What do know improves recruitment to trials: and what might improve the situation?

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What do you think we know?

1. How often do clinical trials fail to recruit to target?

2. Which of the following strategies have been shown to increase recruitment rates?
   a) Open designs
   b) Opt out V Opt in
   c) Telephone reminders
   d) Audiovisual aids
   e) Trial Booklets
   f) Study Questionnaires
   g) Financial Incentives

3. What other strategies might be effective?
   a) Intervention modelling
   b) Via EMRs (Incident, Prevalent)
   c) PBRNs
1. How often do clinical trials fail to recruit to target?

<table>
<thead>
<tr>
<th>Study</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treweek (2007)</td>
<td>50</td>
</tr>
<tr>
<td>McDonald 2006</td>
<td>25</td>
</tr>
<tr>
<td>Foy 2003</td>
<td>50</td>
</tr>
<tr>
<td>Haidich 2001</td>
<td>50</td>
</tr>
<tr>
<td>Charlston 1984</td>
<td>50</td>
</tr>
</tbody>
</table>

Seget S, Optimizing patient recruitment and retention in late stage clinical trials, 2010 Business Insights Ltd
• 45% failed to reach 80% of the pre-specified sample size.
• Sampling frame 60 studies funded by the MRC & HTA
2. What works?

6 comparisons 41 comparisons

Methods to improve recruitment to randomised controlled trials: Cochrane systematic review and meta-analysis

Shaun Treweek, Pauline Lockhart, Marie Pitkethly, Jonathan A Cook, Monica Kjeldström, Marit Johansen, Taina K Taskiela, Frank M Sullivan, Sue Wilson, Catherine Jackson, Ritu Jones, Elizabeth D Mitchell

This is an abridged version of a Cochrane Review previously published in the Cochrane Database of Systematic Reviews 2010, Issue 4, Art. No.: MR000013. DOI: 10.1002/14651858.MR000013.pub5 (see www.thecochranelibrary.com for information). Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and Cochrane Database of Systematic Reviews should be consulted for the most recent version of the review.

ARTICLE SUMMARY

Objective: To identify interventions designed to improve recruitment to randomised controlled trials, and to quantify their effect on trial participation.

Design: Systematic review.

Data sources: The Cochrane Methodology Review Group Specialised Register in the Cochrane Library, MEDLINE, EMBASE, ERIC, Science Citation Index, Social Sciences Citation Index, C2I-SPECTR, the National Research Register and PubMed. Most searches were undertaken up to 2010; no language restrictions were applied.

Study selection: Randomised and quasi-randomised controlled trials, including those recruiting to hypothetical studies. Studies on retention strategies, examining ways to increase questionnaire response or evaluating the use of incentives for clinicians were excluded. The study population included any potential trial participant (eg, patient, clinician and member of the public), or individual or group of individuals.

Key messages:
- There are promising strategies for increasing recruitment to trials, most notably reminders, open trial designs, opt-out and financial incentives.
- Many trials of recruitment methods involve ethical trials, and the applicability of the results to the real world is still unknown.
- There is a dearth of knowledge with regard to the strategies at those recruiting to trials.

Strengths and limitations of this study:
- This Cochrane review utilised a comprehensive search strategy, thereby.
The absence of evidence is not the evidence of absence.

a) Open designs
b) Reducing the burden of consent
c) Telephone reminders
d) Audiovisual aids
e) Trial Booklets
f) Study Questionnaires
g) Financial incentives
Flow of studies into the review.

Articles identified via database search and screened for retrieval (n=16,334)

- Studies excluded following review of abstract (n=16,033)
  - Identified from previous reviews (n=11)
  - Potentially eligible studies retrieved for detailed evaluation (n=312)
    - Studies excluded due to not meeting the inclusion criteria – no recruitment intervention; no randomisation; not recruiting to a trial; reporting retention only; not reporting recruitment results; intervention to improve survey response; opinion piece; review – duplication, or unable to locate or translate (n=267)

Number of randomised controlled trials included in the review (n=45)

a Recruitment with open and blinded trial design.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Open Events</th>
<th>Open Total</th>
<th>Blinded Events</th>
<th>Blinded Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemminki 2004</td>
<td>134</td>
<td>180</td>
<td>233</td>
<td>358</td>
<td>41.8%</td>
<td>1.14 [1.02, 1.28]</td>
</tr>
<tr>
<td>Avenell 2004</td>
<td>1027</td>
<td>2159</td>
<td>796</td>
<td>2136</td>
<td>58.2%</td>
<td>1.28 [1.19, 1.37]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>2339</td>
<td>2494</td>
<td>100.0%</td>
<td></td>
<td></td>
<td>1.22 [1.09, 1.36]</td>
</tr>
</tbody>
</table>

Total events: 1161 (open) vs 1029 (blinded)

Heterogeneity: Tau² = 0.00; Chi² = 2.74, df = 1 (P = 0.10); I² = 64%

Test for overall effect: Z = 3.54 (P = 0.0004)
### Analysis 4.1. Comparison 4 Opt-out consent vs opt-in consent, Outcome: 1 Participant recruited.

**Review:** Strategies to improve recruitment to randomised controlled trials

**Comparison:** 4 Opt-out consent vs opt-in consent

**Outcome:** 1 Participant recruited

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Opt-out n/N</th>
<th>Opt-in n/N</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Weight %</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>40/60 Trevena 2006</td>
<td>44/92</td>
<td></td>
<td></td>
<td>100.0 %</td>
<td>1.39 [1.06, 1.84]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>60</strong></td>
<td><strong>92</strong></td>
<td></td>
<td><strong>100.0 %</strong></td>
<td><strong>1.39 [1.06, 1.84]</strong></td>
</tr>
</tbody>
</table>

- Total events: 40 (Opt-out), 44 (Opt-in)
- Heterogeneity: not applicable
- Test for overall effect: Z = 2.34 (P = 0.019)
- Test for subgroup differences: Not applicable

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**b Opt out V Opt in**
Recruitment with telephone reminder V standard follow-up.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Odds Ratio)</th>
<th>SE</th>
<th>Weight %</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harris 2008</td>
<td>0.405</td>
<td>0.212</td>
<td>60.1</td>
<td>1.50 [0.99, 2.27]</td>
</tr>
<tr>
<td>Nystuen 2004</td>
<td>1.061</td>
<td>0.363</td>
<td>39.9</td>
<td>2.89 [1.42, 5.89]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td>100.0</td>
<td>1.95 [1.04, 3.66]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.13; \chi^2 = 2.44, df = 1 (P = 0.12); I^2 = 59\%$
Test for overall effect: $Z = 2.08 (P = 0.04)$
Recruitment with audiovisual V standard trial information.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>AV information</th>
<th>Standard information</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Du 2008</td>
<td>16</td>
<td>63</td>
<td>10</td>
<td>63</td>
</tr>
<tr>
<td>Du 2009</td>
<td>10</td>
<td>98</td>
<td>6</td>
<td>98</td>
</tr>
<tr>
<td>Hutchison 2007</td>
<td>62</td>
<td>86</td>
<td>66</td>
<td>87</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>247</td>
<td>248</td>
<td>100.0%</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>88</td>
<td>82</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.09$; $\chi^2 = 4.00$, df = 2 ($P = 0.14$); $I^2 = 50$

Test for overall effect: $Z = 0.75$ ($P = 0.46$)
Recruitment with clinical trials booklet V standard trial information.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Trials booklet</th>
<th>Standard information</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>Ellis 2002</td>
<td>12</td>
<td>30</td>
<td>14</td>
</tr>
<tr>
<td>Ives 2001</td>
<td>15</td>
<td>23</td>
<td>11</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>27</td>
<td>53</td>
<td>57</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.11; Chi² = 2.38, df = 1 (P = 0.12), I² = 58%

Test for overall effect: Z = 0.53 (P = 0.59)

Recruitment with invitation including study questionnaire vs standard invitation.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Odds Ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>Odds Ratio</th>
<th>SE</th>
<th>Weight</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harris 2008</td>
<td>-0.105</td>
<td>0.197</td>
<td>44.3%</td>
<td>0.90</td>
<td>0.61, 1.32</td>
<td>44.3%</td>
<td>0.90</td>
</tr>
<tr>
<td>Kendrick 2001</td>
<td>0.372</td>
<td>0.113</td>
<td>55.7%</td>
<td>1.45</td>
<td>1.16, 1.81</td>
<td>55.7%</td>
<td>1.45</td>
</tr>
</tbody>
</table>

Total (95% CI)

Heterogeneity: Tau² = 0.09; Chi² = 4.41, df = 1 (P = 0.04); I² = 77%
Test for overall effect: Z = 0.68 (P = 0.50)
Analysis 40.1.  Comparison 40 Financial incentive vs no incentive, Outcome 1 Participant recruited.

Review: Strategies to improve recruitment to randomised controlled trials
Comparison: 40 Financial incentive vs no incentive
Outcome: 1 Participant recruited

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Financial incentive</th>
<th>No incentive</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed, 95% CI</td>
<td></td>
<td>M-H,Fixed, 95% CI</td>
</tr>
<tr>
<td>Free 2010</td>
<td>13/246</td>
<td>1/245</td>
<td>[ ]</td>
<td>100.0 %</td>
<td>12.95 [ 1.71, 98.21 ]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>246</td>
<td>245</td>
<td></td>
<td>100.0 %</td>
<td>12.95 [ 1.71, 98.21 ]</td>
</tr>
</tbody>
</table>

Total events: 13 (Financial incentive), 1 (No incentive)
Heterogeneity: not applicable
Test for overall effect: Z = 2.48 (P = 0.013)
Test for subgroup differences: Not applicable

Favours no incentive  Favours incentive
What other strategies might be effective?

a) Intervention modelling

b) Via EMRs (Prevalent, Incident)
   i. TrialTorrent
   ii. Searches
      Local
      Integrated with EMR
      Central
   iii. SHARE

c) Practice Based Research Networks
Web-Based Intervention Modelling (WIME) uses the LifeGuide system

www.lifeguideonline.org
Pragmatic randomised trials using routine electronic health records
eLung (Antibiotics in COPD) RetroPro (Statins in 1y prevention)
Embedding recruitment in software

- At appointment booking
- Before appointment
- In waiting room
- In consultation
Remote Query on Central database of EMR data
Key PBRN Concepts when engaging with practices and potential subjects for trial recruitment

- Subject & GP interest
- In research Question
- Hassle Minimisation
- Payment
- Skills
- Infrastructure

Climate
What do you think we know now?

1. How often do clinical trials fail to recruit to target?

2. Which of the following strategies have been shown to increase recruitment rates?
   a) Open designs
   b) Opt out V Opt in
   c) Telephone reminders
   d) Audiovisual aids
   e) Trial Booklets
   f) Study Questionnaires
   g) Financial Incentives

3. What other strategies might be effective?
   a) Intervention modelling
   b) Via EMRs (Incident, Prevalent)
   c) PBRNs
Research Implications

1. Few effective strategies identified
2. Insufficient/Inadequate research
   - 45 papers included
3. Low contribution from primary care
   - 7
     • 4 UK, 1 USA, 1 Can, 1 Aus
4. Novel ideas promising
5. PBRNs offer a valuable laboratory to test new approaches