WORKSHEET to accompany PROPOSED ARC Evidence-Based GUIDELINES

Worksheet Author: James Tibballs	**ARC Subcommittee:** Basic
Guideline(s) applicable (e.g. 4.3.5):9.4.2	**Date submitted to council: 20/3/2014**

Clinical Question: In a victim envenomated by a Red-back spider (P), does the use of antivenom given either intramuscularly or intravenously (I) compared with no antivenom (C) provide analgesia (O)

Step 1: Gather the evidence

Define your search strategy.
(e.g. ((cardiopulmonary-resuscitation*:me or heart-arrest*:me) not (atrial-fibrillation:me of electrophysiology:me)) and hypothermia:ab))

("spider bites"[MeSH Terms] OR ("spider"[All Fields] AND "bites"[All Fields]) OR "spider bites"[All Fields] OR ("spider"[All Fields] AND "bite"[All Fields]) OR "spider bite"[All Fields]) AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields]) AND ("humans"[MeSH Terms] OR "humans"[All Fields] OR "human"[All Fields])

List electronic databases searched (at least MEDLINE (http://igm.nlm.nih.gov/) Embase, Cochrane database for systematic reviews and Central Register of Controlled Trials (http://www.cochrane.org.au/), and hand searches of journals, review articles, and books.
PubMed, Medline, Cochrane, Embase, Books

• Describe search results; describe best sources for evidence.
Pubmed: 619 articles
Medline-Ovid (1946-week 1 Mar 2014): 341 articles
Embase-Ovid (174-present[Mar 2014]): 133 articles
Cochrane Database: (Mar 2014): 6 articles
Australian Animal Toxins 2001

••State major criteria you used to limit your search; state inclusion or exclusion criteria (e.g., only human studies with control group? no animal studies? N subjects
   > minimal number? type of methodology? peer-reviewed manuscripts only? no abstract-only studies?)
Only human studies,

Number of articles/sources meeting criteria for further review:
Four studies of ttreatment of Lactrodectus envenomation with antivenom either intramuscularly or intravenously or treatment with placebo control (Dart 2013; Isbister 2008a; Isbister 2008b; Ellis 2005).

Create a citation marker for each study (use the author initials and date or Arabic numeral, e.g., "Elam 1958"). . If possible, please supply file of best references; End Note 4+ preferred as reference manager, though other reference databases acceptable.

Step 2: Determine the Level of Evidence for each study.
For each article/source from step 1, assign a level of evidence—based on study design and methodology.

Level of Evidence	Definitions (See manuscript for full details)	Articles found (Use citation marker: e.g. Elam 1958)
Level I	Evidence obtained from a systematic review of all relevant randomised controlled trials	
Level II	Evidence obtained from at least one properly designed randomised controlled trial	Dart 2013, Ellis 2005; Isbister 20088a ; Isbister 2008b,
Level III-1	Evidence obtained from well designed properly pseudo-randomised controlled trials (alternate allocation or other method)	
Level III-2	Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case control studies, or interrupted time series with a control group	
Level III-3	Evidence obtained from comparative studies with	

	historical control, two or more single arm studies, or interrupted time series without a parallel control group	
Level IV	Evidence obtained from case series, either post-test or pre-test and post-test	
Other	Please specify (e.g. animal, manikin)	

Step 2B: Critically assess each article/source in terms of research design and methods.

Was the study well executed? Suggested criteria appear in the table below. Assess design and methods and provide an overall rating. Ratings apply within each Level; a Level I study can be good or poor as a clinical trial, just as a Level II study could be good or poor. Where applicable, please append a code (A to E, as shown below) to categorize the primary endpoint of each study.

Component of Study and Rating	Good	Fair	Poor
Methodology	The methodological quality of the study is high with the likelihood of any significant bias being minimal	The methodological quality of the study is reasonable with the potential for significant bias being likely.	The methodological quality of the study is weak possessing considerable and significant biases.
Articles (use citation marker and code for outcome applicable: e.g. Elam 1998 D)	Dart 2013E, Isbister 2008aE, Isbister 2008bE	Ellis 2005	

A = Return of spontaneous circulation　　　C = Survival to hospital discharge　　　E = Other endpoint
B = Survival of event　　　D = Intact neurological survival

STEP 3. DETERMINE THE CLASS OF RECOMMENDATION. Select from these summary definitions.

CLASS	DEFINITION
Class A *Recommended*	Class A treatment recommendations are given to those guidelines which are considered to be beneficial and should be used
Class B: *Acceptable*	Class B treatment recommendations are given to those guidelines which may be beneficial and are acceptable to be used if considered appropriate in that setting

State a **Class of Recommendation** for the Guideline Proposal. State either **a) the intervention**, and then the conditions under which the intervention is either Class A or Class B; or **b) the condition,** and then whether the intervention is Class A or Class B

Guideline or intervention (Class of recommendation):

For pain relief after Red-back spider envenomation, antivenom should be given either intramuscularly or intravenously (Class A).

REVIEWER'S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK: Summarize your final evidence integration and the rationale for the class of recommendation. Consider the frequency of adverse events and the possibility of harm? Describe any value or utility judgments you may have made, separate from the evidence. For example, you believe evidence-supported interventions should be limited to in-hospital use because you think proper use is too difficult for pre-hospital providers. Please include relevant key figures or tables to support your assessment

Spiders of the genus *Lactrodectus* include but are not limited to a species in Australia (*hasselti*), new Zealand (*katipo*) and several in the United States including *mactans*. All species cause a similar envenomation syndrome ('Latrodectism') and are considered to have a similar toxin(s) in their venoms. Antivenom treatment in countries other than Australia has therefore also been considered. Untreated, the envenomation syndrome (including principally pain, hypertension, sweating, arthralgia and paraesthesia) may be prolonged. Before availability of an antivenom, envenomation caused a number of deaths by respiratory failure in Australian human victims but the present concern is whether or not antivenom effectively relieves of pain. Antivenoms are equine derivatives and carry a risk of adverse reactions but the incidence is small (approximately 0.5%) and not severe. No deaths from treatment have

been recorded in Australia but one death has occurred in United States. Antivenom should be administered in locations staffed and equipped to treat anaphylaxis.

Dart 2013
A randomized, double-blind, placebo-controlled trial of a highly purified equine F(ab)2 antibody black widow spider antivenom.
Dart RC. Bogdan G. Heard K. Bucher Bartelson B. Garcia-Ubbelohde W. Bush S. Arnold T. Clark RC. Hendey GW. Holstege C. Spradley EA. Annals of Emergency Medicine. 61(4):458-67, 2013 Apr.

AB STUDY OBJECTIVE: Black widow spider antivenom has never been tested in a randomized clinical trial, to our knowledge. We explore various efficacy measures for a novel F(ab)2 antivenom in patients with moderate to severe pain caused by black widow spider envenomation. METHODS: A randomized, placebo-controlled, double-blind, clinical trial was conducted in 12 academic emergency departments. We included patients at least 10 years old with moderate to severe latrodectism. Subjects received either a single intravenous infusion of antivenom or placebo. Pain was assessed with the visual analog scale. The primary efficacy outcome was the difference in pre- and posttreatment visual analog scale score. Prospectively defined secondary outcomes included treatment failures and time to clinically important decrease in pain. RESULTS: Twenty-four subjects were enrolled between October 2005 and October 2006; 13 were randomized to antivenom and 11 to placebo. The median change in visual analog scale at 150 minutes posttreatment was -50.0 mm (Interquartile Range [IQR] -67, -41 mm) in the antivenom treatment group and -46.0 mm (IQR -51, 0 mm) in the placebo treatment group (P=.14). There were 7 treatment failures (64%; 95% confidence interval 35% to 92%) in the placebo group and 3 (23%; 95% confidence interval 0.2% to 46%) in the antivenom group (P=.06). The median time to a clinically important decrease in pain after treatment was shorter in the antivenom group compared with the placebo group (30 minutes [IQR 30, 60 minutes] versus 90 minutes [IQR 30, 90 minutes]; P=.03). No serious adverse events or deaths were reported. CONCLUSION: Although the overall reduction in pain was similar for antivenom- and placebo-treated subjects, antivenom reduced pain more rapidly than placebo. No significant adverse events occurred in either group.

Ellis 2005
A double-blind, randomized trial of intravenous versus intramuscular antivenom for red-back spider envenoming.
Ellis RM. Sprivulis PC. Jelinek GA. Banham ND. Wood SV. Wilkes GJ. Siegmund A. Roberts BL.
Emergency Medicine Australasia. 17(2):152-6, 2005 Apr.

AB OBJECTIVE: To compare the efficacy of intravenous versus intramuscular antivenom (AV) in the treatment of Red-back spider (RBS) envenoming. METHODS: Randomized, double-dummy, double-blind, multicentre trial of patients with red-back spider envenoming requiring AV treatment recruited from five hospital EDs in Western Australia. RESULTS: Thirty-five patients were recruited; two were excluded; 33 were available for initial analysis, but two who were unblinded after one ampoule of trial AV and given i.v. AV had limited data; 31 remained in the study and had more complete data. After AV, pain scores for both i.m. and i.v. groups improved rapidly. At 24 h, the i.v. group was better with a 55% absolute difference (76% vs. 21%; 95% CI 25-85% difference) in the proportion pain-free. There were no safety issues. CONCLUSIONS: Red-back spider antivenom was initially effective by both i.m. and i.v. routes. The study generates the hypothesis that at 24 h, significantly more patients are pain-free with i.v. administration. Definitive recommendations on the optimal route of administration of RBS AV await the results of further studies.

Isbister 2008a
A randomised controlled trial of intramuscular vs. intravenous antivenom for latrodectism--the RAVE study.
Isbister GK. Brown SG. Miller M. Tankel A. Macdonald E. Stokes B. Ellis R. Nagree Y. Wilkes GJ. James R. Short A. Holdgate A.
Qjm. 101(7):557-65, 2008 Jul.

AB BACKGROUND: Widow spider-bite causes latrodectism and is associated with significant morbidity worldwide. Antivenom is given by both the intravenous (IV) and intramuscular (IM) routes and it is unclear which is more effective. AIM: To compare the effectiveness of IV vs. IM redback spider antivenom. DESIGN: Randomized controlled trial. METHODS: Patients with latrodectism were given either IV or IM antivenom according to a randomized double-dummy, double-blind protocol. The first antivenom treatment was followed by another identical treatment after two hours if required. The primary outcome was a clinically significant reduction in pain two hours after the last treatment. A fully Bayesian analysis was used to estimate the probability of the desired treatment effect, predetermined as an absolute difference of 20%. RESULTS: We randomly allocated 126 patients to receive antivenom IV (64) and IM (62). After antivenom treatment pain improved in 40/64(62%) in the IV group vs. 33/62(53%) in the IM group (+9%; 95% Credible Interval [CrI]: -8% to +26%). The probability of a difference greater than zero (IV superior) was 85% but the probability of a difference >20% was only 10%. In 55 patients with systemic effects, these improved in 58% after IV antivenom vs. 65% after IM antivenom (-8%; 95% CrI: -32% to +17%). Twenty-four hours after antivenom pain had improved in 84% in the IV group vs. 71% in the IM group (+13%; 95% CrI: -2% to +27%). A meta-analysis including data from a previous trial found no difference in the primary outcome between IV and IM administration. DISCUSSION: The difference between IV and IM routes of administration of widow spider antivenom is, at best, small and does not justify routinely choosing one route over the other. Furthermore, antivenom may provide no benefit over placebo.

Isbister 2008b
A comparison of serum antivenom concentrations after intravenous and intramuscular administration of redback (widow) spider antivenom.
Isbister GK. O'Leary M. Miller M. Brown SG. Ramasamy S. James R. Schneider JS.
British Journal of Clinical Pharmacology. 65(1):139-43, 2008 Jan.

AB AIMS: There are no studies measuring antivenom concentrations following intramuscular administration. This study aimed to compare antivenom concentrations following intravenous and intramuscular administration of redback spider antivenom (RBSAV). METHODS: Twenty patients recruited to a controlled trial comparing intramuscular and intravenous administration of antivenom had serial blood samples collected at 30 min intervals for 2 h after the administration of one or two doses of antivenom. Antivenom concentration was measured using an enzyme immunoassay. RESULTS: Ten patients received intramuscular antivenom but antivenom could not be detected in serum after either one or two vials, at any time point. The median time of the final sample after commencement of antivenom treatment in these patients was 3.2 h (1.8-5 h). Ten patients received intravenous antivenom (three one vial and seven two or more vials) and antivenom was detected in all patients. CONCLUSIONS: RBS AV given by the intramuscular route is unlikely to be effective in the treatment of redback (widow) spider bite.

Please submit completed document with the following attachments:
- Printed (paper) bibliography; and electronic version using a reference manager (eg. Endnote) if available. It is recommended that the bibliography be printed in annotated format. This will include the article abstract and any notes you would like to make providing specific comments on the quality, methodology and/or conclusions of the study, and/or reasons for exclusion.
- Key figures or tables from evidence-based analysis
- Full hard copies of the critical cited papers