Individual Participant Data (IPD) Reviews and Meta-analyses

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Director, CRD

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MRC CTU Meta-analysis Group

On behalf of the IPD Meta-analysis Methods Group
IPD systematic review / meta-analysis

• Less common than other types of review but used increasingly
• Described as a gold standard of systematic review
• Can take longer and cost more than other reviews (but perhaps not by as much as might be thought)
• Involve central collection, validation and re-analysis of source, line by line data
History

- Established in cancer & cardiovascular disease since late 1980’s
- Increasingly used in other clinical areas
  - Surgical repair for hernia
  - Drug treatments for epilepsy
  - Anti-platelets for pre-eclampsia in pregnancy
  - Antibiotics for acute otitis media
- Mostly carried out on RCTs of interventions
- Increasingly used with different study types
  - Prognostic or predictive studies
  - Diagnostic studies
- Workshop focus on IPD reviews of RCTs of interventions
Why IPD?

- Results of systematic reviews using IPD can differ from those using aggregate data and lead to different conclusions and implications for practice, e.g.
  - chemotherapy in advanced ovarian cancer
    - MAL: 8 trials (788 pts), OR=0.71, p=0.027
    - IPD: 11 trials (1329 pts), HR=0.93, p=0.30
  - Ovarian ablation for breast cancer
    - MAL: 7 trials (1644 pts), OR=0.86, p>0.05
    - IPD: 10 trials (1746 pts), OR=0.76, p=0.0004
The workshop today

• Process of doing an IPD review, providing practical guidance

• Focus on aspects that differ from a review of aggregate data extracted from publications
  – Data collection
  – Data management and checking
  – Data analysis
  – Practical issues around funding and organisation
Collecting Data
Which trials to collect

• Include all relevant trials published and unpublished
• Unpublished trials not peer reviewed, but
  – Trial protocol data allows extensive ‘peer review’
  – Can clarify proper randomisation, eligibility
  – Quality publication no guarantee of quality data
• Proportion of trials published will vary by
  – Disease, intervention, over time
• Extent of unpublished data can be considerable
Extent of unpublished evidence
Chemoradiation for cervical cancer (initiated 2004)
Which trial level data to collect

• Trial information can be collected on forms accompanying the covering letter and protocol

• Useful to collect trial level data at an early stage to:
  – clarify trial eligibility
  – flag / explore any potential risk of bias in the trial
  – better to exclude trials before IPD have been collected!

• Collecting the trial protocol and data forms is also valuable at this stage
Which trial level data to collect

- Data to adequately describe the study e.g.
  - Study ID and title
  - Randomisation method
  - Method of allocation concealment
  - Planned treatments
  - Recruitment and stopping information
  - Information that is not clear from study report

- ‘Administrative’ data
  - Principal contact details
  - Data contact details
  - Up to date study publication information
  - Other studies of relevance
  - Whether willing to take part in the project
  - Preferred method of data transfer
Example form

**Name:** Prof. Dr. Sobodan Zibnaid
**Your trial protocol number:** (08)

**Name of trial:** Randomized research of combined antineoplastic effects of ionizing radiation and cytostatics in oncology.

Are you willing to take part in this meta-analysis?

If yes, please can you supply a copy of the trial protocol and forms when you return this form.

<table>
<thead>
<tr>
<th>Trial Design</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was informed consent obtained from each patient?</td>
<td>✔</td>
<td>☐</td>
</tr>
</tbody>
</table>

| Date trial opened to accrual: | 11 04 2011 |
| Date trial closed to accrual: | 30 09 2011 |

What method of randomisation was used?

<table>
<thead>
<tr>
<th>Simple</th>
<th>✔</th>
<th>Random blocks</th>
<th>☐</th>
<th>Minimization</th>
<th>☐</th>
<th>Other</th>
</tr>
</thead>
</table>

What method was used to conceal randomisation:

<table>
<thead>
<tr>
<th>Sealed envelope</th>
<th>✔</th>
<th>Central telephones</th>
<th>☐</th>
<th>Other</th>
<th>☐</th>
</tr>
</thead>
</table>

What, if any, stratification factors were used? None used

What proportions was the trial designed to have in each arm (e.g. 1:1 the proportion was 1:1)

<table>
<thead>
<tr>
<th>Early Stopping</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did the trial have a target for patient accrual?</td>
<td>✔</td>
<td>☐</td>
</tr>
<tr>
<td>Did the trial reach its target accrual?</td>
<td>✔</td>
<td>☐</td>
</tr>
</tbody>
</table>

Was a formal stopping rule used? Yes

If a formal stopping rule was not used, what was the reason for stopping the trial?

Data Transfer

Please provide data on all patients randomised. You may complete the data forms provided or supply your data as a computer printout on floppy disk (formatted for PC) or by e-mail. Data can be in almost any format (ASCII, Excel, Dbase, FoxPro, etc.), but please indicate which format has been used. Data files should be encrypted. It would be helpful if you used the coding suggested. However, you may code the data in the way that is most convenient to you. Please supply us with full details of the data coding system used.

Are you able to use the suggested coding? Yes

Which method of data encryption would you prefer? (e.g. WinZip etc.) WinZip

Guarantee of Confidentiality of Individual Trial Results

Data will remain the property of the trial investigator who supplied it and will not be used, circulated or distributed in any way that allows access to individual trial data, without prior seeking the permission of the trial investigator.

I want my data to remain confidential Yes

Signature: [Signature]

Date: 29.09.2006

Please complete and return to:
Claire Vale, Meta-analysis Group, MRC Clinical Trials Unit, 222 Easton Road, London NW1 2DA, UK
Fax: +44 (0)12 7570 4916
**META-ANALYSIS OF CONCOMITANT CHEMORADIOThERAPY FOR LOCALLY ADVANCED CANCER OF THE UTERINE CERVIX**

**Name:** [Redacted]

**Method of Staging**
- Tumour staging: Ultrasound, CT scan, gynecological exam
- Nodal staging: Ultrasound, CT scan, lymphography, MRI if needed

**Measurement of haemoglobin**
- How was haemoglobin measured during treatment? (e.g., on day 1 and then every 2 weeks until the end of treatment)
- Treatment: before treatment and once a week during therapy
- Control: for every control exam

Did your trial include a policy for the treatment of anaemia?  Yes [✓]  No [ ]

If yes, at what level of haemoglobin was anaemia treated?  85 [mg/dL]

What method was used to treat anaemia?  Blood transfusion [✓]  Growth factors [ ]

**Planned Chemotherapy**
- Please describe the planned chemotherapy regimen, e.g.,

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose per cycle (mg/m²)</th>
<th>Given on day(s)</th>
<th>Every</th>
<th>Weeks for</th>
<th>Cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1, 5</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4, 8</td>
<td>1</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

What percentage of patients randomized to the treatment arm only:
- Completed chemotherapy as planned: 86.7%
- Did not start chemotherapy: 5.7%

**Planned Radiotherapy**
- If planned radiotherapy differed for different groups of patients (e.g., by stage), please supply details separately for each.

<table>
<thead>
<tr>
<th>External beam RT (XRT)</th>
<th>Total dose (Gy)</th>
<th>No. of fractions</th>
<th>Duration of XRT (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>46</td>
<td>2.2</td>
<td>35</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Brachytherapy (Brachy)</th>
<th>Total dose point A (Gy)</th>
<th>No. of Insertions</th>
<th>Duration of Brachy (hours / days)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

Planned total duration of all RT (e.g., 55 days XRT + 7 days rest + 14 days Brachy = 76 days) 45 days

**What percentage of all randomized patients:**
- Completed radiotherapy as planned: 86.7%
- Did not start radiotherapy: 5.7%
- Experienced a delay: 6.7%

**Signature:** [Redacted]

**Date:** 10-03-2006

Please complete and return to:
Claire Vaux, Meta-analysis Group, MRC Clinical Trials Unit, 222 Euston Road, London NW1 2DA, UK
Fax: +44 (0)20 7678 4816
Which participant data to collect?

• Collect data on all participants in the study, including any that were excluded from the original study analysis.

• Trial investigators frequently exclude participants from analyses and reports
  – Maybe legitimate reasons for exclusion
  – BUT can introduce bias if related to treatment and outcome
Which participant data to collect?

• May be helpful to think about the analyses and work back to what variables are required
  – Avoid collecting unnecessary data

• Publications can indicate
  – Which data are feasible
  – Note there may be more available than reported

• Provide a provisional list of planned variables in protocol/form to establish feasibility
Which participant data to collect?

• Basic identification of participants
  – anonymous patient ID, centre ID
• Baseline data for description or subgroup analyses
  – age, sex, disease or condition characteristics
• Intervention of interest
  – date of randomisation, treatment allocated
• Outcomes of interest
  – survival, toxicity, pre-eclampsia, wound healing
• Whether excluded from study analysis and reasons
  – ineligible, protocol violation, missing outcome data, withdrawal, ‘early’ outcome
### Example Form

#### Meta-analysis of Concomitant ChemoRadiotherapy for Locally Advanced Cancer of the Uterine Cervix

| Name: | Prof. dr Silvadon Tikarić | Address: Institute for Oncology and Radiology of Serbia, St. Petar B. Vukotića 44, Belgrade, Serbia and Montenegro |
| Name: | dr Aleksandar Trinašević | Address: St. Đorđe G. Jankovića 48/1, Belgrade, Serbia and Montenegro |

If different from above, please give details of the appropriate contact for the collection of your trial data.

- **Are the details of your trial correct?**
  - Yes [✓] No

- **Is the most recent publication of your trial listed in Appendix A of the protocol?**
  - Yes [✓] No

If not, please give details.

- **Do you know of any other relevant trials not listed in Appendix A of the protocol?**
  - Yes [✓] No

If yes, please give details.

#### Which of the following data would you be able to supply for each patient randomised?

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient identifier (preferably not patient name)</td>
<td>[✓]</td>
<td></td>
</tr>
<tr>
<td>Centre identifier</td>
<td>[✓]</td>
<td>[✓]</td>
</tr>
<tr>
<td>Date of birth or age at randomisation</td>
<td>[✓]</td>
<td>[✓]</td>
</tr>
<tr>
<td>Histology</td>
<td>[✓]</td>
<td>[✓]</td>
</tr>
<tr>
<td>Clinical Stage (FIGO)</td>
<td>[✓]</td>
<td>[✓]</td>
</tr>
<tr>
<td>Grade</td>
<td>[✓]</td>
<td>[✓]</td>
</tr>
</tbody>
</table>

#### Local treatment characteristics

<table>
<thead>
<tr>
<th>Surgery</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brachytherapy</td>
<td>[✓]</td>
<td>[✓]</td>
</tr>
</tbody>
</table>

#### Other

<table>
<thead>
<tr>
<th>Whether excluded from the analysis</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
</table>

#### Outcomes

<table>
<thead>
<tr>
<th>Turnover response</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Locoregional progression/recurrence status</td>
<td>[✓]</td>
<td>[✓]</td>
</tr>
<tr>
<td>Date of locoregional recurrence/progression</td>
<td>[✓]</td>
<td>[✓]</td>
</tr>
<tr>
<td>Distant metastases status</td>
<td>[✓]</td>
<td>[✓]</td>
</tr>
<tr>
<td>Date of distant metastases</td>
<td>[✓]</td>
<td>[✓]</td>
</tr>
</tbody>
</table>

#### Exploratory analyses of haemoglobin

<table>
<thead>
<tr>
<th>Pre-treatment haemoglobin</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>On treatment haemoglobin</td>
<td>[✓]</td>
<td>[✓]</td>
</tr>
</tbody>
</table>

#### Signature:

![Signature]

Date: 23.03.2006

Please complete and return with a copy of the trial protocol to:

Claire Vale, Meta-analysis Group, MRC Clinical Trials Unit, 222 Euston Road, London NW1 2DA, UK
Fax: +44 (0)20 7670 4615
IPD variable definitions

- Form the basis of the meta-analysis database
- Define variables in a way that is unambiguous and facilitates data collection and analysis
IPD variable definitions
Chemoradiation for cervical cancer

✓ **Age**
  age in years
  unknown = 999

✓ **Survival status**
  0 = Alive
  1 = Dead

✓ **Date of death or last follow-up**
  date in dd/mm/yy format
  unknown day = --/mm/yy
  unknown month = --/--/yy
  unknown date = --/--/--

✓ **Performance status**
  Accept whatever scale is used, but request details of the system used

✓ **Tumour stage**
  1 = Stage Ia
  2 = Stage Ib
  3 = Stage IIa
  4 = Stage IIb
  5 = Stage IIIa
  6 = Stage IIIb
  7 = Stage IVa
  8 = Stage IVb
  9 = Unknown
IPD variable definitions
Anti-platelet therapy for pre-eclampsia in pregnancy

✓ Pre-eclampsia
  Highest recorded systolic BP in mmHg

  Highest recorded diastolic BP in mmHg

  Proteinurea during this pregnancy
  0 = no
  1 = yes
  9 = unknown

  Date when proteinurea first recorded

These variables allow common definition of pre-eclampsia and early onset pre-eclampsia
IPD variable definitions

Anti-platelet therapy for pre-eclampsia in pregnancy

- **Gestation at randomisation**
  Gestation in completed weeks
  9 = unknown
  
  Poor choice of code for missing value, woman could be randomised at 9 weeks gestation

- **Severe maternal morbidity**
  1 = none
  2 = stroke
  3 = renal failure
  4 = liver failure
  5 = pulmonary oedema
  6 = disseminated intravascular coagulation
  7 = HELP syndrome
  8 = eclampsia
  9 = not recorded

Collection as a single variable does not allow the possibility of recording more than one event
### Meta-analysis of Concomitant ChemoRadiotherapy for Locally Advanced Cancer of the Uterine Cervix

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Suggested Coding</th>
<th>Local treatment characteristics</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Date of birth</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date in dd/mm/yy or dd/mm/yyyy format.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown day –/mm/yy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown month dd/–/yy</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Unknown date –/-/-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 squamous</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 adenosquamous</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 adenocarcinoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 other</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 unknown</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clinical Stage (FIGO)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 IA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 IB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 IIA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 IIB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 IIIA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 IIIB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 IVA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 IVB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 unknown</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Grade</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 well differentiated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 moderately differentiated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 poorly differentiated / undifferentiated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 unknown</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Performance status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Code as convenient, but please supply full details of the system used (e.g. ECOG, Karnosky, WHO, CMS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pelvic lymph node involvement</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 not involved</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 involved</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 unknown</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Para-aortic lymph node involvement</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 not involved</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 involved</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 unknown</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Surgery</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 no</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 hysterectomy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 hysterectomy + pelvic lymphadenectomy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 hysterectomy + pelvic + para-aortic lymphadenectomy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 other</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 unknown</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>External beam radiotherapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 no</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 pelvic field</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 extended field (pelvic + para-aortic)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 other</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 unknown</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Brachytherapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 no</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 unknown</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Survival Status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 alive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 dead</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dates of death or last follow up</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date in dd/mm/yy or dd/mm/yyyy format.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Loco-regional progression / recurrence status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 no progression / recurrence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 progression / recurrence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Date of loco-regional progression / recurrence</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date in dd/mm/yy or dd/mm/yyyy format.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Distant metastases status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 no metastases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 metastases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Date of distant metastases</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Acute toxicity data</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haematological toxicity (any)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemoglobin toxicity / anaemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
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Data collection: Principles

• Flexible data formats
  – Data forms, database printout, flat text file (ASCII), spreadsheet (e.g. Excel), database (e.g. Dbase, Foxpro), other (e.g. SAS dataset)

• Accept transfer by electronic or other means
  – Chemotherapy for ovarian cancer (published 1991)
    44% on paper, 39% on disk, 17% by e-mail
  – Chemotherapy for bladder cancer (published 2003)
    10% on paper, 10% on disk, 80% by e-mail
  – Chemoradiation for cervical cancer (published 2008)
    100% by e-mail
Data collection: Principles

• Accept trialists coding and re-code
  – But suggest data coding (most people use it)

• Security issues
  – Request anonymous patient IDs
  – Encrypt electronic transfer data
  – Secure ftp transfer site

• Offer assistance
  – Site visit, language translation, financial?
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...
Data management and checking
General principles

• Use same rigor as for running a trial
  – Improved software automates more tasks
• Retain copy of study data as supplied
• Convert incoming data to database format
  – Excel, Access, Foxpro, SPSS, SAS, Stata (Stat Transfer)
• Re-code data to meta-analysis coding and calculate or transform derived variables
  – Record all changes to trial data
• Check, query and verify data with trialist
  – Record all discussions and decisions made
• Add study to meta-analysis database
Rationale

• Reasons for checking
  – Not to centrally police trials or to expose fraud
  – Improve accuracy of data
  – Ensure appropriate analysis
  – Ensure all study participants are included
  – Ensure no non-study participants are included
  – Improve follow-up

• Reduce the risk of bias
What are we checking?

• All study designs
  – Missing data, excluded participants
  – Internal consistency and range checks
  – Compare baseline characteristics with publication
    • May differ if IPD has more participants
  – Reproduce analysis of primary outcome and compare with publication
    • May differ if IPD has more participants, better follow-up, etc.
What are we checking? E.g.

- **Published analysis:**
  - Based on 243 patients
    - 25 excluded
  - Control arm (116 pts)
    - Median age 38
    - Range 20-78
  - HR estimate for overall survival
    - 0.51 (p=0.007)

- **IPD supplied for MA**
  - Based on 268 patients
    - All randomised
  - Control arm (133 pts)
    - Median age 39
    - Range 20-78
  - HR estimate for overall survival
    - 0.46 (p<0.001)
What are we checking?

- For RCTs
  - Balance across arms and baseline factors
  - Pattern of randomisation
- For long term outcomes
  - Follow-up up-to-date and equal across arms
Data checking: Pattern of randomisation

Chemoradiation for cervical cancer

![Graph showing the pattern of randomisation for patients with cervical cancer, comparing Chemoradiation and Control groups. The graph plots the number of patients randomised over time, with dates ranging from January 1987 to November 1990. The Chemoradiation group shows a steady increase in the number of patients randomised, while the Control group shows a similar trend but at a lower rate.](image-url)
Data checking: Pattern of randomisation

Radiotherapy vs Chemotherapy in Multiple Myeloma
Data checking: Weekday randomised
Chemotherapy for bladder cancer

Number of randomisations

ARM
- Neoad CT
- Control

MONDAY
- Neoad CT: 35
- Control: 30

TUESDAY
- Neoad CT: 34
- Control: 28

WEDNESDAY
- Neoad CT: 32
- Control: 24

THURSDAY
- Neoad CT: 21
- Control: 16

FRIDAY
- Neoad CT: 33
- Control: 29
Data checking: Weekday randomised
Post-operative radiotherapy in lung cancer

Number of randomisations

Arm
- RT
- Control

Weekday randomised

Post-operative radiotherapy in lung cancer

Number of randomisations

Arm
- RT
- Control

Weekday randomised

Post-operative radiotherapy in lung cancer
Querying and verifying

• Query any errors, inconsistencies, unusual patterns etc. with trialist

• When all queries resolved as far as possible
  – Send tables, data and trial analysis to trialist for verification

• Then append trial to meta-analysis database
Analysis and reporting
Planning analyses

• Pre-specify in the protocol
  – Main analyses of outcomes
    • by trial characteristics
    • by patient characteristics
      – Usually only possible with IPD
  – Sensitivity analyses
  – Planned areas for exploratory analyses (e.g. prognostic factors, baseline risk etc.)

• Provide clear details of methods
2-stage analysis: General principles

- Most common
- Same summary statistics used
  - hazard ratio, odds ratio, risk ratio, mean difference...
- Derive summary measures from IPD for each trial
- Combine in meta-analysis, stratified by trial
- Statistical output looks similar to summary data meta-analysis
- Results displayed on forest plot
- Easy to implement

Exploring trial-level differences

• ‘Subgroup’ analysis or meta-regression by trial characteristics
  – Group by treatments, dose, treatment scheduling
• Compares the size of treatment effect on outcome across different trial groups
  – Test for interaction
• Easy to do with published summary data or IPD
• May obtain more trial-level data when collecting IPD

• Alternatively explore through sensitivity analyses
### Exploring trial-level differences

**Chemotherapy for bladder cancer**

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<tbody>
<tr>
<td></td>
<td>CT</td>
<td>Control</td>
<td></td>
</tr>
<tr>
<td><strong>Wallace [2]</strong></td>
<td>59/83</td>
<td>50/76</td>
<td></td>
</tr>
<tr>
<td><strong>Martinez-Pineiro [3]</strong></td>
<td>43/62</td>
<td>38/59</td>
<td></td>
</tr>
<tr>
<td><strong>Raghavan [2]</strong></td>
<td>34/41</td>
<td>37/55</td>
<td></td>
</tr>
<tr>
<td><strong>Sub-total</strong></td>
<td>136/186</td>
<td>125/190</td>
<td></td>
</tr>
<tr>
<td><strong>Cortesi unpublished</strong></td>
<td>43/82</td>
<td>41/71</td>
<td></td>
</tr>
<tr>
<td><strong>Grossman [10]</strong></td>
<td>98/158</td>
<td>108/159</td>
<td></td>
</tr>
<tr>
<td><strong>Bassi [5]</strong></td>
<td>53/102</td>
<td>60/104</td>
<td></td>
</tr>
<tr>
<td><strong>MRC/EORTC [9]</strong></td>
<td>275/491</td>
<td>301/485</td>
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</tr>
<tr>
<td><strong>Malmström [4]</strong></td>
<td>68/151</td>
<td>84/160</td>
<td></td>
</tr>
<tr>
<td><strong>Sherif [7]</strong></td>
<td>79/158</td>
<td>90/159</td>
<td></td>
</tr>
<tr>
<td><strong>Sengeløv [8]</strong></td>
<td>70/78</td>
<td>60/75</td>
<td></td>
</tr>
<tr>
<td><strong>Sub-total</strong></td>
<td>686/1220</td>
<td>744/1213</td>
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</tr>
<tr>
<td><strong>Total</strong></td>
<td>822/1406</td>
<td>869/1403</td>
<td>46.75</td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>O-E</th>
<th>Variance</th>
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</thead>
<tbody>
<tr>
<td>Wallace [2]</td>
<td>2.74</td>
<td>27.18</td>
</tr>
<tr>
<td>Martinez-Pineiro [3]</td>
<td>0.33</td>
<td>20.11</td>
</tr>
<tr>
<td>Raghavan [2]</td>
<td>5.85</td>
<td>16.51</td>
</tr>
<tr>
<td>Sub-total</td>
<td>8.92</td>
<td>63.80</td>
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<tr>
<td>Cortesi unpublished</td>
<td>-1.87</td>
<td>20.84</td>
</tr>
<tr>
<td>MRC/EORTC [9]</td>
<td>-23.69</td>
<td>143.61</td>
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<tr>
<td>Sherif [7]</td>
<td>-6.37</td>
<td>42.18</td>
</tr>
<tr>
<td>Sengeløv [8]</td>
<td>1.79</td>
<td>31.96</td>
</tr>
<tr>
<td>Sub-total</td>
<td>-55.67</td>
<td>355.65</td>
</tr>
</tbody>
</table>

**Hazard Ratio**

- HR=1.15 p=0.264
- HR=0.86 p=0.003
- HR=0.89 p=0.022

**Interaction** p=0.029
Exploring patient-level differences

- Subgroup analyses by patient characteristics
  - Age, sex, tumour stage, tumour grade
- Compares size of treatment effect across patient subgroups (not prognosis)
  - Test for interaction or trend
- Difficult or unreliable with summary data
- Easy to do with IPD which allows
  - Many combinations of subgroups and outcomes
  - Consistent definition of subgroups across trials
Exploring patient-level differences
Post-operative radiotherapy for lung cancer

Hazard Ratio

Age
- \( \leq 54 \)
- 55-59
- 60-64
- \( \geq 65 \)

Sex
- Female
- Male

Histology
- Adenocarcinoma
- Squamous
- Other

Test for trend
\( p=0.335 \)

Test for interaction
\( p=0.944 \)

Test for interaction
\( p=0.751 \)
Exploring patient-level differences
Chemoradiotherapy for cervical cancer

Survival

<table>
<thead>
<tr>
<th>Group</th>
<th>Hazard Ratio</th>
<th>Test for trend: p=0.017</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a-2a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3a-4a</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Disease free survival

<table>
<thead>
<tr>
<th>Group</th>
<th>Hazard Ratio</th>
<th>Test for trend: p=0.073</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a-2a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3a-4a</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
2-stage: Software

• Most IPD groups use own software
  – MRC (SCHARP) does 2-stage analyses and produces tabular and graphical output

• Input into RevMan5
  – Primary analysis needs to be done elsewhere
  – For time-to-event outcomes use “O-E/V” or “generic inverse variance” outcome type
  – For others use appropriate outcome type e.g. “dichotomous” for risk ratios, etc
  – Not easy to enter (patient level) subgroup analyses, but can upload figures from elsewhere
1-stage analysis: General principles

• Less common, but becoming used more frequently
• Regression/modelling approach stratified or adjusted by trial
• Can explore simultaneously impact of trial and patient characteristics on treatment effect
• Needs greater statistical and programming expertise
• Output will look different (often tabular)
1-stage: Software

- Any statistical package
  - SPSS, SAS, S-PLUS, R, etc.
- Use regression analysis
  - linear, logistic, Cox, Poisson, etc.
- Unless more complex models are required
  - E.g. multi-level models and MLwiN
- Forest plots can be made in RevMan, excel, CMA or MIX
1-stage: Example

Cervical stitch (cerclage) for preventing pregnancy loss

• No benefit in Cochrane review and heterogeneity
• IPD collected to investigate further
• Multilevel logistic regression of RCTs
  – Stratified by trial
  – Included treatment, obstetric history, cervical length, multiple gestation
• Cerclage may reduce pregnancy loss or neonatal death before discharge from hospital
• Cerclage in multiple pregnancies should be avoided
• Efficacy of cerclage was not influenced by either cervical length or obstetric history
Analysis: Sensitivity

• Assess the robustness of main IPD results e.g.
  – With and without a particular trial
  – With or without particular types of patients (excluded in a consistent way across all trials)

• Compared to published data when IPD could not be obtained
  – Important because if unavailability of data related to findings would introduce bias
  – Less important where a high percentage of the known randomised data has been obtained
Practical issues
Organisation

• Carried out by international collaborative group
  – Small local project management group
  – Multi-disciplinary advisory group
  – Trialists who provide data

• Developing and maintaining this group requires good organisation, good communication and often careful management
  – Cultural and language barriers
  – Powerful individuals/groups
Initiating collaboration

• Initial letter regarding collaboration explaining
  – Why a systematic review is needed
    • Highlight the benefits of IPD over aggregate data
  – Main aims and objectives
  – Importance of the collaborative group
  – Offer an official agreement re:
    • Confidentiality of data
    • Publication policy (published under ‘group’ name)
  – Include (draft) review protocol
• If necessary, arrange a meeting
Maintaining contact with trialists

• Important to maintain good communication throughout
  – Regular correspondence
    • Newsletters
    • E-mails

• Often deal with more than one person per trial
  – Clinical coordinator, statistician, data centre
  – Keep everyone informed with no crossed wires
Collaborators’ meeting

• Integral part of IPD approach
• IPD meta-analyses are collaborative projects
• Incentive to collaborate
• Trialists have opportunity to
  – Discuss results and challenge analyses
  – Discuss interpretation & implication of results
  – Suggest new research
  – Decide on conference/journal
• Sets a deadline to which project team and trialists have to work
Presenting and publishing results

• Project management group draft presentation / report with input from Advisory Group
  – According to PRISMA
• Circulate to all collaborators for comment once, twice..
  – Summarise and respond to comments
  – Achieve consensus (or compromise) in presentation / report
• In name of (or on behalf of) collaborative group
  – Present at conference
  – Submit to journal
  – Submit to CDSR
Resource and Funding

• IPD reviews more resource intensive than other types of systematic review
  – Tend to be initiated by research groups and the day to day work undertaken by paid staff.
  – Some groups indicated that obtaining funding for IPD reviews can be difficult

• Surveyed IPD MA MG to find out why funding applications failed/succeeded
  – Feedback used to compile list of “top tips”
  – May be useful to researchers submitting a funding application
Funding applications: Top Tips

• Show that project group has IPD MA experience
  – Emphasise experience of team and/or research institute
  – Collaborate with a more experienced group
  – Form an Advisory Group containing members with statistical, clinical and IPD meta-analysis experience

• Describe aims/methodology clearly and explicitly
  – Important if funder has no direct experience of IPD MAs
Funding applications: Top Tips

• Explain the importance of using IPD
  – Why question can only be addressed using IPD
    • If this is not the case, should you really be doing it?
  – What IPD review offers over a published data review
    • e.g. clinical importance of particular patient subset
      – Only really feasible with IPD

• Be clear about extent/cost of resources requested
  – Why an IPD meta-analysis might require more resource than a conventional published data meta-analysis
Funding applications: Top Tips

• Anticipating funders concerns:
  – Provide reassurance about obtaining the raw data, e.g.
    • Obtain data agreements in advance
    • Provide evidence of successfully obtaining data for past projects
  – Demonstrate value for money
    • Question could be answered without the need for a new trial
  – Additional projects that could add value for money? e.g.
    • Improving methodology
    • Prognostic sub-studies
Summary
Improve data quality

• Obtain more extensive, complete and appropriate data
  – Get round poor, incomplete or absence of reporting
  – Check data to reveal errors and potential biases which may be rectified, accounted for, or described
  – Consistent outcome and baseline data across studies
  – Establish new definitions of outcomes
  – Combine / transform different scales into a common scale
  – Collect up-to-date or long-term follow up where appropriate

• Assess risk of bias based on underlying data not study reports
## Benefits of IPD

<table>
<thead>
<tr>
<th>Entry</th>
<th>Judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Yes</td>
<td><strong>Random number list. Also, data checks on IPD provided suggest adequate sequence generation</strong></td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td><strong>Central telephone</strong></td>
</tr>
<tr>
<td>Blinding? (Patient-reported outcomes)</td>
<td>Yes</td>
<td>Quote: “double blind, double dummy”; “High and low dose tablets or capsules were indistinguishable in all aspects of their outward appearance. For each drug an identically matched placebo was available (the success of blinding was evaluated by examining the drugs before distribution).” Comment: Probably done.</td>
</tr>
<tr>
<td>Blinding? (Mortality)</td>
<td>Yes</td>
<td>Obtained from medical records; review authors do not believe this will introduce bias.</td>
</tr>
<tr>
<td>Incomplete outcome data addressed? (Short-term outcomes (2-6 wks))</td>
<td>Yes</td>
<td><strong>IPD supplied for all randomised patients and for all outcomes of interest</strong></td>
</tr>
<tr>
<td>Incomplete outcome data addressed? (Longer-term outcomes (&gt;6 wks))</td>
<td>Yes</td>
<td><strong>IPD supplied for all randomised patients and for all outcomes of interest</strong></td>
</tr>
<tr>
<td>Free of selective reporting?</td>
<td>Yes</td>
<td><strong>IPD supplied for all outcomes</strong></td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>No</td>
<td><strong>Stopped early, but extra follow-up data supplied</strong></td>
</tr>
</tbody>
</table>
Improve analysis quality

- Effects for each study derived from IPD rather than relying on reported estimates
- Consistent and appropriate analyses across studies
  - Analyse by intention-to-treat
  - Better analysis of different study designs e.g. 3-arm or factorial designs
- Better exploration of effects at participant level
  - Assess if effect differs across participant subgroups
- Allows from simple through to complex modelling approaches
Further benefits

• Improve trial identification, interpretation and dissemination via collaborative approach

• Collaboration can lead directly to new trials and other studies

• Improve methods for IPD and other meta-analyses
  – Use IPD as resource for methodological research
    • e.g. Exploring sources of bias, analysis methods, imputing missing data etc.
  – See list on IPD MA Methods Group website
That’s all there is to it!

• Visit IPD Meta-analysis Methods Group website
  – www.ctu.mrc.ac.uk/cochrane/ipdmg
  – Stewart & Tierney. To IPD or Not to IPD? Advantages and disadvantages of systematic reviews using individual patient data. Eval Health Prof 2002;25(1):76-97.

• For specific advice or to join IPD Methods Group
  – Contact Methods Group at IPD@ctu.mrc.ac.uk