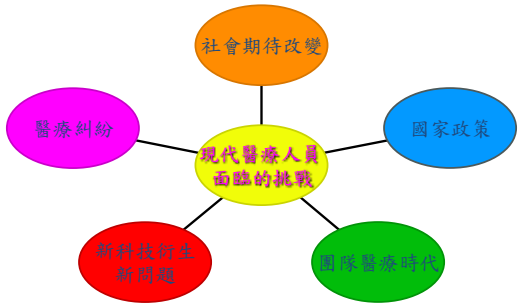
EBM: acupuncture for Herpes zoster neuralgia

R2 蔡孟言
指導醫師：陳星諭 醫師



EBM (Evidence-based Medicine)

- **實證醫學**

→從龐大的醫學資料庫中**搜尋**相關文獻

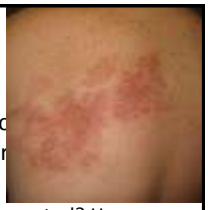
→以流行病學及統計學方法**過濾**出值得信賴的文獻

→再經過嚴格**評讀**及綜合分析後

→將獲取之最佳研究證據 (evidence) 、臨床經驗 (experience) 及患者期望 (expectation) 相互**整合**

→**配合**診療情境後制定出一套最佳的臨床醫療決策，並可用來協助醫護人員進行終身學習。

Scenario



- 60 y/o female, suffered from lo for 3 days, went to Acupunctur for help
  - Is acupuncture effective for pain control? How about the efficacy when compared with standard western medicine treatment?
  - Could it used for prevention?
  - How about the cost?

Herpes zoster

- The presenting clinical manifestations of herpes zoster are usually characterized by rash and acute neuritis.
- The thoracic and lumbar dermatomes are the most commonly involved sites of herpes zoster.
- Recurrence of clinical zoster in the immunocompetent host is rare, but does occur in the immunosuppressed host.
- The most common complication of herpes zoster is postherpetic neuralgia. Other complications include herpes zoster ophthalmicus or oticus, acute retinal necrosis, aseptic meningitis, and encephalitis.

Herpes zoster

- Immunocompromised hosts are at risk for cutaneous and visceral dissemination.
- The diagnosis is usually made clinically; available diagnostic techniques include viral culture, direct fluorescent antibody testing, and the polymerase chain reaction assay.
- The principle other main infectious agent to consider in the differential diagnosis of vesicular lesions is herpes simplex.

Postherpetic neuralgia

- Tricyclic antidepressants
- Anticonvulsants
- Opioids
- Capsaicin
- Botulinum toxin
- Intrathecal glucocorticoids
- Topical lidocaine
- NMDA receptor antagonists
- Cryotherapy
- Surgery
- Other

執行實證醫學五大步驟

- 提出問題(Ask: PICO)
  - Formulate an answerable question
- 搜尋證據(Acquire)
  - Track down the best evidence
- 嚴格評讀(Appraisal: VIP)
  - Critically appraise the evidence
- 恰當應用(Apply: 3E)
  - Integrate with clinical expertise and patient values
- 評估結果(Audit)
  - Monitoring your performance

Step 1: Asking

提問

Therapy/Prevention 治療/預防的問題	研究治療或預防方法的有效性
Diagnosis 診斷問題	研究檢查方法或臨床表徵對疾病診斷的有效性
Harm/Etiology 危害/病因問題	研究暴露的危害或疾病的原因
Prognosis 預後	建立疾病預後的預測模式

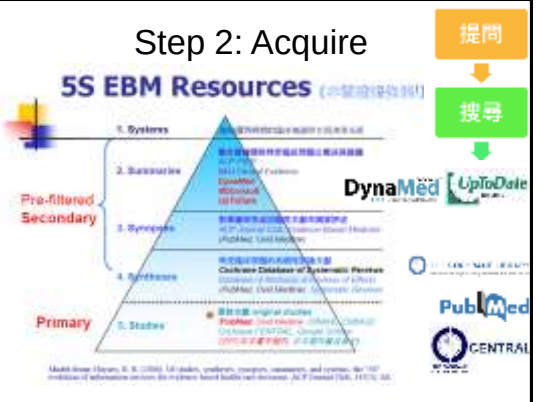
Step 1: Asking

提問

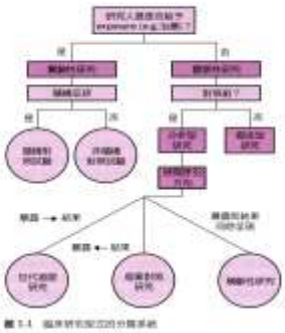
Problem 病人問題	Postherpetic neuralgia
Intervention 介入處置	Acupuncture
Comparison 對照的處置	Standard pharmacological treatment (ST)
Outcome 臨床結果	VAS score, recurrent rate

Step 2.
尋找文獻證據

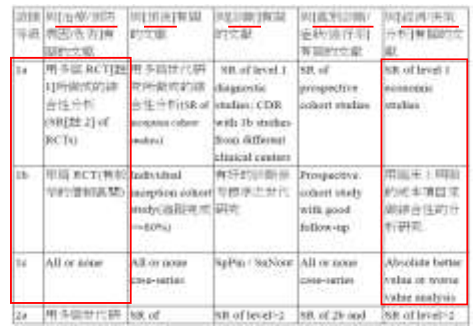
Step 2: Acquire



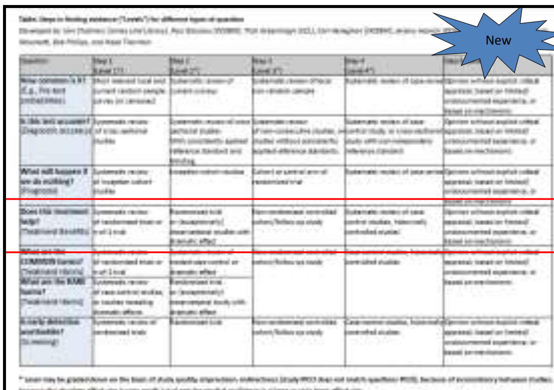
研究設計分類
(A taxonomy of clinical research)



證據等級
Oxford Centre for Evidence-based Medicine Levels of Evidence (March 2009)
http://www.cebm.net/index.aspx?o=1025



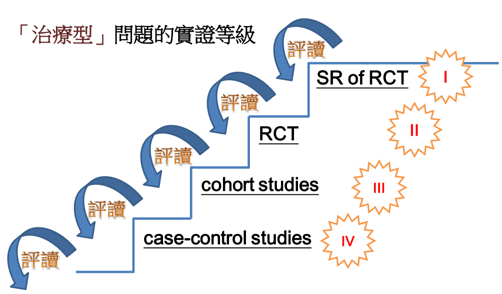
證據等級(續)



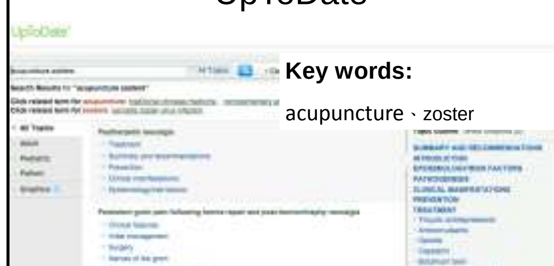
http://www.cebm.net/index.aspx?o=5653 *10 June 2010*

Search Strategy

- 「治療型」問題的實證等級



UpToDate



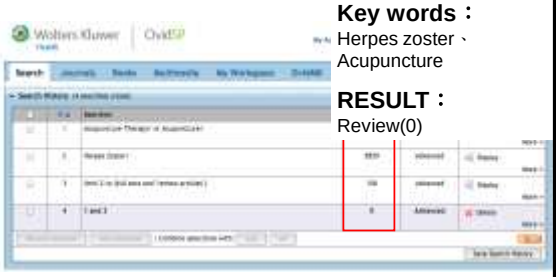
Other — The effectiveness of therapies such as TENS and acupuncture has not been proven.

DynaMed

Key words：

Acupuncture、zoster

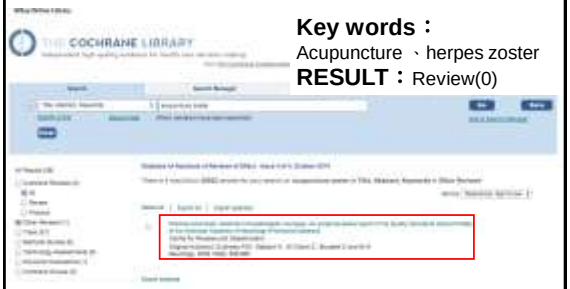
EBM ALL



Key words：
Herpes zoster、Acupuncture

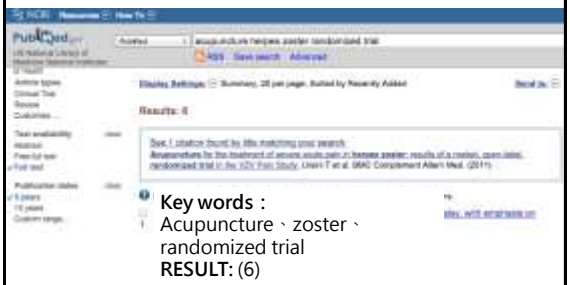
RESULT：
Review(0)

EBM ALL



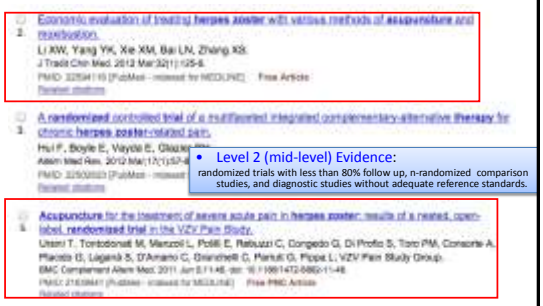
Key words：
Acupuncture 、herpes zoster
RESULT： Review(0)

Pubmed



Key words：
Acupuncture、zoster、randomized trial
RESULT: (6)

Pubmed

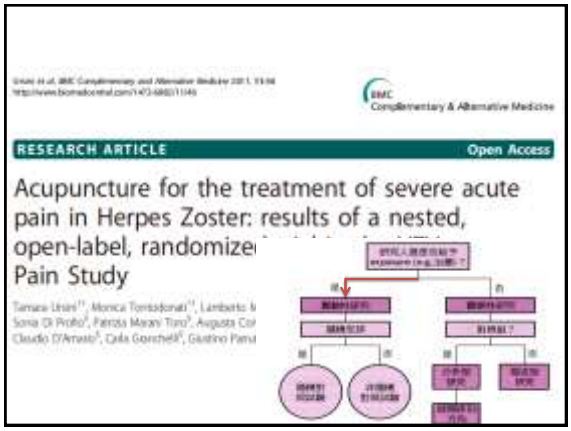


- Level 2 (mid-level) Evidence:
  randomized trials with less than 80% follow up, n-randomized comparison studies, and diagnostic studies without adequate reference standards.

Step 3.
嚴格評讀文獻

（1）Acupuncture for the treatment of severe acute pain in Herpes Zoster: **results of a nested, open-label, randomized trial in the VZV Pain Study**

（2）**Economic Evaluation** of Treating Herpes Zoster with Various Methods of Acupuncture and Moxibustion



Step 3: Appraisal

- Critical appraisal sheet of CEBM, university of Oxford
  - Are the results of the review valid?

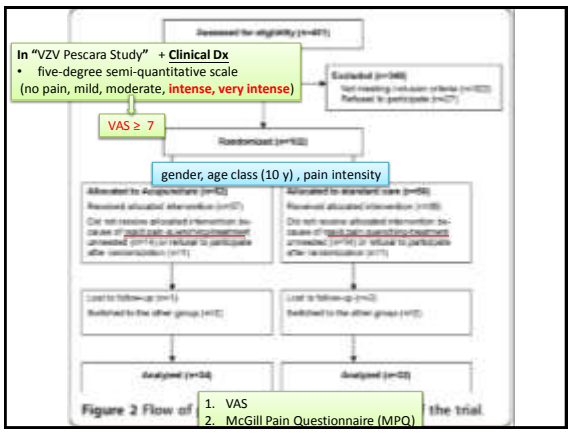
- 單一原始研究證據(RCT)之評讀
- **papers appraised**：Critical appraisal sheet of CEBM, university of Oxford
- Level of Evidence：【?】

一、此文獻之研究目的（purpose）

- ***What question did the study ask?***
- Data on the potential efficacy of acupuncture (AC) **[Intervention]** in controlling intense or very intense pain in patients with Herpes Zoster (HZ) **[Patients]** has not been so far adequately assessed in comparison with standard pharmacological treatment (ST) **[Comparison]** by a controlled trial design.

➔**Outcome(s): ?**

二、此文獻之研究設計（THE STUDY DESIGN）



Randomize…

None of the investigators had any role in the allocation of patients.

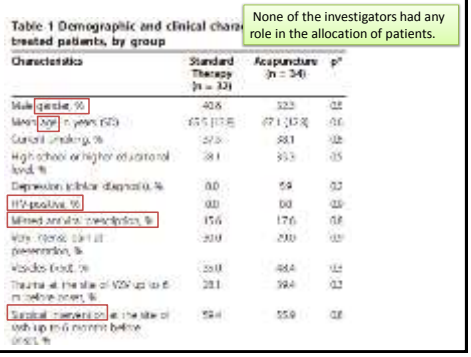


Table 1 Demographic and clinical characteristics of treated patients, by group

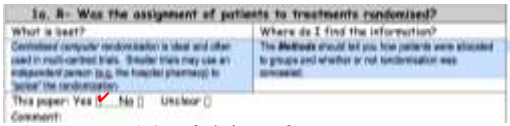
Characteristics	Standard Therapy (n = 32)	Acupuncture (n = 54)	p*
Site of pain			
Focal	0.4	23.5	0.12
Cervical	0.3	8.8	0.7
Thoracic	5.31	44.1	0.5
Lumbar	21.2	23.5	0.8
Extension of lesions			
Subdermatomal	28.1	76.5	0.9
Dermatomal	59.4	67.6	0.5
Multidermatomal	12.5	5.9	0.3
Antiviral therapy			
Acyclovir	40.6	52.9	0.5
Famciclovir	0	5.9	0.2
Valacyclovir	3.1	23.5	0.1
Brivudin	0.4	11.8	0.2
Other antiviral	5.1	2.9	0.5
Missed antiviral prescription	13.6	17.6	0.2

☑ RCT研究的偏差來源及解決方法

RCT**的論文如果沒有**adequate allocation concealment，**則**treatment effect**會容易膨脹**35-40%。

Kunz R, Vist G, Oxman AD: "Randomisation to protect against selection bias in healthcare trials." Cochrane Database Syst Rev 2007,Issue 2. Art No.:MR000012.

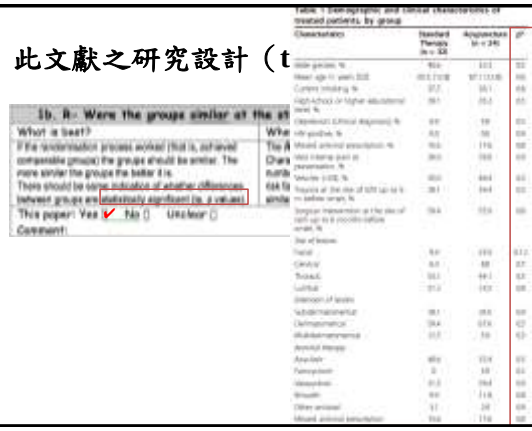
此文獻之研究設計（the study design）



1. 病人的治療分派是隨機的嗎？
   隨機分派過程是否隱匿？

None of the investigators had any role in the allocation of patients.

此文獻之研究設計（t



AC arm		ST arm	
治療	適應症	藥物	劑量
Traditional Chinese Acupuncture	All	pregabalin	75 mg/d ~needs (maximum dose: 600 mg/d
頻率 twice weekly		local anaesthesia	4-7 ml of chirocaine(1.5 mg/mL)
次數 8 sessions	lumbar or sacral localization	intermittent peridural neural blockade	
取穴 中脘、關元 合谷、內關 曲池、血海 內庭、行間	uncontrolled pain	intermittent perineural peripheral blockade	
		Local anaesthesia	Every second day, up to 5 administrations
施術者 by 2 experienced acupuncture physicians	very intense or refractory pain	opioids	1. transdermal buprenorphine (35-90 mcg/h) 2. oral oxycodone(50-400 mg daily)
For **immediate pain relief**: i.v. or oral paracetamol (250 to 1000) was allowed up to 3 times daily in both study arms.			
The duration planned for both treatments was 4 weeks.			

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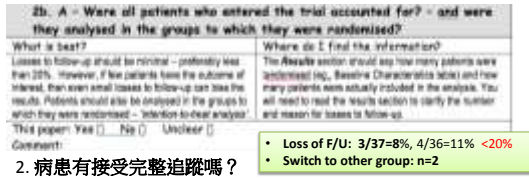


- **Loss of F/U: 3/37=8%**, 4/36=11% <20%
- **Switch to other group: n=2**

2. **病患有接受完整追蹤嗎？**
   而且分析時有按照病患原來安排的治療方式來分析嗎？

☑ RCT研究的偏差來源及解決方法

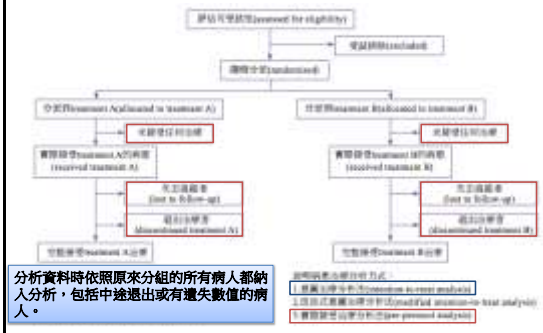
☑ 依治療意願分析(intention to treat analysis)

- 分析資料時依照原來分組的所有病人都納入分析，包括中途退出或有遺失數值的病人。

- 好處

1. 依治療意願分析是為了維持隨機化的意義。
   achieved by randomization.
2. 減少因遺失數值missing values所產生的偏誤，可能造成研究結果扭曲。

- 壞處: 低估治療效果



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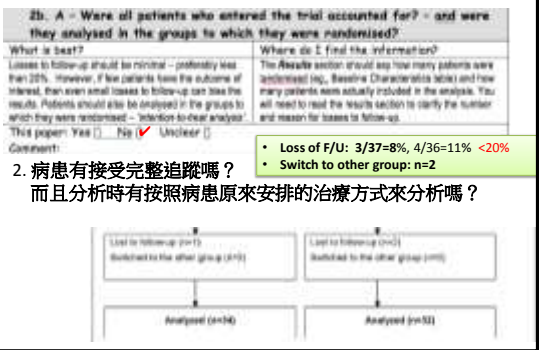

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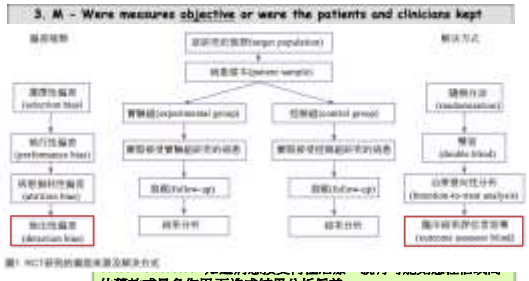


成功遮盲所得之潛在效益

遮盲對象	潛在效益
參試者	•較不可能對治療的心理或生理反應懷有成見 •較可能順從試驗藥物用法 •較不可能找尋其他的附屬治療 •較不可能未提供結果資料，就半途離開試驗導致追蹤期間損失流失
研究者	•較不可能將他們的傾向或態度轉移至參試者 •較不可能差別實施輔助治療 •較不可能差別調整劑量 •較不可能差別排除參試者 •較不可能差別地鼓勵或勸阻參試者持續參加試驗的進行
評估者	•較不可能懷有成見地影響結果評定，尤其是對主觀評定的試驗結果

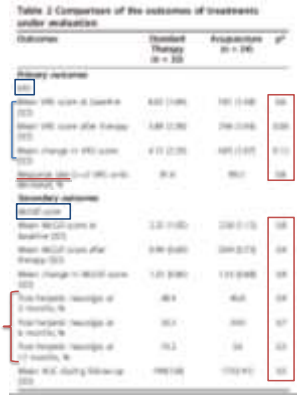
三、What were the results?

1. 治療效果有多大？多重要？

- 決定研究中所描述的治療可能利益(或傷害)是否重要.
- 使用統計分析比較介入處置是否有統計差異.

1. How large was the treatment effect?

2. 治療效果的估計有多精確?



Result

1. Both interventions were largely effective.
2. No significant differences were observed in
   - response rates
   - mean reduction of VAS
   - mean reduction of MPQ scores
   - incidence of PHN after 3 months
   - mean AUC during follow-up
3. No serious treatment-related adverse event was observed in both groups.

Result-2

- Patients with intense or very intense pain at presentation showed a significant and similar degree of pain relief using acupuncture and standard pharmacological therapy.
- Also, no differences between treatments were observed in the incidence of severe adverse events.
- Given that patients treated with acupuncture carry a lower risk of cumulative drug toxicity.

Discussion

(1) First RCT: acupuncture in acute HZ patient

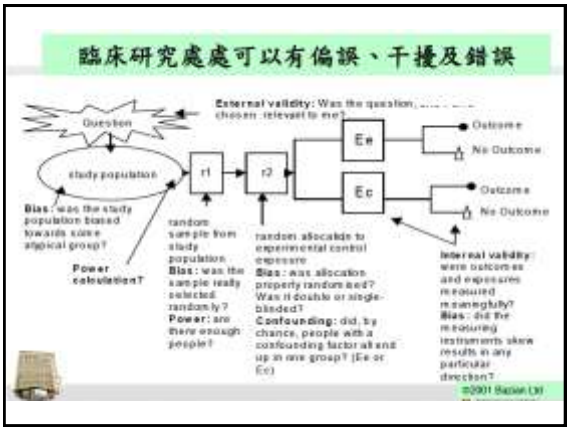
- Sample size estimation(Min=34 per group, 80% satistical power)

p 值 < 0.05 其實只代表該論文的研究結果具有統計學上意義，統計學上的有意義並不代表臨床上的有意義

(2) Adequate allocation: good

- Gender, age , drug/therapy, HIV(-)

(3) Standard evaluation(VAS) and therapy



Limitation

(1) Relatively small sample of treated patient(n=66)

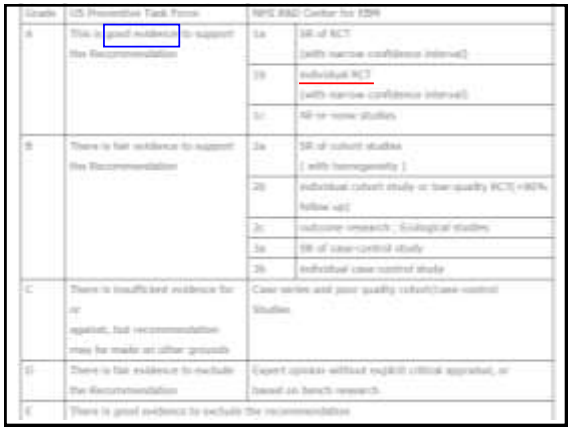
- VAS>7, refused, rapid pain reduction(n=28)

(2) Without intention to treat analysis: rare

- severe pain, rapid pain reduction?

(3) Lack both control arm:

- mock acupuncture, short acting analgestics



四、Will the results help me in caring for my patient?

1. 研究的背景：是在醫學中心還是社區醫院？
2. 病患選擇：年紀、性別
3. 病患特徵：在國外發表的研究由於其病患族群不同，研究結果不一定適用於我國的病患。
4. Difference between trial protocol and routinepractice：
   平常你所做的正規治療和此項研究的治療是否有明顯差別？
5. Adverse effects of treatment：此篇研究的adverse effects是否也會發生在我的病患身上（人種有差別時副作用會有差別嗎？）

(A) Is the economic evaluation likely to be usable?

1. Was a well-defined question posed? ☑Yes ☐Can't tell ☐No

[Method] To analyze the cost effect of surrounding acupuncture plus electric acupuncture, cotton-sheet moxibustion, puncturing with red-hot needles, tapping plus cupping on herpes zoster.

(A) Is the economic evaluation likely to be usable?

2. Was a comprehensive description of the competing alternatives given? ☑Yes ☐Can't tell ☐No

Five hundred patients with herpes zoster were randomly divided

surrounding acupuncture electric acupuncture

cotton-sheet moxibustion

puncturing with red-hot needles

tapping cupping

Western medicine

Valacyclovir 300mg
Vitamin B1 10 mg
BID

(A) Is the economic evaluation likely to be usable?

3. Does the paper provide evidence that the programme would be effective (i.e. would the programme do more good than harm)? ☑Yes ☐Can't tell ☐No

(A) Is the economic evaluation likely to be usable?

4. Were the effects of the intervention identified, measured and valued appropriately? ☑Yes ☐Can't tell ☐No

(B) How were consequences and costs assessed and compared?

成都、武漢等大醫院

(B) How were consequences and costs assessed and compared?

8. Was an incremental analysis of the consequences and cost of alternatives performed? ☑Yes ☐Can't tell ☐No

N (comprehensive index of curative effect)
=(accumulated score before treatment – accumulated score after treatment)
÷ accumulated score before treatment x100%.

9. Was an adequate sensitivity analysis performed? ☐Yes ☑Can't tell ☐No

DISCUSSION

Group	Cost	95%	Rate of obvious effect	χ^2	P value
A	94	81	86.17	7.88	0.96
B	94	78	79.47		
C	93	78	83.92		
D	95	72	75.79		
E	95	68	72.63		

Group	Cost (RMB)	Obvious effect (day)	Increased health (day)	CE	Increased cost	Increment ratio
A	298.68	6.45±1.83	16.80±11.82	21.90	16.92	1.35
B	294.52	7.97±1.89	11.66±24.45	21.87	12.76	2.81
C	221.76	6.16±1.82	8.53±21.73	26.89	-	-
D	225.56	6.21±2.15	11.85±22.65	28.23	4.8	0.21
E	371.68	7.49±1.85	-	-	149.92	-

(C) Will the results help in purchasing for local people?

11. Are the costs transferable to your setting? ☐Yes ☐Can't tell ☑No

12. Is it worth doing in your setting? ☐Yes ☑Can't tell ☐No

附件 1

第四部 中 醫

第四章 針灸治療

全民健康保險醫療服務給付項目及支付標準

編號	診療項目	支付點數
	針灸治療處置費(含材料費)	
B41	－另開內服藥	210
B42	－未開內服藥	210
	電針治療	
B43	－另開內服藥	210
B44	－未開內服藥	210

藥名	克數	劑型	點數	劑量
Acetaminophen	300mg	錠劑	0.25	
Pregabalin	75mg	錠劑	23.5	75mg/d Max: 600mg/d
lidocaine	1.5mg	針劑	3.92	
buprenorphine	0.2mg	針劑	87	35-90 mcg/h
Surgery			?	

Discussion

- 健保給付
- 未依照 Standard treatment
- 嚴謹度不足（施術者, 副作用未提及, etc）
- 替代方案的可能性考量

STEP 4.
應用

Step 4: Apply

1. 我們的病人是否與研究中的病人類似？
   - 有。
2. 此治療目前是否可行？
   - 可行
3. 我們的病人是否可以從該項治療中獲益？
   - 若病患因其它考量不想使用西藥時，可以考慮使用針刺治療替代，且相關副作用多屬輕微
4. 我們的病人如何看待此治療結果？
   - 正向，可參考

STEP 5.
評估

回到最初的Scenario

- 60 y/o female, suffered from lower back pain for 3 days, went to Acupuncture department for help
  - Is acupuncture effective for pain control? How about the efficacy when compared with standard western medicine treatment? ✔
  - Could it used for prevention? ✔
  - How about the cost? ✔

自我評估

- Step1:
  - 1. 我有提出任何臨床問題嗎？Yes
  - 2. 我提出的是結構完整的問題？Yes
- Step 2:
  - 1. 我知道在我的臨床領域中現有的最佳證據來源？Yes
  - 2. 在搜尋方面我變得更有效率？Yes
- Step 3:
  - 1. 對我而言，應用此研究證據之評讀指引變得更簡單？Yes
  - 2. 我可以更正確、更有效率的使用一些審慎評估度量工具？Yes
- Step 4:
  - 1. 我盡力將審慎評估之結果融入診療中？Yes
  - 2. 為了適用於我的病人，我在調整一些嚴格評讀的度量值。方面越來越精準及有效率？Yes