Coordination with the Cochrane Renal Group: Making best use of the Renal Trial Registry

Angela Webster
Editor, Cochrane Renal Group
CRG

• Based in Sydney (since 2000)
• Core work
  – Producing and updating systematic reviews
  – Renal trials registry - RCTs
  – Trial registration (prospective)
  – Diagnostic test accuracy studies and reviews
  – Training and support
  – Collaboration
CRG

• Based in Sydney (since 2000)
• Core work
  – Producing and updating systematic reviews
    • All aspects of renal disease
    • Overlap with other review groups – endocrine, hypertension, PVD
    • Co-publication in medical journals
  – Renal trials registry
  – Trial registration (prospective)
  – Diagnostic test accuracy studies
  – Training and support
Producing and updating reviews

- Completed reviews
- Draft reviews
- Registered titles
- Updated reviews
Review authors

<table>
<thead>
<tr>
<th>Region</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asia</td>
<td>58</td>
</tr>
<tr>
<td>Australia/NZ</td>
<td>72</td>
</tr>
<tr>
<td>Europe</td>
<td>145</td>
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<tr>
<td>Nth America</td>
<td>35</td>
</tr>
<tr>
<td>Sth America</td>
<td>21</td>
</tr>
<tr>
<td>Middle East</td>
<td>12</td>
</tr>
<tr>
<td>Low/middle income countries</td>
<td>93</td>
</tr>
<tr>
<td>High income countries</td>
<td>252</td>
</tr>
</tbody>
</table>
Updating reviews

- Reviews are often out of date after 2-3 years
- Updating is a unique feature of Cochrane reviews
- We ‘encourage’ our authors to update every 2 years
  - Regular re-runs of search strategy
  - Forwarding copies of new trial reports
IL2Ra for kidney transplant recipients

**REVIEW 2004**
- Excluded 686
- Other Sources (61)

**Database Search**
- MEDLINE; EMBASE; Cochrane Resources

**Full Text Review**
- 162

**UPDATE 2003-2006**
- Excluded 715
- Other Sources (15)

113 reports of 38 trials
72 reports of 14 new trials

Total included: 185 reports of 52 trials (6663 recipients)
Updating makes a difference…

<table>
<thead>
<tr>
<th>Study</th>
<th>Without update</th>
<th>With 2006 update</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sheashaa 2003</td>
<td>0/50</td>
<td>1/19</td>
</tr>
<tr>
<td>Pisani 2001</td>
<td>1/19</td>
<td>1/13</td>
</tr>
<tr>
<td>Kyllonen 2002</td>
<td>2/52</td>
<td>4/52</td>
</tr>
<tr>
<td>Davies/Lawen 2000</td>
<td>3/59</td>
<td>5/64</td>
</tr>
<tr>
<td>Kirkman 1991</td>
<td>9/40</td>
<td>8/40</td>
</tr>
<tr>
<td>de Boccardo 2002</td>
<td>11/151</td>
<td>14/151</td>
</tr>
<tr>
<td>Ponticelli 2001</td>
<td>13/168</td>
<td>18/172</td>
</tr>
</tbody>
</table>

Subtotal (95% CI): 539 ± 542

Total events: 39 (IL2Ra), 53 (placebo)
Test for heterogeneity: \( \chi^2 = 2.41, df = 6 (P = 0.88), I^2 = 0\%
Test for overall effect: \( Z = 1.28 (P = 0.20) \)

Without update: 7 Trials, 1081 Participants

<table>
<thead>
<tr>
<th>Study</th>
<th>0.86 ± 0.14 [0.01, 2.70]</th>
<th>0.13 ± 0.08 [0.05, 2.98]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sheashaa 2003</td>
<td>1.03 ± 0.14 [0.01, 2.70]</td>
<td>0.13 ± 0.08 [0.05, 2.98]</td>
</tr>
<tr>
<td>Pisani 2001</td>
<td>2.70 ± 0.50 [0.10, 2.61]</td>
<td>0.42 ± 0.08 [0.08, 2.08]</td>
</tr>
<tr>
<td>Kyllonen 2002</td>
<td>3.84 ± 0.65 [0.16, 2.61]</td>
<td>0.90 ± 0.29 [0.29, 2.76]</td>
</tr>
<tr>
<td>Davies/Lawen 2000</td>
<td>5.83 ± 0.90 [0.29, 2.76]</td>
<td>10.33 ± 1.13 [0.48, 2.62]</td>
</tr>
<tr>
<td>Kirkman 1991</td>
<td>10.33 ± 1.13 [0.48, 2.62]</td>
<td>11.27 ± 0.64 [0.28, 1.44]</td>
</tr>
<tr>
<td>Kahan 1999</td>
<td>12.33 ± 1.18 [0.55, 2.56]</td>
<td>12.90 ± 0.79 [0.37, 1.67]</td>
</tr>
<tr>
<td>Nashan 1997</td>
<td>12.90 ± 0.79 [0.37, 1.67]</td>
<td>15.93 ± 0.74 [0.37, 1.46]</td>
</tr>
<tr>
<td>de Boccardo 2002</td>
<td>15.93 ± 0.74 [0.37, 1.46]</td>
<td>16.72 ± 0.66 [0.39, 1.26]</td>
</tr>
<tr>
<td>Ponticelli 2001</td>
<td>16.72 ± 0.66 [0.39, 1.26]</td>
<td>100.00 ± 0.73 [0.56, 0.96]</td>
</tr>
</tbody>
</table>

Subtotal (95% CI): 1253 ± 1263

Total events: 83 (IL2Ra), 120 (placebo)
Test for heterogeneity: \( \chi^2 = 8.40, df = 12 (P = 0.75), I^2 = 0\%
Test for overall effect: \( Z = 2.27 (P = 0.02) \)

With 2006 update: 13 Trials, 2516 Participants
Cumulative meta-analysis

- Evidence of reduction in graft loss since 2003
- 1047 persons have since been randomised
CRG

• Based in Sydney (since 2000)

• Core work
  – Producing and updating systematic reviews
  – Renal trials registry
    • Databases 1970
    • Hand-searching all major conferences 1980
  – Trial registration (prospective)
  – Diagnostic test accuracy studies
  – Training and support
CRG Renal trials register

- MEDLINE 58%
- Handsearching (38%)
  - Conference proceedings
  - Non-indexed journals
- CENTRAL (1%)
  - Other registers
  - Handsearching by other groups
- EMBASE (1%)
- Ongoing studies (2%)
CRG Renal trials register

- MEDLINE 58%
- Handsearching (38%)
  - Conference proceedings
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  - Other registers
  - Handsearching by other groups
- EMBASE (1%)
- Ongoing studies (2%)
- Over 370 conferences of 83 organisations, including:
  - ASN, ATC
  - ANZSN, TSANZ
  - EDTA, ERA
  - ISN, WTC
- One off meetings - journals
Trials versus reports: a trial based register
Handsearching and publication bias

*Figure 4. Analysis of published clinical trials indicates considerably better survival of patients with advance compared with monotherapy with alkylating agent. Analysis of registered trials failed to confirm this.*
Impact of duplicate publication

- **IL2 versus placebo/no treatment**
  - Falsely increased precision of estimate (acute rejection)
  - Falsely significant estimate of effect (graft loss)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Relative risk (95% CI)</th>
<th>Trial based analysis</th>
<th>Report based analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute rejection 6 months</td>
<td></td>
<td>0.66 (0.59, 0.74)</td>
<td>0.65 (0.61, 0.70)</td>
</tr>
<tr>
<td>Graft loss 1 year</td>
<td></td>
<td>0.84 (0.66, 1.05)</td>
<td>0.69 (0.58, 0.83)</td>
</tr>
</tbody>
</table>
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Prospective register of RCTs

- Established in July 2005
- data set requested complies with the fields described in WHO International Clinical Trials Registry Platform (ICTRP)
- unique registration number assigned after data completeness checked
- Currently 120 trials from 19 countries
  - topic areas include: peritoneal dialysis, diabetic nephropathy, glomerulonephritis and transplantation
  - Regular yearly contact with trialists
<table>
<thead>
<tr>
<th>crg_id</th>
<th>titleoftrial</th>
<th>leadsurname</th>
<th>leadgivernames</th>
<th>View &gt;&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRG05060001</td>
<td>A RANDOMIZED, CONTROLLED TRIAL OF STRAIGHT VERSUS COILED TENCKHOFF CATHETERS IN PERITONEAL DIALYSIS PATIENTS</td>
<td>Johnson</td>
<td>David Wayne</td>
<td></td>
</tr>
<tr>
<td>CRG05060002</td>
<td>A RANDOMIZED, CONTROLLED TRIAL OF FLUDROCORTISONE FOR THE TREATMENT OF HYPERKALAEMIA IN HAEMODIALYSIS PATIENTS</td>
<td>Johnson</td>
<td>David Wayne</td>
<td></td>
</tr>
<tr>
<td>CRG05060003</td>
<td>A randomised study comparing universal valacyclovir prophylaxis with quantitative PCR based preemptive therapy for cytomegalovirus (CMV) disease in renal transplant recipients.</td>
<td>Reischig</td>
<td>Tomas</td>
<td></td>
</tr>
<tr>
<td>CRG06050004</td>
<td>A randomised double blind, placebo controlled, cross-over study of the effect of amiloride over 6 weeks, on renal water handling in individuals with a bipolar or unipolar disorder, requiring lithium therapy?.</td>
<td>Walker</td>
<td>Robert</td>
<td></td>
</tr>
<tr>
<td>CRG040600073</td>
<td>Clinical benefits of icodextrin-based solutions in high-transporter, prevalent, diabetic patients in peritoneal dialysis: A randomized clinical trial</td>
<td>Paniagua</td>
<td>Ramon</td>
<td></td>
</tr>
</tbody>
</table>

**ID PENDING**

**Influence on hemodynamics of conversion from Calcineurin Inhibitor to Sirolimus in Renal and Liver Transplant patients**

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Register of diagnostic test accuracy studies (DTAS)

- CRG a pilot group for DTAS reviews and for developing a DTAS trials register
- Trial identification not straightforward
  - development of database search strategies and (re-)handsearching
- 1% of published articles in KI, JASN and AJKD are DTAS (pilot study 2004)
Reviews of Diagnostic Test Accuracy Studies

Information about this initiative can be found on the Cochrane Collaboration's website at http://www.cochrane.org/docs/diagnostic_test_reviews.htm

New Register of Diagnostic Test Accuracy Studies

We have successfully submitted a proposal to the Cochrane Collaboration Steering Group for two-year funding to develop a Cochrane-wide study-based register of reports of diagnostic test accuracy.

This exciting initiative will ultimately lead to better support for authors and review groups doing Cochrane systematic reviews of diagnostic test accuracy, by providing a clean and comprehensive register of potential studies for their reviews.

Searching for diagnostic test accuracy studies is more difficult and time consuming than for reports of randomised controlled trials. This is due to poor reporting by the authors of these studies, and inconsistent indexing in Medline and other databases, making it difficult to develop search strategies that are both sensitive and specific i.e. that will retrieve all relevant studies without too many irrelevant records.\(^1\),\(^2\),\(^3\) This adds an extra burden of time for systematic review authors, who often have to screen thousands of records to find a few relevant to their reviews.

Our objectives for the next two years include:

- setting up a database to house the register
- developing and implementing search strategies and protocols for retrieving relevant studies from Medline
- developing coding to enable accurate retrieval of studies from the register
- developing and implementing a training package for trials search coordinators in how to search for these studies on Medline and screen search results.
- providing support in search strategy development for the authors and trials search coordinators of pilot reviews

http://www.cochrane.org/
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Education and training

• 2-day systematic review workshops
  – How to write a review protocol
    • Plan and structure, search strategy design, rationale for inclusion and exclusion criteria, quality assessment
  – Introduction to analysis and meta-analysis
    • Data extraction, analysis and interpretation

• Finding the evidence
  – One day workshop on how to search the electronic databases

• Workshops with renal conferences
  – WTC 2008 critical appraisal of evidence

• Direct support for reviewers
  – Copies of trial reports
  – Desk space
  – Occasional bursaries, undergraduate summer scholarships
CRG

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  – Producing and updating systematic reviews
  – Renal trials registry
  – Trial registration (prospective)
  – Diagnostic test accuracy studies and reviews
  – Training and support
  – Collaboration
    • Guidelines!
    • new RCTs in clinically relevant areas
    • improved explicitly reported RCTs
Guideline collaborations

- CARI guidelines
- EBPG guidelines
- KDIGO transplant
- Others in discussion
CRG involved in 16 CARI guidelines between 2002 and 2006
EBPG

- 2005 and presently in talks again
- 4 haemodialysis guidelines
  - Dialysis access
  - Nutrition
  - Dialysis strategies
  - Stability
- CRG registry searches
  - 1 guideline comprises up to 20 questions
  - Hard copy
- Diagnostic test search
- Cohort and observational searches
KDIGO transplantation

- All tx related systematic reviews
- all tx-related trial reports from CRG trial register
  - Hard/ electronic copy as required
- searches for diagnostic test accuracy
- PICO tables
  - Iterations
  - 49 questions for transplant
  - 7 questions for DTAS
### 2. Maintenance:

<table>
<thead>
<tr>
<th>Design etc</th>
<th>Population</th>
<th>Intervention/comparator</th>
<th>Outcomes of Interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systematic Reviews (RCTs N ≥ 100)</td>
<td>KTX</td>
<td>Tac vs CSA (CsA or microemulsion) (with AZA, mmf, sirolimus, everolimus)</td>
<td>Same as 1, except:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CNI vs non-CNI regimens</td>
<td>Fracture</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MMF vs AZA</td>
<td>HTN</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MMF formulation vs other MMF formulation</td>
<td>Hyperuricemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CNI-sparing (withdrawal), CNI-free, Steroid withdrawal, Steroid avoidance</td>
<td>Quality of life</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AE: Sirolimus: lipids</td>
</tr>
</tbody>
</table>

### CVD RISK FACTOR

**25, 26, 28, 30, 31 b. CVD Risk Factors Interventions**

<table>
<thead>
<tr>
<th>Design etc</th>
<th>Population</th>
<th>Intervention/comparator</th>
<th>Outcomes of Interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT N≥20 6 mo</td>
<td>KTX, with CVD risk factor</td>
<td>Smoking cessation</td>
<td>Reduction in risk factor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DM: Intensive vs standard</td>
<td>Death</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HTN: ABPM vs Home BP</td>
<td>CVA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Obesity: Weight loss</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hcy: Vitamins</td>
<td></td>
</tr>
</tbody>
</table>

### 28Bc. Renal Artery Stenosis diagnosis

<table>
<thead>
<tr>
<th>Design etc</th>
<th>Population</th>
<th>Intervention/Comparator</th>
<th>Outcomes of Interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort N≥100(?)</td>
<td>KTX</td>
<td>Diagnostic test for RAS</td>
<td>Sn / Sp etc.</td>
</tr>
</tbody>
</table>
CRG delivered output

• Separate file of references by question
• excluding
  – pre-1985 trial reports
  – all conference proceedings abstracts
  – all Transplantation Proceedings reports
  – Trials <100 participants
• Not involved in searching for non RCT evidence
Developing guidelines...

Beware the Puddle of Doom!
Contribution of CRG to the guideline process

Guidelines

- Systems
- Synopses
- Syntheses
- Studies

Examples

- Computerized decision support systems (CDSSs)
- Evidence-based journal abstracts
- Cochrane reviews
- Original published articles in journals

Use Cochrane reviews
Let us help you do reviews
Trials Register

Figure. '4S' levels of organization of evidence from research.
Future involvement?

• Minimise duplication of effort
  – CRG core work
• Maximise efficiency now and future guideline updates
  – Perform the systematic reviews that need doing in parallel to guideline development
  – Harness CRG training and support
• Add-ons
  – Searching for non-randomised studies
  – Potential for spin-off: methodology projects
Editorial team

• Co-ordinating editor
  – Jonathan Craig
• Review group co-ordinator
  – Narelle Willis
• Trials search co-ordinators
  – Gail Higgins
  – Ruth Mitchell
• Administrative assistant
  – Leslee Edwards

• Editors
  – Cecile Couchoud (Fra)
  – Denis Fouque (Fra)
  – Elisabeth Hodson (Aus)
  – Les Irwig (Aus)
  – Bert Kasiske (USA)
  – Petra Macaskill (Aus)
  – Alison MacLeod (UK)
  – Sir Peter Morris (UK)
  – Giuseppe Remuzzi (Ita)
  – Teut Risler (Ger)
  – Paul Roderick (UK)
  – Giovanni Strippoli (Ita)
  – Angela Webster (UK)