematic review
Nichol (2008)	Interventions not analyzed
Polderman (2008)	Patho-physiology not clinical outcomes
Pourzitaki (2008)	Quasi-systematic
Uray (2008)	Single-arm "feasibility trial" (case series of 15) without neurologic outcomes.
Kim (2007)	• "Pilot RCT"; • Neurologic outcomes not reported.
Tiainen (2007)	Covered by Arrich (2009)
Müllner (2003)	duplicate Arrich (2009)

TECHNOLOGY ASSESSMENT PROGRAM

Mission Statement

To enhance the health of veterans and the nation by providing and fostering technology assessment for evidence-based health care

Values

Integrity and pride in the work that we do

Quality products that are clinically valid and methodologically transparent

Objectivity in evaluating and presenting research evidence

Commitment to continuous quality improvement and to the guiding principles of evidence based practices

Flexibility in responding to changes in VA and the larger healthcare environment

Innovation in designing products and their dissemination to best meet VA's needs

Accessibility of products and services