Individual Participant Data (IPD) Reviews and Meta-analyses

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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

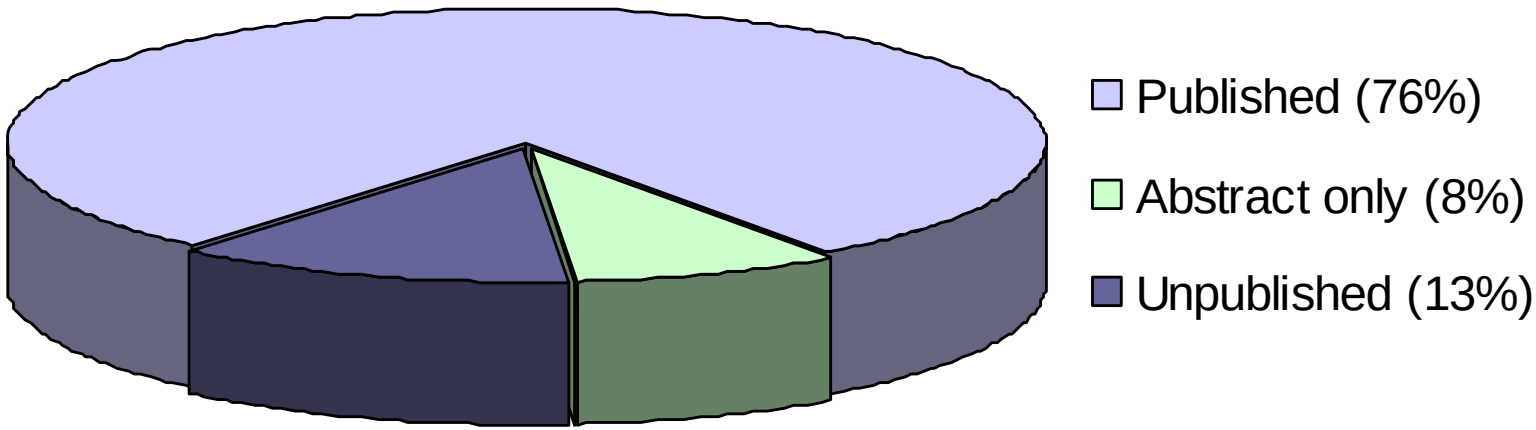
Collecting Data

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- Include all relevant trials published and unpublished
- Unpublished trials not peer reviewed, but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- Extent of unpublished data can be considerable

Extent of unpublished evidence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

META-ANALYSIS OF CONCOMITANT CHEMORADIOTHERAPY FOR LOCALLY ADVANCED CANCER OF THE UTERINE CERVIX

Name: Prof. dr Slobodan Čikarić Your trial/protocol number: 1683

Name of trial: Randomized research of combined antitumorous effects of ionizing irradiation and cytostatics in oncogynecology

Are you willing to take part in this meta-analysis? Yes ☑ No ☐

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

Trial Design

Was informed consent obtained from each patient? Yes ☑ No ☐

Date trial opened to accrual: dd 08 mm 04 yy 08 Date trial closed to accrual: dd 21 mm 03 yy 05

What method of randomisation was used?

Simple ☑ Permuted blocks ☐ Minimisation ☐ Other ____

What method was used to conceal randomisation:

Sealed envelope ☑ Central telephone ☐ Other ____

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

Early Stopping

	Yes	No		Yes	No
Did the trial have a target for patient accrual?	☑	☐	Did the trial stop early?	☐	☑
Did the trial reach its target accrual?	☑	☐	Was a formal stopping rule used?	☐	☐

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 ☑ No ☐

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

Guarantee of Confidentiality of Individual Trial Results

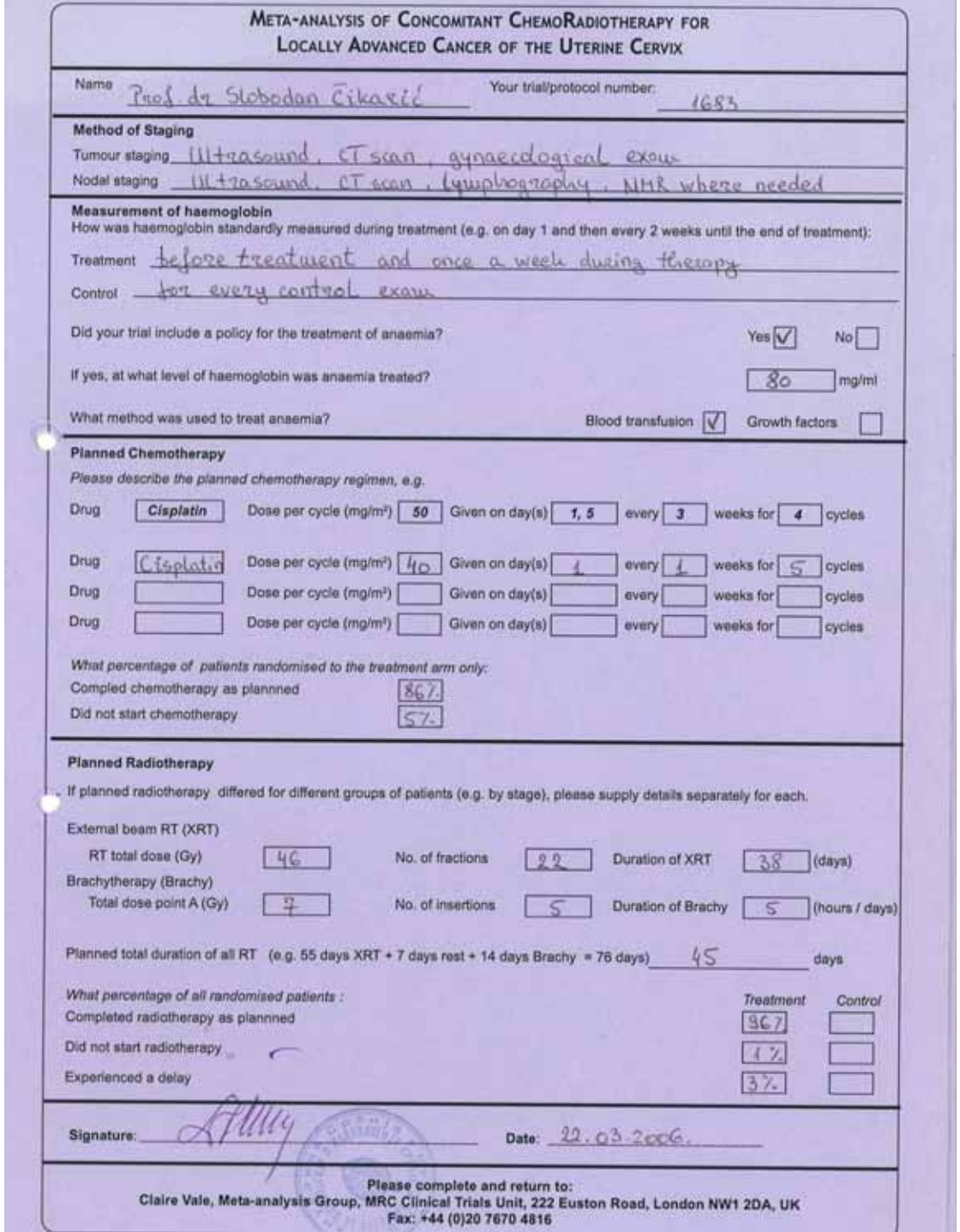
Data will remain the property of the trial investigator who supplied it and will not be used, circulated or distributed in any way that allows access to individual trial data, without first seeking the permission of the trial investigator.

I want my data to remain confidential Yes ☑ No ☐

Signature: [signature] Date: 22.03.2006

Please complete and return to:
Claire Vale, Meta-analysis Group, MRC Clinical Trials Unit, 222 Euston Road, London NW1 2DA, UK
Fax: +44 (0)20 7670 4816

Example form



META-ANALYSIS OF CONCOMITANT CHEMORADIOTHERAPY FOR LOCALLY ADVANCED CANCER OF THE UTERINE CERVIX

Name: Prof dr Slobodan Cikarić — Your trial/protocol number: 1683

Method of Staging

Tumour staging: Ultrasound, CT scan, gynaecological exam

Nodal staging: Ultrasound, CT scan, lymphography, NMR where needed

Measurement of haemoglobin

How was haemoglobin standardly 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? 80 mg/ml

What method was used to treat anaemia? Blood transfusion ☑ Growth factors ☐

Planned Chemotherapy

Please describe the planned chemotherapy regimen, e.g.

Drug	Cisplatin	Dose per cycle (mg/m²)	50	Given on day(s)	1, 5	every	3	weeks for	4 cycles
Drug	Cisplatin	Dose per cycle (mg/m²)	40	Given on day(s)	1	every	1	weeks for	5 cycles
Drug		Dose per cycle (mg/m²)		Given on day(s)		every		weeks for	cycles
Drug		Dose per cycle (mg/m²)		Given on day(s)		every		weeks for	cycles

What percentage of patients randomised to the treatment arm only:

Compled chemotherapy as plannned: 86%

Did not start chemotherapy: 5%

Planned Radiotherapy

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

External beam RT (XRT)

RT total dose (Gy): 46 — No. of fractions: 22 — Duration of XRT: 38 (days)

Brachytherapy (Brachy)

Total dose point A (Gy): 7 — No. of insertions: 5 — Duration of Brachy: 5 (hours / days)

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 randomised patients :	*Treatment*	*Control*
Completed radiotherapy as plannned	96%	
Did not start radiotherapy	1%	
Experienced a delay	3%	

Signature: [signature] Date: 22.03.2006.

Please complete and return to:
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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

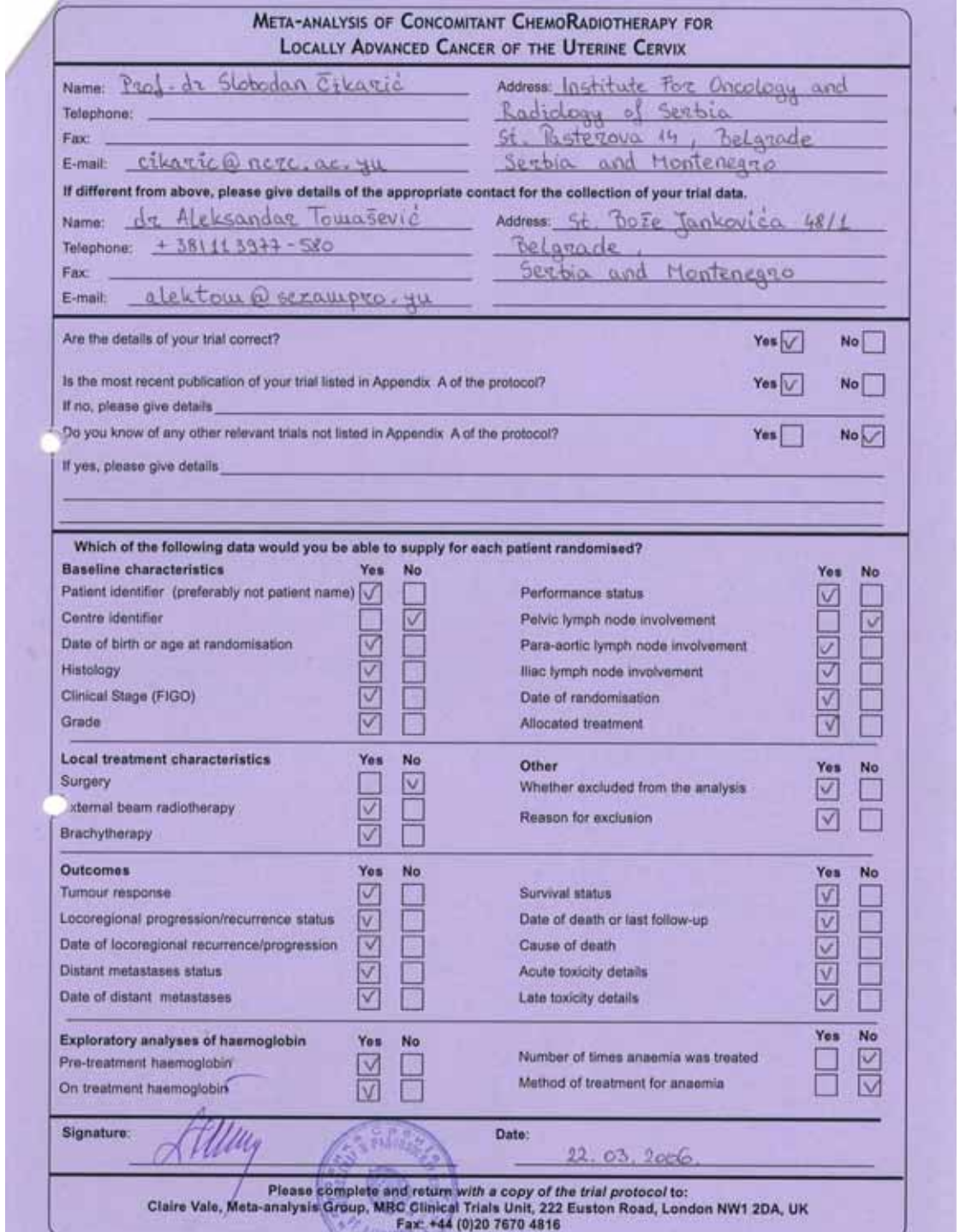
Which participant data to collect?

- 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 Slobodan Čikarić
Telephone:
Fax:
E-mail: cikaric@nerc.ac.yu
Address: Institute For Oncology and Radiology of Serbia St. Pasterova 14, Belgrade Serbia and Montenegro

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

Name: dr Aleksandar Tomašević
Telephone: + 381 11 3977-580
Fax:
E-mail: alektom@sezampro.yu
Address: St. Bože Jankovića 48/1 Belgrade, Serbia and Montenegro

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 no, 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?

Baseline characteristics	Yes	No		Yes	No
Patient identifier (preferably not patient name)	☑	☐	Performance status	☑	☐
Centre identifier	☐	☑	Pelvic lymph node involvement	☐	☑
Date of birth or age at randomisation	☑	☐	Para-aortic lymph node involvement	☑	☐
Histology	☑	☐	Iliac lymph node involvement	☑	☐
Clinical Stage (FIGO)	☑	☐	Date of randomisation	☑	☐
Grade	☑	☐	Allocated treatment	☑	☐

Local treatment characteristics	Yes	No	Other	Yes	No
Surgery	☐	☑	Whether excluded from the analysis	☑	☐
External beam radiotherapy	☑	☐	Reason for exclusion	☑	☐
Brachytherapy	☑	☐			

Outcomes	Yes	No		Yes	No
Tumour response	☑	☐	Survival status	☑	☐
Locoregional progression/recurrence status	☑	☐	Date of death or last follow-up	☑	☐
Date of locoregional recurrence/progression	☑	☐	Cause of death	☑	☐
Distant metastases status	☑	☐	Acute toxicity details	☑	☐
Date of distant metastases	☑	☐	Late toxicity details	☑	☐

Exploratory analyses of haemoglobin	Yes	No		Yes	No
Pre-treatment haemoglobin	☑	☐	Number of times anaemia was treated	☐	☑
On treatment haemoglobin	☑	☐	Method of treatment for anaemia	☐	☑

Signature:
Date: 22.03.2006.

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 4816

IPD variable definitions

- Form the basis of the meta-analysis database
- Define variables in 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

Example coding

META-ANALYSIS OF CONCOMITANT CHEMORADIOTHERAPY FOR LOCALLY ADVANCED CANCER OF THE UTERINE CERVIX

Suggested Coding

Baseline characteristics

Date of birth

Date in dd/mm/yy or dd/mm/yyyy format.
Unknown day --/mm/yy
Unknown month dd/--/yy
Unknown date --/--/--

Histology

1 squamous
2 adenosquamous
3 adenocarcinoma
7 other
9 unknown

Clinical Stage (FIGO)

1 IA
2 IB
3 IIA
4 IIB
5 IIIA
6 IIIB
7 IVA
8 IVB
9 unknown

Grade

1 well differentiated
2 moderately differentiated
3 poorly differentiated / undifferentiated
9 unknown

Performance status

Code as convenient, but please supply full details of the system used (e.g. ECOG, Karnofsky, WHO, OMS)

Pelvic lymph node involvement

0 not involved
1 involved
9 unknown

Para-aortic lymph node involvement

0 not involved
1 involved
9 unknown

Local treatment characteristics

Surgery

0 no
1 hysterectomy
2 hysterectomy + pelvic lymphadenectomy
3 hysterectomy + pelvic + para-aortic lymphadenectomy
7 other
9 unknown

External beam radiotherapy

0 no
1 pelvic field
2 extended field (pelvic + para-aortic)
7 other
9 unknown

Brachytherapy

0 no
1 yes
9 unknown

Outcomes

Survival Status

0 alive
1 dead

Dates of death or last follow up

Date in dd/mm/yy or dd/mm/yyyy format (as for date of birth)

Loco-regional progression / recurrence status

0 no progression / recurrence
1 progression / recurrence

Date of locoregional progression / recurrence

Date in dd/mm/yy or dd/mm/yyyy format (as for date of birth).

Distant metastases status

0 no metastases
1 metastases

Date of distant metastases

Toxicity

Acute toxicity data

Haematological toxicity (any)
Haemoglobin toxicity / anaemia
Thrombocytopenia
White blood cell toxicity (any)
Gastrointestinal toxicity (any)
Genitourinary toxicity (any)
Skin toxicity (any)
Other toxicity (any)
Please supply the most severe grade experienced for each category. Code as convenient giving full details of the grading system used (e.g. CTC, etc).

Late toxicity data

Intestinal toxicity (any)
Rectal toxicity (any)
Bladder toxicity (any)
Vaginal toxicity (any)
Other toxicity (any)

Please supply the most severe grade experienced for each category. Code as convenient giving full details of the grading system used (e.g. CTC, etc).

Other

Whether excluded from the analysis

0 no
1 yes
9 unknown

Reason for exclusion

Supply as convenient but please provide details, for example:
ineligible - too old
ineligible - metastatic disease found after randomisation
protocol violation - clinician withdrew patient
lost to follow-up - patient withdrew from trial
etc.

Exploratory analysis of haemoglobin

Pre-treatment haemoglobin

Precise definitions and coding will be

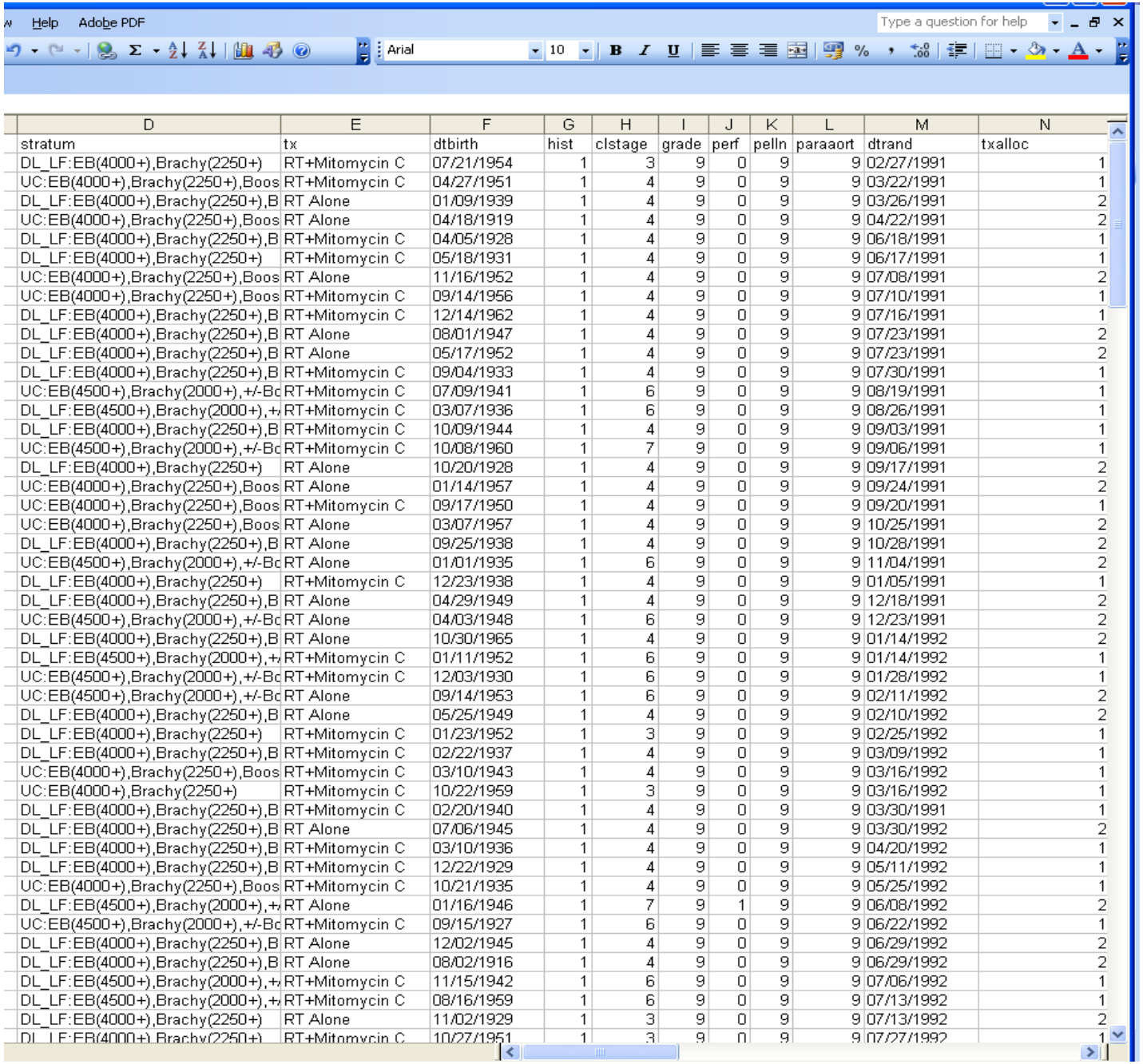
Data collection: Principles

- 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?



Help Adobe PDF

Type a question for help

Arial 10

D	E	F	G	H	I	J	K	L	M	N
stratum	tx	dtbirth	hist	clstage	grade	perf	pelln	paraaort	dtrand	txalloc
DL_LF:EB(4000+),Brachy(2250+)	RT+Mitomycin C	07/21/1954	1	3	9	0	9	9	02/27/1991	1
UC:EB(4000+),Brachy(2250+),Boos	RT+Mitomycin C	04/27/1951	1	4	9	0	9	9	03/22/1991	1
DL_LF:EB(4000+),Brachy(2250+),B	RT Alone	01/09/1939	1	4	9	0	9	9	03/26/1991	2
UC:EB(4000+),Brachy(2250+),Boos	RT Alone	04/18/1919	1	4	9	0	9	9	04/22/1991	2
DL_LF:EB(4000+),Brachy(2250+),B	RT+Mitomycin C	04/05/1928	1	4	9	0	9	9	06/18/1991	1
DL_LF:EB(4000+),Brachy(2250+)	RT+Mitomycin C	05/18/1931	1	4	9	0	9	9	06/17/1991	1
UC:EB(4000+),Brachy(2250+),Boos	RT Alone	11/16/1952	1	4	9	0	9	9	07/08/1991	2
UC:EB(4000+),Brachy(2250+),Boos	RT+Mitomycin C	09/14/1956	1	4	9	0	9	9	07/10/1991	1
DL_LF:EB(4000+),Brachy(2250+),B	RT+Mitomycin C	12/14/1962	1	4	9	0	9	9	07/16/1991	1
DL_LF:EB(4000+),Brachy(2250+),B	RT Alone	08/01/1947	1	4	9	0	9	9	07/23/1991	2
DL_LF:EB(4000+),Brachy(2250+),B	RT Alone	05/17/1952	1	4	9	0	9	9	07/23/1991	2
DL_LF:EB(4000+),Brachy(2250+),B	RT+Mitomycin C	09/04/1933	1	4	9	0	9	9	07/30/1991	1
UC:EB(4500+),Brachy(2000+),+/-Bc	RT+Mitomycin C	07/09/1941	1	6	9	0	9	9	08/19/1991	1
DL_LF:EB(4500+),Brachy(2000+),+/	RT+Mitomycin C	03/07/1936	1	6	9	0	9	9	08/26/1991	1
DL_LF:EB(4000+),Brachy(2250+),B	RT+Mitomycin C	10/09/1944	1	4	9	0	9	9	09/03/1991	1
UC:EB(4500+),Brachy(2000+),+/-Bc	RT+Mitomycin C	10/08/1960	1	7	9	0	9	9	09/06/1991	1
DL_LF:EB(4000+),Brachy(2250+)	RT Alone	10/20/1928	1	4	9	0	9	9	09/17/1991	2
UC:EB(4000+),Brachy(2250+),Boos	RT Alone	01/14/1957	1	4	9	0	9	9	09/24/1991	2
UC:EB(4000+),Brachy(2250+),Boos	RT+Mitomycin C	09/17/1950	1	4	9	0	9	9	09/20/1991	1
UC:EB(4000+),Brachy(2250+),Boos	RT Alone	03/07/1957	1	4	9	0	9	9	10/25/1991	2
DL_LF:EB(4000+),Brachy(2250+),B	RT Alone	09/25/1938	1	4	9	0	9	9	10/28/1991	2
UC:EB(4500+),Brachy(2000+),+/-Bc	RT Alone	01/01/1935	1	6	9	0	9	9	11/04/1991	2
DL_LF:EB(4000+),Brachy(2250+)	RT+Mitomycin C	12/23/1938	1	4	9	0	9	9	01/05/1991	1
DL_LF:EB(4000+),Brachy(2250+),B	RT Alone	04/29/1949	1	4	9	0	9	9	12/18/1991	2
UC:EB(4500+),Brachy(2000+),+/-Bc	RT Alone	04/03/1948	1	6	9	0	9	9	12/23/1991	2
DL_LF:EB(4000+),Brachy(2250+),B	RT Alone	10/30/1965	1	4	9	0	9	9	01/14/1992	2
DL_LF:EB(4500+),Brachy(2000+),+/	RT+Mitomycin C	01/11/1952	1	6	9	0	9	9	01/14/1992	1
UC:EB(4500+),Brachy(2000+),+/-Bc	RT+Mitomycin C	12/03/1930	1	6	9	0	9	9	01/28/1992	1
UC:EB(4500+),Brachy(2000+),+/-Bc	RT Alone	09/14/1953	1	6	9	0	9	9	02/11/1992	2
DL_LF:EB(4000+),Brachy(2250+),B	RT Alone	05/25/1949	1	4	9	0	9	9	02/10/1992	2
DL_LF:EB(4000+),Brachy(2250+)	RT+Mitomycin C	01/23/1952	1	3	9	0	9	9	02/25/1992	1
DL_LF:EB(4000+),Brachy(2250+),B	RT+Mitomycin C	02/22/1937	1	4	9	0	9	9	03/09/1992	1
UC:EB(4000+),Brachy(2250+),Boos	RT+Mitomycin C	03/10/1943	1	4	9	0	9	9	03/16/1992	1
UC:EB(4000+),Brachy(2250+)	RT+Mitomycin C	10/22/1959	1	3	9	0	9	9	03/16/1992	1
DL_LF:EB(4000+),Brachy(2250+),B	RT+Mitomycin C	02/20/1940	1	4	9	0	9	9	03/30/1991	1
DL_LF:EB(4000+),Brachy(2250+),B	RT Alone	07/06/1945	1	4	9	0	9	9	03/30/1992	2
DL_LF:EB(4000+),Brachy(2250+),B	RT+Mitomycin C	03/10/1936	1	4	9	0	9	9	04/20/1992	1
DL_LF:EB(4000+),Brachy(2250+),B	RT+Mitomycin C	12/22/1929	1	4	9	0	9	9	05/11/1992	1
UC:EB(4000+),Brachy(2250+),Boos	RT+Mitomycin C	10/21/1935	1	4	9	0	9	9	05/25/1992	1
DL_LF:EB(4500+),Brachy(2000+),+/	RT Alone	01/16/1946	1	7	9	1	9	9	06/08/1992	2
UC:EB(4500+),Brachy(2000+),+/-Bc	RT+Mitomycin C	09/15/1927	1	6	9	0	9	9	06/22/1992	1
DL_LF:EB(4000+),Brachy(2250+),B	RT Alone	12/02/1945	1	4	9	0	9	9	06/29/1992	2
DL_LF:EB(4000+),Brachy(2250+),B	RT Alone	08/02/1916	1	4	9	0	9	9	06/29/1992	2
DL_LF:EB(4500+),Brachy(2000+),+/	RT+Mitomycin C	11/15/1942	1	6	9	0	9	9	07/06/1992	1
DL_LF:EB(4500+),Brachy(2000+),+/	RT+Mitomycin C	08/16/1959	1	6	9	0	9	9	07/13/1992	1
DL_LF:EB(4000+),Brachy(2250+)	RT Alone	11/02/1929	1	3	9	0	9	9	07/13/1992	2
DL_LF:EB(4000+),Brachy(2250+)	RT+Mitomycin C	10/27/1951	1	3	9	0	9	9	07/27/1992	1

File Edit View Tools Program Table Window Help

Patref	Trialid	Patid	Centid	Dob	Age	Hist	Stage	Grade	Perfstat	Pvlymp	Palymp	Illymp	Dor	Arm	Locsur	Locrt	Locbrt	Tumresp	Locrec	Dolr	Distmet	Dodm	Surv	Dolf
1	19	1	Domingo Luciani	21/07/1954	36	1	3	9	0	9	9	9	27/02/1991	1	0	1	1	9	0	26/03/2001	0	26/03/2001	0	26/03/20
2	19	2	Univ.Caracas(UC	27/04/1951	39	1	4	9	0	9	9	9	22/03/1991	1	0	7	1	9	1	11/06/1991	0	07/10/1991	1	07/10/19
3	19	3	Domingo Luciani	09/01/1939	52	1	4	9	0	9	9	9	26/03/1991	2	0	7	1	9	0	15/12/2001	0	15/12/2001	0	15/12/20
4	19	4	Univ.Caracas(UC	18/04/1919	72	1	4	9	0	9	9	9	22/04/1991	2	0	7	1	9	0	29/01/1999	0	29/01/1999	0	29/01/19
5	19	5	Domingo Luciani	05/04/1928	63	1	4	9	0	9	9	9	18/06/1991	1	0	7	1	9	1	10/06/1993	0	10/06/1994	0	10/06/19
6	19	6	La Floresta (LF	18/05/1931	60	1	4	9	0	9	9	9	17/06/1991	1	0	1	1	9	0	30/08/1995	1	29/08/1995	1	30/08/19
7	19	7	Univ.Caracas(UC	16/11/1952	38	1	4	9	0	9	9	9	08/07/1991	2	0	7	1	9	1	05/11/1993	1	29/11/1993	1	26/12/19
8	19	8	Univ.Caracas(UC	14/09/1956	34	1	4	9	0	9	9	9	10/07/1991	1	0	7	1	9	1	20/09/1991	0	03/01/1992	1	03/01/19
9	19	9	Domingo Luciani	14/12/1962	28	1	4	9	0	9	9	9	16/07/1991	1	0	7	1	9	0	16/06/1993	0	16/06/1993	0	16/06/19
10	19	10	Domingo Luciani	01/08/1947	43	1	4	9	0	9	9	9	23/07/1991	2	0	7	1	9	0	15/02/1994	1	27/01/1994	1	15/02/19
11	19	11	Domingo Luciani	17/05/1952	39	1	4	9	0	9	9	9	23/07/1991	2	0	7	1	9	0	15/07/1992	0	15/07/1992	1	15/07/19
12	19	12	Domingo Luciani	04/09/1933	57	1	4	9	0	9	9	9	30/07/1991	1	0	7	1	9	0	23/05/2001	0	23/05/2001	0	23/05/20
13	19	13	Univ.Caracas(UC	09/07/1941	50	1	6	9	0	9	9	9	19/08/1991	1	0	7	1	9	0	27/09/1999	0	27/09/1999	0	27/09/19
14	19	14	Domingo Luciani	07/03/1936	55	1	6	9	0	9	9	9	26/08/1991	1	0	7	1	9	0	03/12/1997	0	03/12/1997	0	03/12/19
15	19	15	Domingo Luciani	09/10/1944	46	1	4	9	0	9	9	9	03/09/1991	1	0	7	1	9	0	09/09/1992	0	09/09/1992	1	09/09/19
16	19	16	Univ.Caracas(UC	08/10/1960	30	1	7	9	0	9	9	9	06/09/1991	1	0	7	1	9	1	29/11/1991	0	12/06/1992	1	12/06/19
17	19	17	Domingo Luciani	20/10/1928	62	1	4	9	0	9	9	9	17/09/1991	2	0	1	1	9	0	07/06/2000	0	07/06/2000	0	07/06/20
18	19	18	Univ.Caracas(UC	14/01/1957	34	1	4	9	0	9	9	9	24/09/1991	2	0	7	1	9	1	16/06/1992	0	15/08/1993	1	15/08/19
19	19	19	Univ.Caracas(UC	17/09/1950	41	1	4	9	0	9	9	9	20/09/1991	1	0	7	1	9	0	18/06/1999	0	18/06/1999	0	18/06/19
20	19	20	Univ.Caracas(UC	07/03/1957	34	1	4	9	0	9	9	9	25/10/1991	2	0	7	1	9	0	13/03/1992	0	13/03/1992	0	13/03/19
21	19	21	La Floresta (LF	25/09/1938	53	1	4	9	0	9	9	9	28/10/1991	2	0	7	1	9	0	28/07/1999	1	16/03/1992	0	28/07/19
22	19	22	Univ.Caracas(UC	01/01/1935	56	1	6	9	0	9	9	9	04/11/1991	2	0	7	1	9	0	22/07/2001	0	22/07/2001	0	22/07/20
23	19	23	Domingo Luciani	23/12/1938	52	1	4	9	0	9	9	9	05/01/1991	1	0	1	1	9	0	26/08/1996	0	26/08/1996	0	26/08/19
24	19	24	Domingo Luciani	29/04/1949	42	1	4	9	0	9	9	9	18/12/1991	2	0	7	1	9	0	05/02/1997	0	05/02/1997	0	05/02/19
25	19	25	Univ.Caracas(UC	03/04/1948	43	1	6	9	0	9	9	9	23/12/1991	2	0	7	1	9	1	17/07/1992	0	10/12/1993	1	10/12/19
26	19	26	Domingo Luciani	30/10/1965	26	1	4	9	0	9	9	9	14/01/1992	2	0	7	1	9	0	27/11/1996	1	28/01/1993	0	27/11/19
27	19	27	Domingo Luciani	11/01/1952	40	1	6	9	0	9	9	9	14/01/1992	1	0	7	1	9	1	27/03/1992	1	18/11/1992	1	17/12/19
28	19	28	Univ.Caracas(UC	03/12/1930	61	1	6	9	0	9	9	9	28/01/1992	1	0	7	1	9	1	06/03/1997	0	27/03/1998	0	27/03/19
29	19	29	Univ.Caracas(UC	14/09/1953	38	1	6	9	0	9	9	9	11/02/1992	2	0	7	1	9	0	06/07/2001	0	06/07/2001	0	06/07/20
30	19	30	Domingo Luciani	25/05/1949	42	1	4	9	0	9	9	9	10/02/1992	2	0	7	1	9	0	06/02/2001	0	06/02/2001	0	06/02/20
31	19	31	Domingo Luciani	23/01/1952	40	1	3	9	0	9	9	9	25/02/1992	1	0	1	1	9	1	10/11/1992	0	18/01/1993	1	18/01/19
32	19	32	La Floresta (LF	22/02/1937	55	1	4	9	0	9	9	9	09/03/1992	1	0	7	1	9	0	01/09/1999	0	01/09/1999	0	01/09/19
33	19	33	Univ.Caracas(UC	10/03/1943	49	1	4	9	0	9	9	9	16/03/1992	1	0	7	1	9	0	05/11/1993	0	05/11/1993	0	05/11/19
34	19	34	Univ.Caracas(UC	22/10/1959	32	1	3	9	0	9	9	9	16/03/1992	1	0	1	1	9	0	30/03/2001	0	30/03/2001	0	30/03/20
35	19	35	Domingo Luciani	20/02/1940	51	1	4	9	0	9	9	9	30/03/1991	1	0	7	1	9	0	30/07/1993	1	07/04/1993	1	30/07/19
36	19	36	Domingo Luciani	06/07/1945	46	1	4	9	0	9	9	9	30/03/1992	2	0	7	1	9	1	19/11/1992	1	19/11/1992	1	26/02/19
37	19	37	Domingo Luciani	10/03/1936	56	1	4	9	0	9	9	9	20/04/1992	1	0	7	1	9	1	03/07/1992	0	22/12/1992	1	22/12/19
38	19	38	Domingo Luciani	22/12/1929	62	1	4	9	0	9	9	9	11/05/1992	1	0	7	1	9	0	12/07/2001	0	12/07/2001	0	12/07/20
39	19	39	Univ.Caracas(UC	21/10/1935	56	1	4	9	0	9	9	9	25/05/1992	1	0	7	1	9	0	15/06/1997	1	10/11/1995	1	15/06/19
40	19	40	Domingo Luciani	16/01/1946	46	1	7	9	1	9	9	9	08/06/1992	2	0	1	0	9	0	21/12/1992	0	21/12/1992	1	21/12/19
41	19	41	Univ.Caracas(UC	15/09/1927	64	1	6	9	0	9	9	9	22/06/1992	1	0	7	1	9	0	30/06/1993	0	30/06/1993	1	30/06/19
42	19	42	Domingo Luciani	02/12/1945	46	1	4	9	0	9	9	9	29/06/1992	2	0	7	1	9	1	04/06/1994	0	05/06/1994	1	05/06/19
43	19	43	La Floresta (LF	02/08/1916	75	1	4	9	0	9	9	9	29/06/1992	2	0	7	1	9	0	29/01/2001	0	29/01/2001	0	29/01/20
44	19	44	Domingo Luciani	15/11/1942	49	1	6	9	0	9	9	9	06/07/1992	1	0	7	1	9	1	25/09/1992	0	25/09/1992	0	25/09/19
45	19	45	Domingo Luciani	16/08/1959	32	1	6	9	0	9	9	9	13/07/1992	1	0	7	1	9	0	25/10/2000	0	25/10/2000	0	25/10/20
46	19	46	Domingo Luciani	02/11/1929	62	1	3	9	0	9	9	9	13/07/1992	2	0	1	1	9	1	12/01/1994	1	20/01/1993	1	13/01/19
47	19	47	La Floresta (LF	27/10/1951	40	1	3	9	0	9	9	9	27/07/1992	1	0	1	1	9	0	18/05/2001	0	18/05/2001	0	18/05/20
48	19	48	Univ.Caracas(UC	08/12/1944	47	1	6	9	0	9	9	9	03/08/1992	2	0	7	1	9	1	02/08/1993	1	02/08/1993	1	27/02/19
49	19	49	Univ.Caracas(UC	30/04/1932	60	1	6	9	0	9	9	9	24/08/1992	2	0	7	1	9	0	17/03/1995	1	04/11/1994	0	17/03/19
50	19	50	Univ.Caracas(UC	26/10/1952	39	1	4	9	0	9	9	9	31/08/1992	1	0	7	1	9	0	18/10/1996	0	18/10/1996	0	18/10/19
51	19	51	Univ.Caracas(UC	05/08/1942	50	1	6	9	0	9	9	9	07/09/1992	2	0	7	1	9	0	02/03/2001	0	02/03/2001	0	02/03/20
52	19	52	Univ.Caracas(UC	05/01/1952	40	1	6	9	0	9	9	9	07/09/1992	1	0	7	1	9	0	22/04/1994	0	22/04/1994	0	22/04/19
53	19	53	Domingo Luciani	01/10/1926	65	1	6	9	0	9	9	9	21/09/1992	2	0	7	1	9	0	13/08/1994	1	07/06/1994	1	13/08/19
54	19	54	Domingo Luciani	16/04/1959	33	1	4	9	0	9	9	9	28/09/1992	2	0	7	1	9	1	30/06/1993	1	31/01/1994	1	22/07/19

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.

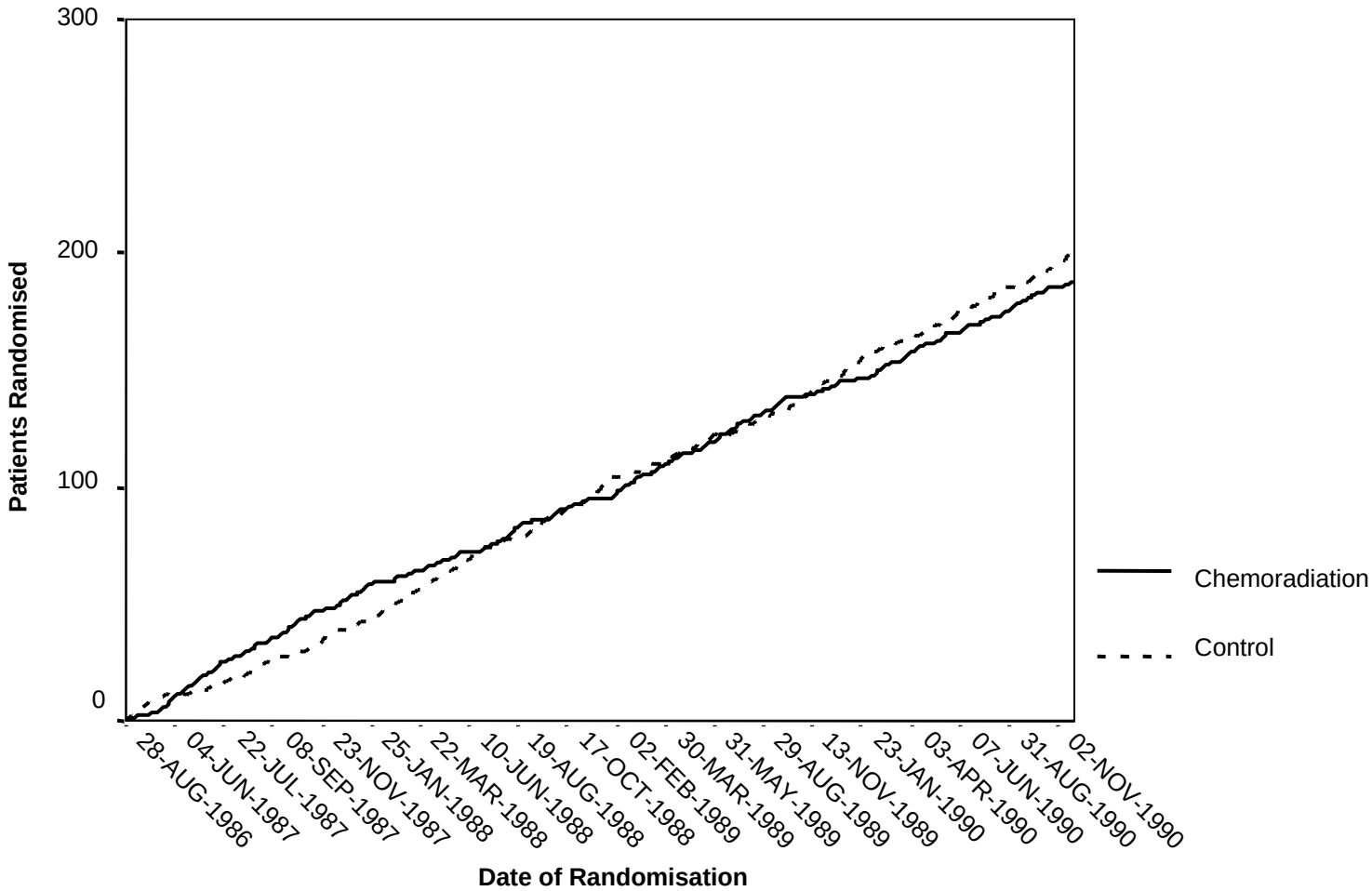
- Published analysis:
  - based on 243 patients
    - 25 excluded
  - Control arm (116 pts)
    - Median age 38
    - Range 20-78
  - HR estimate for overall survival
    - 0.51 (p=0.007)
- IPD supplied for MA
  - Based on 268 patients
    - All randomised
  - Control arm (133 pts)
    - Median age 39
    - 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

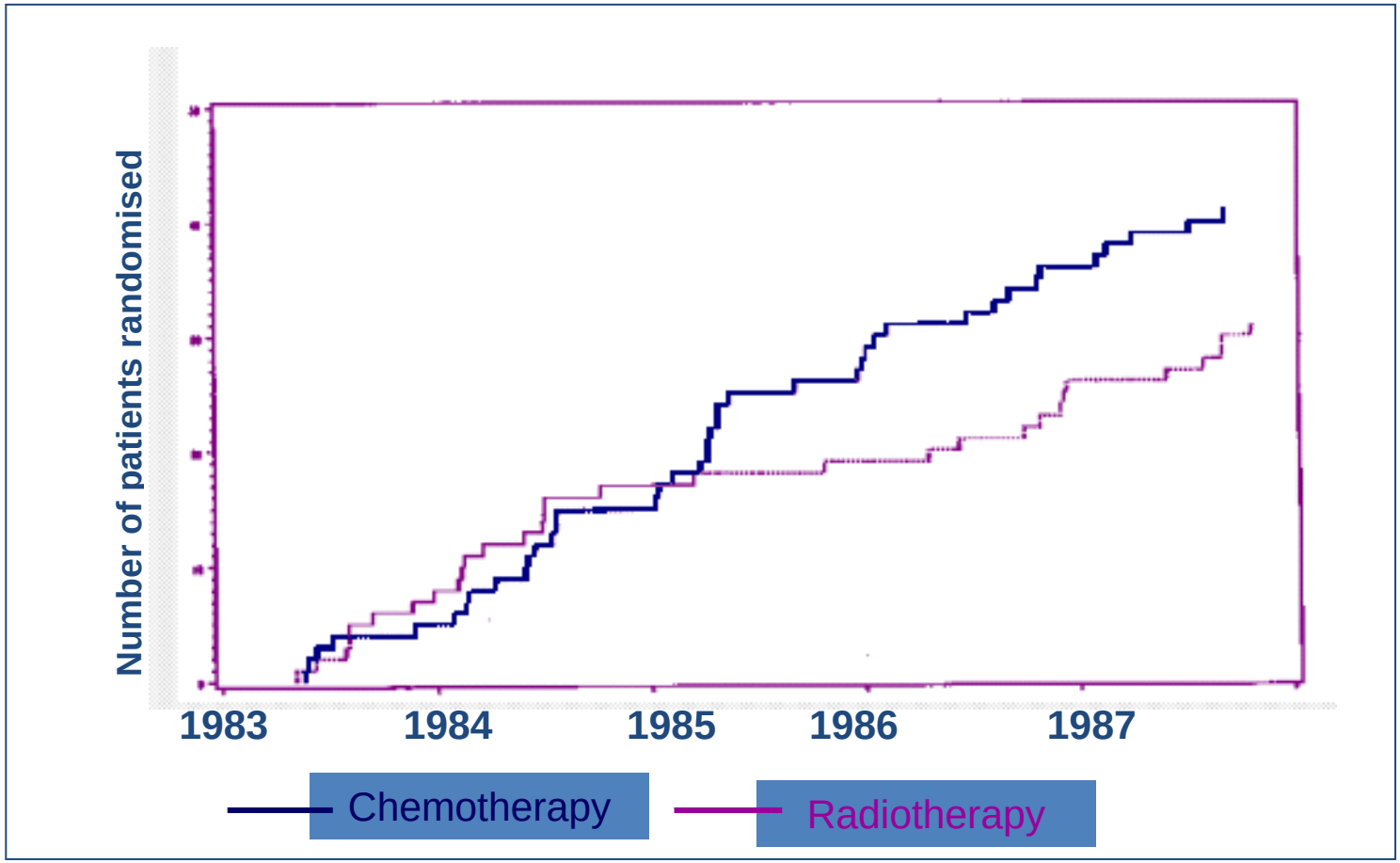
Data checking: Pattern of randomisation

Chemoradiation for cervical cancer



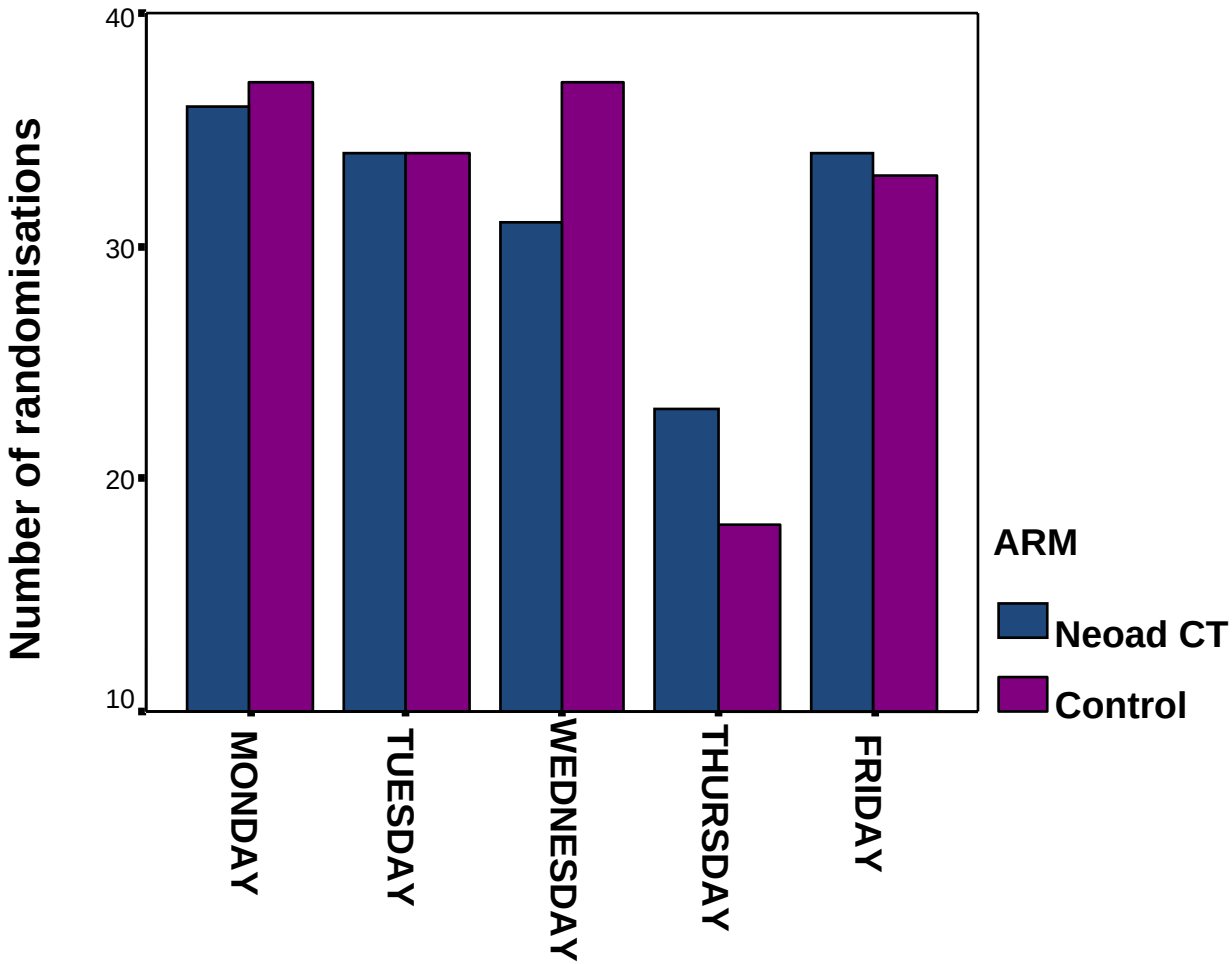
Data checking: Pattern of randomisation

Radiotherapy vs Chemotherapy in Multiple Myeloma



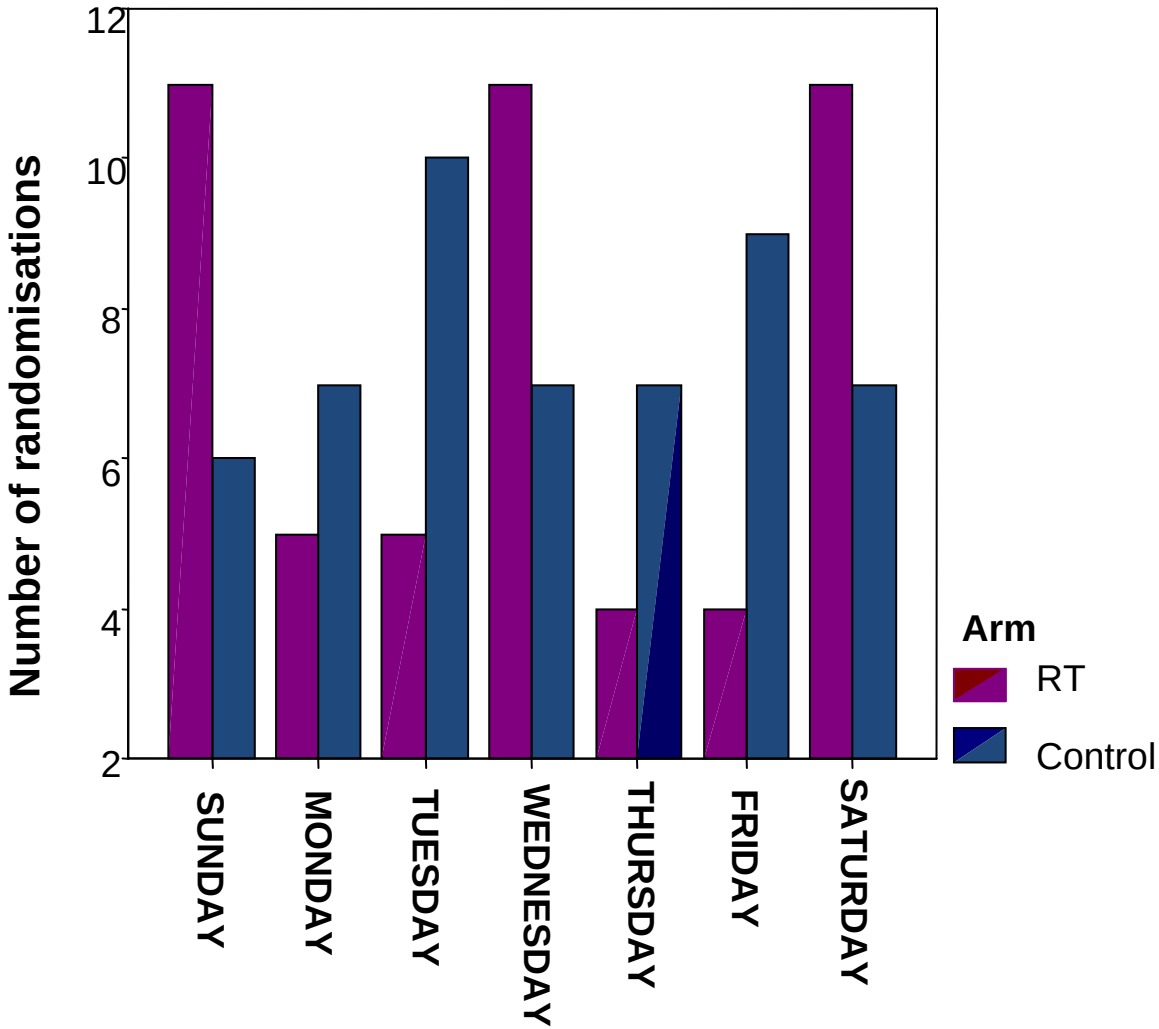
Data checking: Weekday randomised

Chemotherapy for bladder cancer



Data checking: 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

Simmonds et al. Meta-Analysis of individual patient data from Randomized Trials: A review of methods used in practice. Clinical Trials 2005:2;209-17.

Exploring trial-level differences

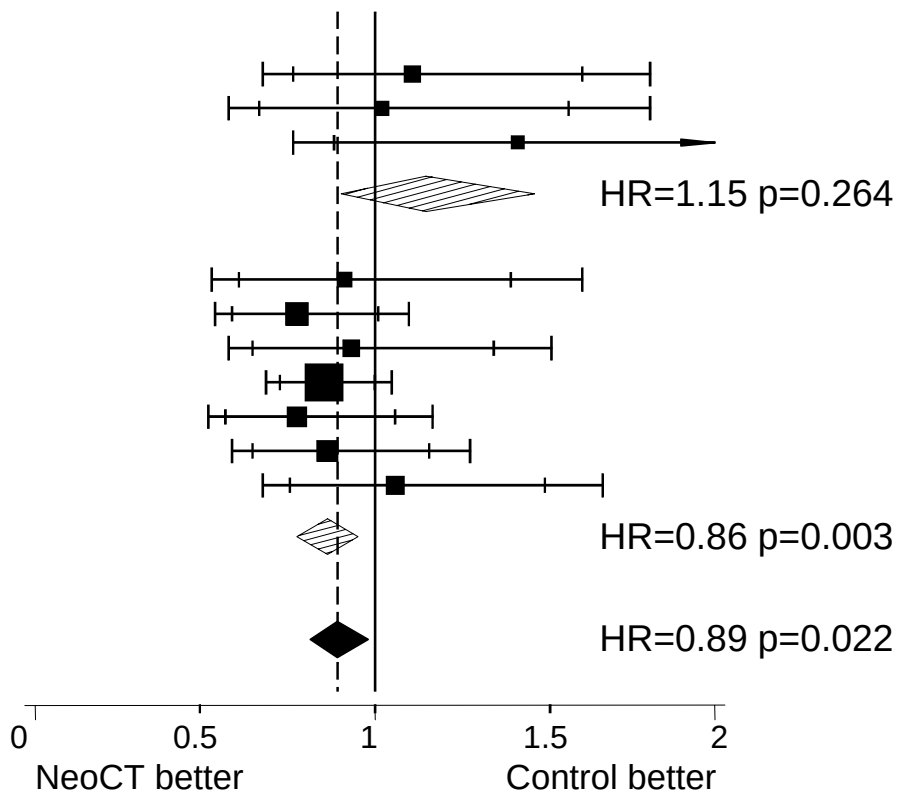
- 'Subgroup' analysis or meta-regression by trial characteristics
  - Group by treatments, dose, treatment scheduling
- Compares the size of treatment effect on outcome across different trial groups
  - Test for interaction
- Easy to do with published summary data or IPD
- May obtain more trial-level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

- Alternatively explore through sensitivity analyses

Exploring trial-level differences

Chemotherapy for bladder cancer

	(no. events/no. entered) CT	Control	O-E	Variance
Single agent platinum				
Wallace [2]	59/83	50/76	2.74	27.18
Martinez-Pineiro [3]	43/62	38/59	0.33	20.11
Raghavan [2]	34/41	37/55	5.85	16.51
Sub-total	136/186	125/190	8.92	63.80
Platinum-based combinations				
Cortesi unpublished	43/82	41/71	-1.87	20.84
Grossman [10]	98/158	108/159	-13.61	51.00
Bassi [5]	53/102	60/104	-1.95	28.13
MRC/EORTC [9]	275/491	301/485	-23.69	143.61
Malmström [4]	68/151	84/160	-9.97	37.94
Sherif [7]	79/158	90/159	-6.37	42.18
Sengeløv [8]	70/78	60/75	1.79	31.96
Sub-total	686/1220	744/1213	-55.67	355.65
Total	822/1406	869/1403	-46.75	419.45



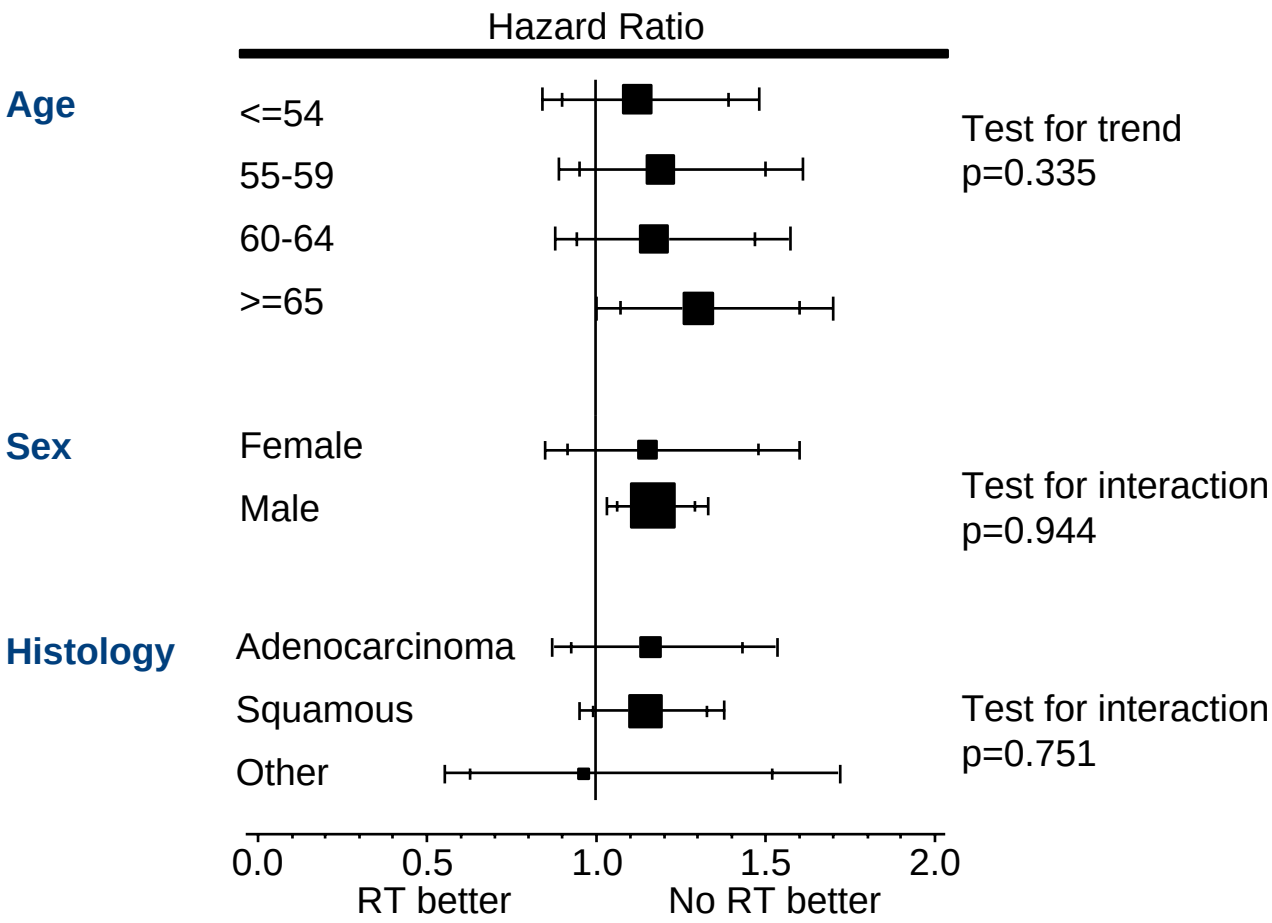
Interaction p=0.029

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

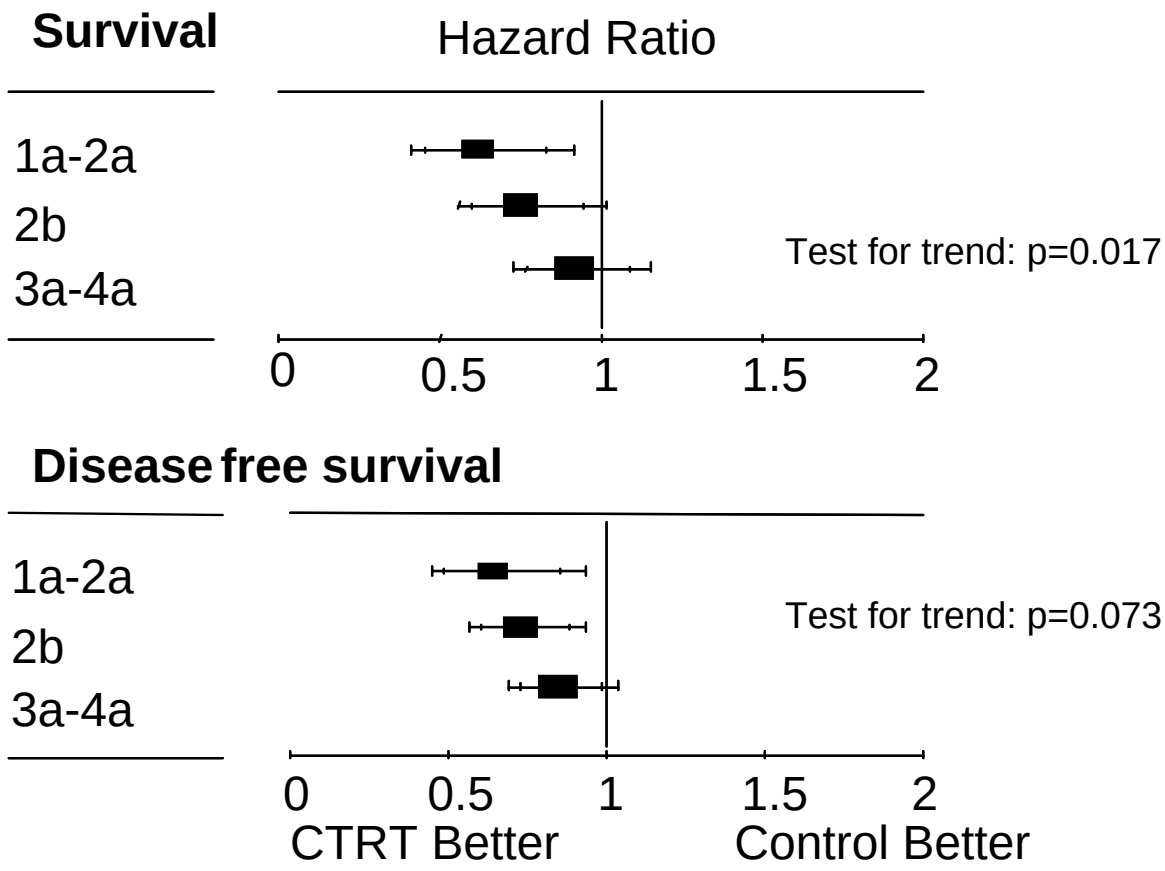
Exploring patient-level differences

Post-operative radiotherapy for lung cancer



Exploring patient-level differences

Chemoradiotherapy for cervical cancer



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

Entry	Judgement	Description
Adequate sequence generation?	Yes.	**Random number list. Also, data checks on IPD provided suggest adequate sequence generation**
Allocation concealment?	**Yes**	**Central telephone**
Blinding? (Patient-reported outcomes)	Yes.	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.
Blinding? (Mortality)	Yes.	Obtained from medical records; review authors do not believe this will introduce bias.
Incomplete outcome data addressed? (Short-term outcomes (2-6 wks))	**Yes**	**IPD supplied for all randomised patients and for all outcomes of interest**
Incomplete outcome data addressed? (Longer-term outcomes (>6 wks))	**Yes**	**IPD supplied for all randomised patients and for all outcomes of interest**
Free of selective reporting?	**Yes**	**IPD supplied for all outcomes**
Free of other bias?	No.	**Stopped early, but extra follow-up data supplied**

Improve analysis quality

- Effects for each study derived from IPD rather that 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 & Clarke. Practical methodology of meta-analyses (overviews) using updated individual patient data. Stat Med 1995;14:2057-79.
  - 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.
  - Richard D Riley et al. Meta-analysis of individual participant data: rationale, conduct, and reporting. BMJ 2010;340:c221
- For specific advice or to join IPD Methods Group
  - Contact Methods Group at IPD@ctu.mrc.ac.uk