**Bedfordshire and Luton Joint Prescribing Committee (JPC)**

April 2013

Review date: April 2016

**Bulletin 178: Hydrocortisone modified-release tablets (Plenadren®)**

**JPC Recommendation:**

The use of Hydrocortisone modified-release tablets (5mg and 20mg) (Plenadren®) for the treatment of adults with adrenal insufficiency is not supported.

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**New Medicine Review**

**Hydrocortisone modified-release tablets (Plenadren®)**

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Plenadren (hydrocortisone) 5mg and 20mg modified-release tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Document status</td>
<td>Final, approved by Bedfordshire and Luton Joint Prescribing Committee</td>
</tr>
<tr>
<td>Date of last revision</td>
<td>March 2013</td>
</tr>
<tr>
<td>Proposed Sector of prescribing</td>
<td>Primary and Secondary Care (initiated in secondary care with GP to continue prescribing)</td>
</tr>
</tbody>
</table>

**Introduction**

Adrenal insufficiency (AI) leads to deficiency of glucocorticoid and, in some cases, mineralocorticoid hormones.¹ ² It can be primary (where the adrenal glands fail to produce enough steroid hormones, as in Addison’s disease) or secondary (where the pituitary gland or hypothalamus do not adequately stimulate the adrenal glands).³ It can be fatal if untreated, and patients need lifelong hormone replacement.² ⁴ Achieving a balance between over- and under-substitution with glucocorticoids is difficult. Impaired QoL, cardiovascular disease, osteoporosis and a two-fold higher mortality rate are reported in patients with AI.⁵ ⁶ ⁷ Increased mortality may be caused by failure to achieve physiological replacement of glucocorticoids, but could also be due to use of excessive maintenance doses in over 50% of patients.⁷

The most common glucocorticoid used is immediate-release (IR) hydrocortisone, in daily doses of 15mg to 30mg.⁸ Ideally it should be taken three times a day (e.g. 10mg on waking, 5mg at noon and 5mg in
the early evening), but is sometimes given in two divided doses with two thirds in the morning. Longer-acting prednisolone or dexamethasone are sometimes used because of improved patient convenience but, unlike hydrocortisone, have no mineralocorticoid activity. Accurate replacement of physiological diurnal and pulsatile ultradian cortisol levels is impossible with currently available glucocorticoids. There are no objective measures to assess effectiveness of treatment and doses are adjusted according to clinical response. Over- and under-replacement need to be avoided as both are associated with increased morbidity and mortality.

Plenadren® is an oral modified-release formulation of hydrocortisone licensed to treat adults with AI. Limited data on its pharmacokinetics (PK), efficacy and safety in primary AI are available from one phase II/III randomised cross-over study (n=64) and an on-going open PIII follow-up study (see appendix 1). There are no studies involving patients with secondary AI. Although designed to more closely mimic natural cortisol release than current glucocorticoids, Plenadren® only partly achieves this. The amount of hydrocortisone absorbed systemically from Plenadren® is about 20% less than from immediate-release (IR) hydrocortisone. This could be beneficial in some patients (over-substitution with current glucocorticoids is common), for others on lower doses (20mg daily or less), it could lead to under-substitution. Mean body weight and blood pressure were reduced to a small extent after 12 weeks’ treatment with Plenadren® compared with the same dose of hydrocortisone IR. Plenadren® and hydrocortisone IR cause similar adverse effects of abdominal pain, diarrhoea, nausea and fatigue. However, patients switched to Plenadren® may feel less well for the first few months as they adjust to the change in cortisol levels.

There is no evidence that Plenadren’s® concentration-time profile and the short-term changes in some surrogate measures of disease reduce morbidity or mortality.

A trial comparing Plenadren® with a 20% lower daily dose of hydrocortisone IR is needed to show whether the metabolic effects could be achieved by reducing the dose of hydrocortisone IR.

Patients prefer Plenadren® once daily to hydrocortisone IR taken three times a day but compliance with the two formulations is similar. Quality of life data are difficult to interpret and should be viewed with caution as they come from open-label studies with small numbers of patients.

Plenadren® is an option for patients with poor compliance, but its use will significantly increase the cost of therapy. Patients should be monitored closely when switching to avoid under-substitution. Prescribers should make sure patients with AI take the lowest effective dose of glucocorticoid – a daily hydrocortisone dose of 15 to 20mg is adequate for most adults with primary AI.

| The intervention Mechanism of action | Plenadren® is an oral modified-release formulation of hydrocortisone designed to more closely mimic the natural cycle of cortisol release than current glucocorticoids. It has a slow-releasing inner core surrounded by an outer layer which quickly releases hydrocortisone. |
| Licensed indication | Treatment of adults with adrenal insufficiency. |
**Usual dosage**

Plenadren is given as maintenance therapy. Oral replacement doses must be individualised according to the clinical response. A common maintenance dose is 20 – 30 mg of Plenadren per day, given once daily in the morning. In patients with some remaining endogenous cortisol production a lower dose may be sufficient; 40 mg is the highest maintenance dose of Plenadren studied. The lowest possible maintenance dosage should be used. In situations when the body is exposed to excessive physical and/or mental stress, patients may need additional substitution of immediate release hydrocortisone tablets especially in the afternoon/evening.

**Treatment alternatives/ place in therapy**

Standard release hydrocortisone tablets

**Future alternatives**

None identified

**National guidance**

Limited data on the PK, efficacy and safety of Plenadren® in primary AI are available from one phase II/III randomised cross-over study and an on-going open PIII follow-up study (see appendix 1). There are no studies involving patients with secondary AI.

In the main cross-over study, 64 adults on stable doses of hydrocortisone IR (20-40mg daily) were randomised to a single dose of Plenadren® before breakfast, or hydrocortisone IR taken in three divided doses at 8am (before food), 12pm and 4pm for 12 weeks. Patients were immediately switched to the same (mg for mg) dose of the alternative formulation for a further 12 weeks, before they were all given Plenadren® for an additional six months (n=59). Patients were told to take double doses if they had an intercurrent illness; because of this, it was considered unethical and unsafe to blind the trial. The primary outcome was serum cortisol exposure-time profile. Because glucocorticoids have diverse effects and there is no specific biomarker for cortisol, the EU Committee for Medicinal Products for Human Use (CHMP) agreed cortisol PKs were a reasonable measure of efficacy. Analysis was by intention-to-treat (ITT). One patient was excluded from the ITT analysis because PK data were unavailable.

Plenadren® treatment resulted firstly in a high peak of serum cortisol after the morning dose, and then a slow, smooth decline during the afternoon, with negligible levels overnight; three peaks after each dose were observed with hydrocortisone IR. Mean total serum cortisol area under the curve (AUC0-24h) was 19.4% lower with Plenadren® vs. hydrocortisone IR. In comparison with the natural cortisol cycle (as seen in healthy volunteers), Plenadren® achieves higher morning levels but lower afternoon and evening levels; it does not mimic the gradual cortisol increase before awakening, the two daytime spikes associated with eating or the frequent pulses. Therefore, Plenadren® only partly mimics the physiological profile of cortisol. The CHMP noted that the lower bioavailability of Plenadren® could be potentially beneficial for some patients as over-substitution is an important drawback of current glucocorticoid therapy. However, avoiding over-substitution could also be achieved by reducing the prescribed hydrocortisone IR dose. Of note,
the immunoassays used in the study were not selective for cortisol and may have also measured metabolites, therefore overestimating cortisol levels. The CHMP acknowledged that, despite this, the PK data are sufficient to show relative comparability.4

In the trial, mean body weight and blood pressure decreased slightly after 12 weeks’ treatment with Plenadren®, but increased with hydrocortisone IR; the difference between the groups was statistically significant. Body weight was further reduced with Plenadren® at six months. Very small changes were seen in glucose and lipid metabolism which hardly reached clinical significance, and were generally not maintained during six months’ follow-up. Two bone markers were measured; there was no change in mean osteocalcin levels from baseline with either formulation at 12 weeks, but N-terminal propeptide of type I procollagen increased significantly with Plenadren®, suggesting increased bone formation. These data are not sufficient to support an improved metabolic profile; longer-term data and a trial comparing Plenadren® with a 20% lower dose of hydrocortisone IR are needed.4,11

Data from three validated quality of life (QoL) questionnaires showed Plenadren® use resulted in a slight decrease in scores of borderline significance at four weeks, especially in physical wellbeing. At 12 weeks this was less pronounced and there was an improvement in psychosocial domains. Initial decreases may be caused by transient hypocortisolism. Energy, measured using an un-validated diurnal fatigue scale, showed an improvement only with Plenadren®. There was little change after a further six months. However, these QoL data should be interpreted cautiously; bias is possible because the trial was not blinded. 85% of patients preferred Plenadren® to hydrocortisone IR. Also, before the study 55% of patients were taking hydrocortisone IR twice daily, so the influence of a switch to three times daily dosing is unknown. During the study few patients increased their dose because of intercurrent illness; the data are reassuring but inadequate to fully assess effectiveness. This is reflected in the SPC which offers a number of options for managing intercurrent illness.4,11

In the on-going long-term follow-up study, unpublished data from 67 of 71 patients who completed 18 months’ evaluation, show most QoL domains remain unchanged from baseline.4 Patient tolerability improves over time. Change of dose during the extension is allowed; most patients stay on the same dose and those who change, decrease (n=9) rather than increase (n=6) their dose.4,11

### Safety

The CHMP assessed limited safety data from a total patient exposure of about 145 patient-years.4 The frequency and type of adverse effects (AEs) are similar with Plenadren® and hydrocortisone IR. They include fatigue, abdominal pain, diarrhoea and nausea. Patients taking Plenadren® report AEs more commonly during the first eight weeks of treatment, especially fatigue. This may indicate a relative under-substitution when changing from hydrocortisone IR to the same dose of Plenadren® because patients may have previously been taking too high a dose (all patients in the trial were taking daily doses of 20mg or higher, and 75% were on 30-40mg daily). The CHMP state that this is not expected to be a problem in clinical practice, as AE rates decline with continued use and patients do not subsequently need a dose increase.4 However, the possibility of under-substitution when switching
Plenadren® should be considered in all patients and especially those on daily doses of 20mg or less. Plenadren® is not recommended for patients with increased gastrointestinal motility; such patients were excluded from clinical studies as absorption of hydrocortisone may be affected.\textsuperscript{4,11}

Most patients can be switched from hydrocortisone IR to the same dose of Plenadren®; however some patients may feel less well for the first few months of therapy. Clinical response should be monitored. Patients will need clear instructions on how to increase their dose during intercurrent illness.\textsuperscript{4,10}

<table>
<thead>
<tr>
<th>Costs</th>
<th>28 days (20mg daily) Plenadren = £224 (excl VAT)\textsuperscript{14}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tariff status Activity costs</td>
<td></td>
</tr>
<tr>
<td>Costs of alternatives</td>
<td>28 days (10mg BD) hydrocortisone standard release = £92.36(excl VAT)\textsuperscript{15}</td>
</tr>
<tr>
<td>Cost effectiveness (if available)</td>
<td>No published data identified</td>
</tr>
<tr>
<td>Potential number of patients in Bedfordshire and Luton Impact per 100,000 population Affordability considerations</td>
<td>Adrenal insufficiency (AI)\textsuperscript{4} is a rare condition with a prevalence of 2 to 4 per 10,000 people. This would equate to 88 to 176 patients for BCCG and 42 to 84 patients for LCCG.</td>
</tr>
<tr>
<td>Number Needed to Treat (NNT) Number Needed to Harm (NNH)</td>
<td></td>
</tr>
<tr>
<td>Ethics Equity</td>
<td>See attached Ethical Framework</td>
</tr>
<tr>
<td>Implementation</td>
<td></td>
</tr>
<tr>
<td>Patient choice/access considerations</td>
<td>Reducing the number of times a medicine is taken in a day increases patient compliance.\textsuperscript{4,15} For a disease like AI in which missed doses can be life-threatening, Plenadren® could offer potential benefits. However adherence to treatment is high in patients with AI, since non-compliance causes uncomfortable symptoms.\textsuperscript{16}</td>
</tr>
<tr>
<td>As Plenadren® is an orphan medicine, producing large amounts of trial data is difficult. An EU registry has been set up to assess whether changes in surrogate measures translate into clinically relevant reductions in morbidity and mortality for patients with AI.\textsuperscript{4}</td>
<td></td>
</tr>
</tbody>
</table>
Decisions from other bodies
Greyliterature
Comments sought from –

| Points for consideration | There are very limited data on the PK, efficacy and safety of Plenadren® in primary AI in the form of a single phase II/III randomised cross-over study and an on-going open PIII follow-up study. There are no studies involving patients with secondary AI. |
| Points for consideration | Though patients prefer Plenadren® once daily to hydrocortisone IR taken three times a day, compliance with the two formulations is similar. |
| Points for consideration | Quality of life data are difficult to interpret and should be viewed with caution as they come from open-label studies with small numbers of patients. |
| Points for consideration | Patients switched to Plenadren® may feel less well for the first few months as they adjust to the change in cortisol levels. |
| Points for consideration | Plenadren® is an option for patients with poor compliance, but its use will significantly increase the cost of therapy. Patients should be monitored closely when switching to avoid under-substitution. |
| Points for consideration | Currently Plenadren® is not a cost effective treatment option, but this should be kept under review due to the escalating costs of immediate release oral hydrocortisone. |

Options for JPC

PAC New Drug Template – Adapted from East Anglia Medicines Information, NHS Suffolk, NHS Cambridgeshire and NHS Derby templates
References/ Sources of Review


A literature search did not identify any new data since publication of the UKMI review.

14. MIMS March 2013
Search Strategy
NeLM/ EMC/ NICE/ SMC/ AWMSG/ Cochrane Library/ NHS Evidence
MHRA/ Embase/Medline

Embase/Medline search history:
1. MEDLINE; exp HYDROCORTISONE/; 60773 results.
2. MEDLINE; exp DELAYED-ACTION PREPARATIONS/; 34057 results.
3. MEDLINE; exp ADRENAL INSUFFICIENCY/; 9930 results.
4. MEDLINE; exp ADDISON DISEASE/; 3939 results.
5. MEDLINE; 3 OR 4; 9930 results.
6. MEDLINE; 1 AND 2 AND 5; 10 results.
7. EMBASE; exp HYDROCORTISONE/; 90207 results.
8. EMBASE; exp SUSTAINED RELEASE PREPARATION/; 32642 results.
9. EMBASE; exp ADRENAL INSUFFICIENCY/; 7098 results.
10. EMBASE; exp ADDISON DISEASE/; 4838 results.
11. EMBASE; 9 OR 10; 11429 results.
12. EMBASE; 7 AND 8 AND 11; 5 results.
13. EMBASE; plenadren.ti,ab; 0 results.
14. MEDLINE; plenadren.ti,ab; 0 results.
15. MEDLINE,EMBASE; Duplicate filtered: [1 AND 2 AND 5], [7 AND 8 AND 11], [plenadren.ti,ab]; 15 results.
Bedfordshire and Luton Joint Prescribing Committee (JPC)
Assessment against Ethical and Commissioning Principles

Treatment assessed (April 2013): Hydrocortisone modified-release tablets (Plenadren®)

<table>
<thead>
<tr>
<th>JPC Recommendation:</th>
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<td>The use of Hydrocortisone modified-release tablets (5mg and 20mg) (Plenadren®) for the treatment of adults with adrenal insufficiency is not supported.</td>
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1) Clinical Effectiveness

Limited data on the pharmacokinetics (PK), efficacy and safety of Plenadren® in primary Al are available from one phase II/III randomised cross-over study and an on-going open PIII follow-up study. There are no studies involving patients with secondary Al. In the main cross-over study, 64 adults on stable doses of hydrocortisone IR (20-40mg daily) were randomised to a single dose of Plenadren® before breakfast, or hydrocortisone IR taken in three divided doses at 8am (before food), 12pm and 4pm for 12 weeks. Patients were immediately switched to the same (mg for mg) dose of the alternative formulation for a further 12 weeks, before they were all given Plenadren® for an additional six months (n=59). Plenadren® was found to only partly mimic the physiological profile of cortisol. The CHMP noted that the lower bioavailability of Plenadren® could be potentially beneficial for some patients as over-substitution is an important drawback of current glucocorticoid therapy. However, avoiding over-substitution could also be achieved by reducing the prescribed hydrocortisone IR dose. Of note, the immunoassays used in the study were not selective for cortisol and may have also measured metabolites, therefore overestimating cortisol levels. The CHMP acknowledged that, despite this, the PK data are sufficient to show relative comparability. The frequency and type of adverse effects are similar with Plenadren® and hydrocortisone IR.

2) Cost Effectiveness

<table>
<thead>
<tr>
<th>No published data</th>
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<tbody>
<tr>
<td>28 days (20mg daily) Plenadren = £224 (excl VAT)</td>
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<tr>
<td>28 days (10mg BD) hydrocortisone standard release = £92.36(excl VAT)</td>
</tr>
<tr>
<td>NB Price of immediate release hydrocortisone is increasing.</td>
</tr>
</tbody>
</table>

3) Equity

No issues identified

4) Needs of the community

Adrenal insufficiency (Al) is a rare condition with a prevalence of 2 to 4 per 10,000 people. This would equate to 88 to 176 patients for BCCG and 42 to 84 patients for LCCG.

5) Need for healthcare (incorporates patient choice and exceptional need)

Plenadren® is an additional treatment option for patients with poor compliance, but its use will significantly increase the cost of therapy. Patients should be monitored closely when switching to avoid under-substitution.

6) Policy drivers

None

7) Disinvestment

Reduction in the use of immediate release oral hydrocortisone tablets

The JPC agreed the following sections within the CCG Ethical and Commissioning Framework were not relevant to JPC discussions: Health Outcomes, Access, and Affordability.
### Appendix I

**Table 1. Phase II/III study of hydrocortisone modified-release (Plenadren®)**

<table>
<thead>
<tr>
<th>Ref no</th>
<th>Trial design</th>
<th>Inclusion and exclusion criteria</th>
<th>Trial population and treatment</th>
<th>Efficacy results (p values for Plenadren vs. hydrocortisone IR)</th>
</tr>
</thead>
</table>
| 1, 2   | Randomised, controlled, open, two-armed, two-period (12-weeks each), cross-over, multicentre PI/III trial, with a 6-month open follow-up phase | **Inclusion criteria:**
- Males and females aged at least 10 years.
- Previously diagnosed (≥6 months) primary AI with a stable dose of glucocorticoid for at least 3 months.
- Oral hydrocortisone dose of 20-40mg daily.  
**Exclusion criteria:**
- Significant cerebral, cardiovascular, respiratory, hepatic, or gastrointestinal disease.
- Serum creatinine >150μmol/L.
- Significant gastrointestinal emaciating or mobility disease.
- Drugs interfering with cortisol metabolism.
- Use of dehydroepiandrosterone or oral oestrogens.
- Diseases requiring treatment with pharmacological doses of glucocorticoids.
- Derived mineralocorticoid status. | ITT population, n=63.
37 male 26 female.
11 patients had diabetes mellitus.  
Baseline data (mean):
- Age 47 years (range 19-71)
- Body weight 79.6kg
- Systolic BP 123.6mmHg
- Diastolic BP 75.8mmHg
- HbA1c 4.9%
- Total cholesterol 5.3mmol/L
- LDL-C 3.1mmol/L
- PINP 57.2μg/microgram/L
- Osteocalcin 11.4μg/microgram/L  
Hydrocortisone MR (Plenadren®) 20mg and 30mg tablets 20-40mg once daily before breakfast during 12 weeks. n=63. | **Primary endpoint at 12 weeks – mean (SD):**
Total serum cortisol AUC<sub>24h</sub> (h x nmol/L): 3,992.0 (1,079.6) 4,879.6 (1,194.4)  
*p-Period-adjusted quotient (55% CI): 0.806 (0.753-0.862) <0.0001** |
|        |              |                                  |                               | **Secondary endpoints:**  
Total serum cortisol AUC<sub>24h</sub> (h x nmol/L): 1,053.7 (432.0) 1,929.7 (409.0)  
*p-Period-adjusted quotient (55% CI): 1.064 (1.032-1.097) 0.0002** |
|        |              |                                  |                               | Total serum cortisol AUC<sub>24h</sub> (h x nmol/L): 1,334.7 (582.5) 1,839.0 (599.0)  
*p-Period-adjusted quotient (55% CI): 0.685 (0.632-0.765) <0.0001** |
|        |              |                                  |                               | Total serum cortisol AUC<sub>24h</sub> (h x nmol/L): 465.0 (352.2) 1,058.0 (752.4)  
*p-Period-adjusted quotient (55% CI): 0.412 (0.338-0.504) <0.0001** |
|        |              |                                  |                               | **Other efficacy endpoints at 12 weeks – mean (SD):**  
Body weight (kg): 78.7 (14.3) 79.7 (14.4) 0.0049  
Systolic BP (mmHg): 119.8 (14.5) 125.4 (17.7) 0.0001  
Diastolic BP (mmHg): 74.5 (8.4) 77.0 (9.5) 0.0043  
HbA1c (%): 4.9 (0.9) 5.0 (1.1) 0.0006  
Total cholesterol (mmol/L): 5.3 (1.0) 5.3 (0.7) 0.6729  
LDL-C (mmol/L): 3.0 (0.9) 3.1 (0.9) 0.9131  
PINP (microgram/L): 63.9 (34.8) 56.1 (29.2) 0.0026  
Osteocalcin (microgram/L): 13.4 (5.3) 12.4 (5.4) 0.2337  
Patient compliance (actual intake as a % of expected, Mean (SD); median (range))  
40.0% (28.0-100.0) (102.4, 97.3-136.0) 103.2 (13.2) (100.6, 61.2-168.2) NR | **Patient compliance for Plenadren® vs. hydrocortisone IR [%]:**  
Plenadren® [%] vs. hydrocortisone IR [%] p-value  
Plenadren® vs. hydrocortisone IR [%] 4.9 4.9 0.0001  
Plenadren® vs. hydrocortisone IR [%] 85.4 85.4 0.0001  
**Situation of life questionnaires, difference between total scores**  
Fatigue impact scale: P > HCIR 0.08  
Psychological general well-being: P > HCIR 0.06  
Short form survey: P = HCIR NS |
|        |              |                                  |                               | **Tolerability (%), rated as very well, well or acceptable:**  
Plenadren®: 91.7 95.1 96.7  
Hydrocortisone IR: 96.7  
Plenadren® vs. hydrocortisone IR: p-value  
Plenadren® vs. hydrocortisone IR: NS |

**Abbreviations:** AI: adrenal insufficiency; AUC: area under the curve; CI: confidence interval; IR: immediate-release; ITT: intention-to-treat; LDL-C: low density lipoprotein cholesterol; NA: not recorded; NS: not significant; PaQ: period-adjusted quotient; PINP: pro-collagen type I; P: statistical significant; PK: pharmacokinetics; SD: standard deviation.

*Quotient: The answer you get after you divide one number by another, e.g., 12 ÷ 3 = 4 is the quotient. PaQ indicates relative size of Plenadren AUC vs. hydrocortisone IR AUC.
## Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

<table>
<thead>
<tr>
<th>Question</th>
<th>Step 1 (Level 5*)</th>
<th>Step 2 (Level 3)</th>
<th>Step 3 (Level 2)</th>
<th>Step 4 (Level 1)</th>
<th>Step 5 (Level 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>How common is the problem?</td>
<td>Local and current random sample surveys (or censuses)</td>
<td>Systematic review of surveys that allow matching to local circumstances**</td>
<td>Local non-random sample**</td>
<td>Case-series**</td>
<td>N/A</td>
</tr>
<tr>
<td>Is this diagnostic or monitoring test accurate? (Diagnosis)</td>
<td>Systematic review of cross sectional studies with consistently applied reference standard and blinding</td>
<td>Individual cross sectional studies with consistently applied reference standard and blinding</td>
<td>Non-consecutive studies, or studies without consistently applied reference standard**</td>
<td>Case-control studies, or &quot;poor or non-independent reference standard&quot;**</td>
<td>Mechanism-based reasoning</td>
</tr>
<tr>
<td>What will happen if we do not add a therapy? (Prognosis)</td>
<td>Systematic review of inception cohort studies</td>
<td>Inception cohort studies</td>
<td>Cohort study or control arm of randomized trial*</td>
<td>Case-series or case-control studies, or poor quality prognostic cohort study**</td>
<td>N/A</td>
</tr>
<tr>
<td>Does this intervention help? (Treatment Benefits)</td>
<td>Systematic review of randomized trials or n-of-1 trials</td>
<td>Randomized trial or observational study with dramatic effect</td>
<td>Non-randomized controlled cohort/follow-up study**</td>
<td>Case-series, case-control studies, or historically controlled studies**</td>
<td>Mechanism-based reasoning</td>
</tr>
<tr>
<td>What are the COMMON harms? (Treatment Harms)</td>
<td>Systematic review of randomized trials, systematic review of nested case-control studies, n-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect</td>
<td>Individual randomized trial or (exceptionally) observational study with dramatic effect</td>
<td>Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**</td>
<td>Case-series, case-control studies, or Historically controlled studies**</td>
<td>Mechanism-based reasoning</td>
</tr>
<tr>
<td>What are the RARE harms? (Treatment Harms)</td>
<td>Systematic review of randomized trials or n-of-1 trial</td>
<td>Randomized trial or (exceptionally) observational study with dramatic effect</td>
<td>Non-randomized controlled cohort/follow-up study**</td>
<td>Case-series, case-control studies, or Historically controlled studies**</td>
<td>Mechanism-based reasoning</td>
</tr>
<tr>
<td>Is this (early detection) test worthwhile? (Screening)</td>
<td>Systematic review of randomized trials</td>
<td>Randomized trial</td>
<td>Non-randomized controlled cohort/follow-up study**</td>
<td>Case-series, case-control studies, or Historically controlled studies**</td>
<td>Mechanism-based reasoning</td>
</tr>
</tbody>
</table>

* Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.

** As always, a systematic review is generally better than an individual study.

How to cite the Levels of Evidence Table:

* CEBM Table of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Iva Moschetti, Bob Phillips, Hazel Thornton, Ollie Goddard and Mary Hodgkinson