Individual Patient Data (IPD) Reviews and Meta-analyses

MRC Clinical Trials Unit

Lesley Stewart, Jayne Tierney, Claire Vale

IPD Meta-analysis Methods Group

Stewart LA, Clarke MJ. Practical methodology of meta-analyses (overviews) using updated individual patient data. Statistics in Medicine 1995;14:2057-2079.

Stewart LA, Tierney JF. To IPD or Not to IPD? Advantages and disadvantages of systematic reviews using individual patient data. Evaluation & the Health Professions 2002;25(1):76-97.

IPD systematic review / meta-analysis

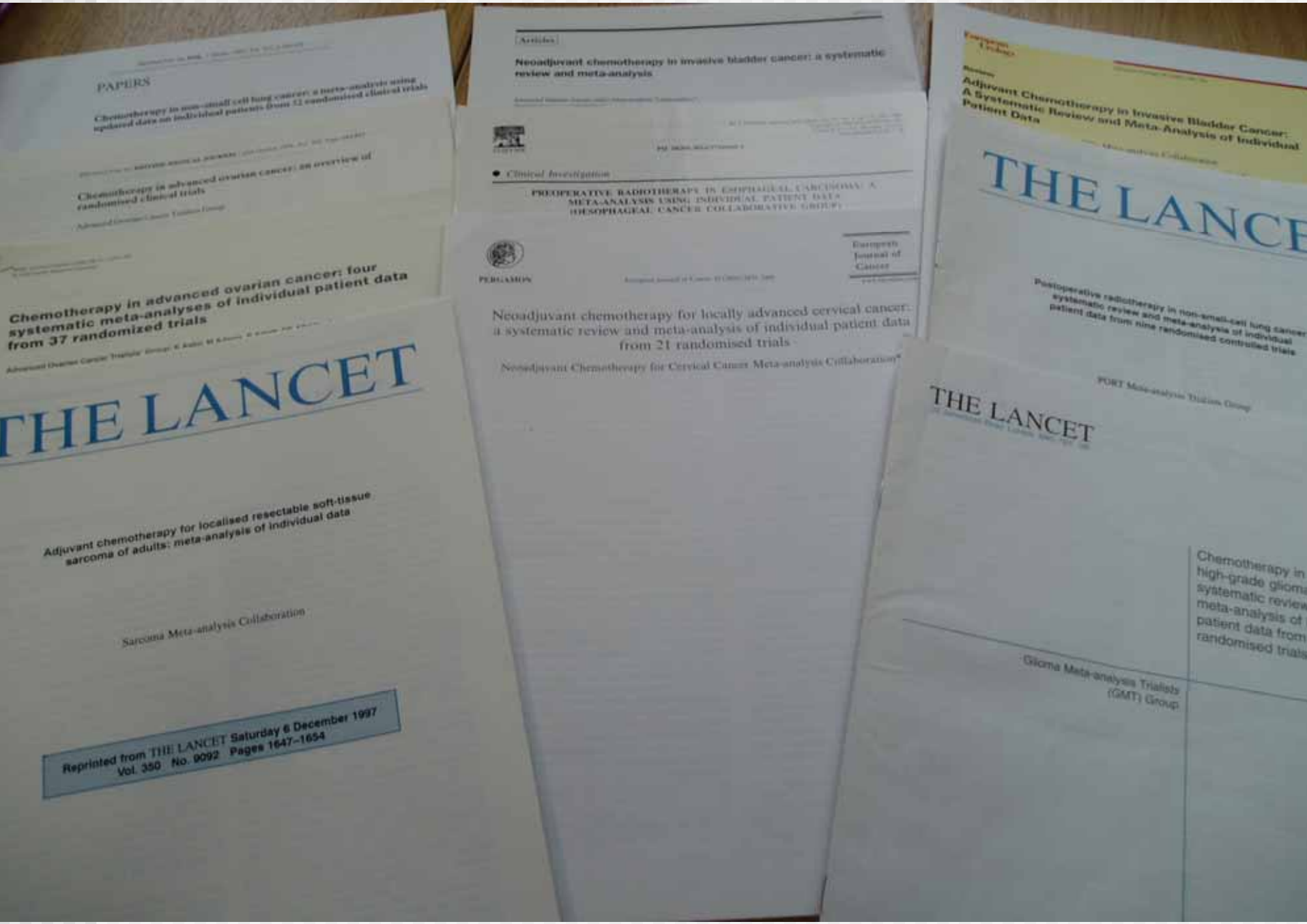
- Described as yardstick and gold standard of systematic review
- Central collection, validation & re-analysis of source data
- Philosophy same as for other Cochrane reviews
- Process differs in terms of data collection and analysis
- Quicker and cheaper than new trial, but longer and more resource intensive than other reviews
- Less common than other types of review but becoming used increasingly

History of IPD reviews/meta-analyses

- Established history in cardiovascular disease
- Established history in range of cancer sites e.g.
  - chemotherapy for ovarian cancer
  - post-operative radiotherapy for lung cancer
  - chemotherapy for bladder cancer
  - chemoradiation for cervical cancer
- Becoming used in a wide range of fields e.g.
  - surgical repair for hernia
  - drug treatments for epilepsy
  - cholinesterase inhibition for Alzheimer's disease
  - anti-platelet treatments for pre-eclampsia in pregnancy
  - compression bandaging for chronic leg ulcers

How IPD meta-analyses are organised

- Carried out by international collaborative group
  - small local secretariat
  - multi-disciplinary advisory group
  - trialists who provide data
- Developing and maintaining this group requires communication and careful management
- Publication in the name of collaborative group


PAPERS
Chemotherapy in advanced ovarian cancer: an overview of randomised clinical trials
Chemotherapy in advanced ovarian cancer: four systematic meta-analyses of individual patient data from 37 randomized trials
THE LANCET
Adjuvant chemotherapy for localised resectable soft-tissue sarcoma of adults: meta-analysis of individual data
Sarcoma Meta-analysis Collaboration
Reprinted from THE LANCET Saturday 6 December 1997
Vol. 350 No. 9092 Pages 1647–1654
Articles
Neoadjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis
Clinical Investigation
PREOPERATIVE RADIOTHERAPY IN ESOPHAGEAL CARCINOMA: A META-ANALYSIS USING INDIVIDUAL PATIENT DATA
OESOPHAGEAL CANCER COLLABORATIVE GROUP
PERGAMON
European Journal of Cancer
Neoadjuvant chemotherapy for locally advanced cervical cancer: a systematic review and meta-analysis of individual patient data from 21 randomised trials
Neoadjuvant Chemotherapy for Cervical Cancer Meta-analysis Collaboration*
Adjuvant Chemotherapy in Invasive Bladder Cancer: A Systematic Review and Meta-Analysis of Individual Patient Data
THE LANCE
Postoperative radiotherapy in non-small-cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomised controlled trials
THE LANCET
Glioma Meta-analysis Trialists (GMT) Group
Chemotherapy in high-grade glioma systematic review meta-analysis of patient data from randomised trials

Why IPD?

- Analyses based on published data can give different answers to an IPD meta-analysis e.g.
  - chemotherapy in advanced ovarian cancer
  - radiotherapy in SCLC
  - chemotherapy in NSCLC
  - ovarian ablation in breast cancer
  - immunisation for recurrent miscarriage
  - chemotherapy for head and neck cancer

Why IPD?

Chemotherapy in advanced ovarian example

	IPD	Published Data
Trials	11	8
Patients	1329	788
Odds Ratio	---	0.71
Hazard Ratio	0.93	---
95% confidence interval	0.83-1.05	0.52-0.96
p-value	0.30	0.027
Absolute benefit at 30 months	2.5%	7.5%
Comments	median follow up 6.5 years	point estimate at 30 months

Platinum based combination vs non-platinum single drugs, *Lancet* 1993; 341: 418-422

Ovarian cancer example conclusions

- Differences due to
  - excluded trials, excluded patients, time point of analysis, extra follow up, analysis method
- Published summary data gives a more statistically ‘convincing’ result
- Estimates of effect size are 7.5% and 2.5% improvement in survival at 30 months
- Balanced against other factors, clinical interpretation of results from two approaches may be different

Why IPD?

- Include all trials published and unpublished
- Get round inadequacies in trial reports
  - measure or define patient characteristics differently
  - measure or define outcomes differently
  - selectively report particular outcomes
  - based on different degrees of follow up
  - exclude patients from analyses
  - inappropriate or biased analyses
  - insufficient details of analyses
- Address questions or carry out analyses that cannot be readily achieved with published data

Why IPD?

- Improve data quality
  - all relevant trials and patients
  - all relevant outcomes
  - combine different scales of measurement
  - data checking
- Improve analysis quality
  - include all patients by intention-to-treat
  - appropriate analyses (e.g. time-to-event analysis)
  - long term outcomes
  - patient subgroups
- Improve trial identification, interpretation & dissemination via collaborative approach

Specific reasons for using IPD

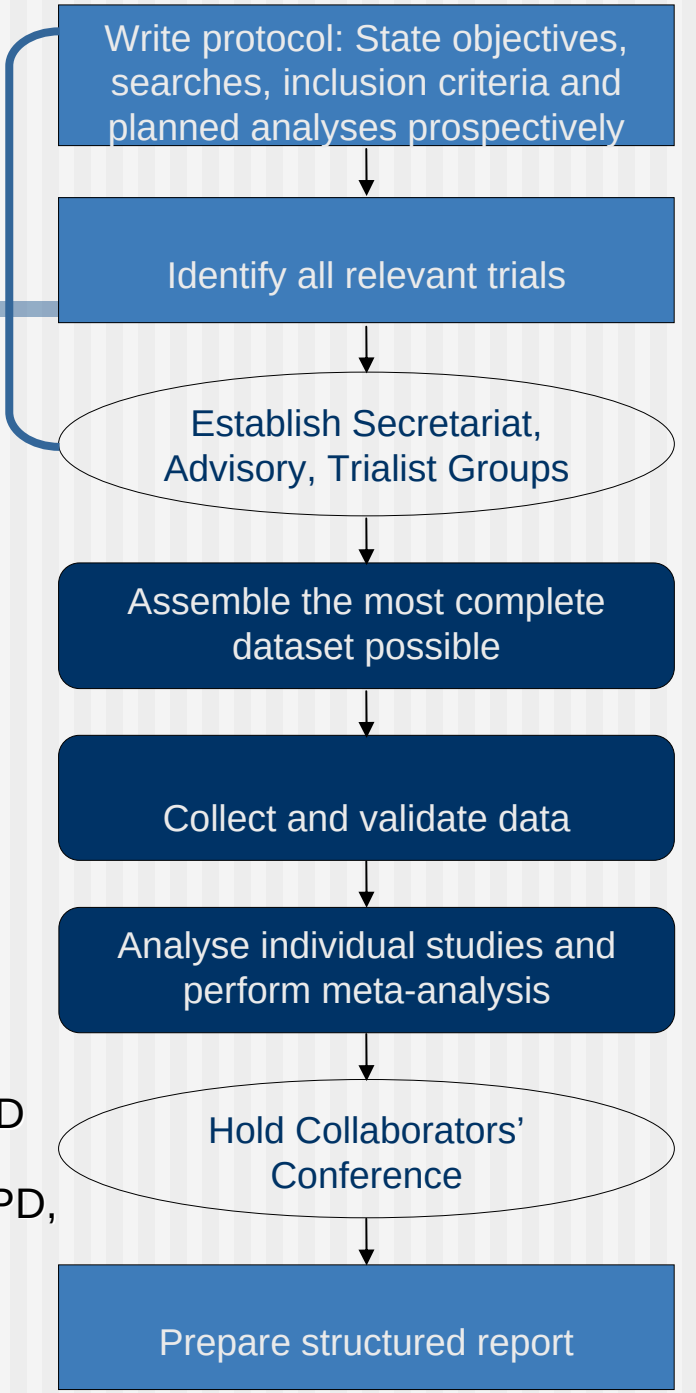
- Neo-adjuvant chemotherapy for bladder cancer
  - better estimate of effect on survival
  - effect on different patient subgroups
- Adjuvant chemotherapy for bladder cancer
  - treatment in use, but published data & analyses poor
  - appropriately analyse and rigorously appraise IPD
- Chemoradiation for cervical cancer
  - effect on different patient subgroups
  - detailed analysis of toxicity
- Anti-platelet therapy for pre-eclampsia in pregnancy
  - explore whether effect differs by women's risk profile

To IPD or not to IPD ?

When IPD may be beneficial	When IPD may not be beneficial
Poor reporting of trials. Information inadequate, selective or ambiguous	Detailed and clear reporting of trials (CONSORT quality)
Long-term outcomes	Short-term outcomes
Time-to-event outcome measures	Binary outcome measures
Multivariate or other complex analyses	Univariate or simple analyses
Differently defined outcome measures	Outcome measures defined uniformly across trials
Subgroup analyses of patient-level characteristics important	Patient subgroups not important
IPD available for high proportion of trials/individuals	IPD available for only a limited number of trials

Doing a systematic review and meta-analysis of IPD

Comparing types of review / meta-analysis



Processes the same for summary data and IPD

Processes are similar for summary data and IPD, but methodology and practical aspects differ

Only applies to IPD approach

Protocol development

- Introduction
- Objectives
- Trials inclusion criteria

Similar to Cochrane reviews

- Identification of trials
- Data collection
- Data analysis

More detailed than for Cochrane reviews

- Publication policy
- Timetable

- Consult with Advisory Group as required

Protocol development

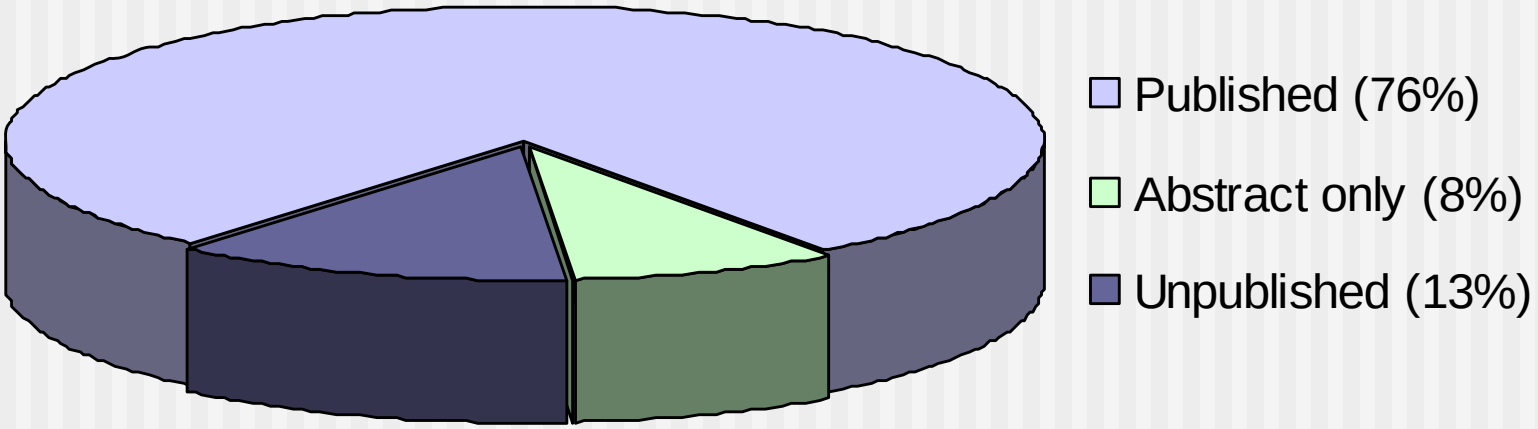
- Identification of trials
- Data collection
- Data analysis

Identification of trials

- Any review restricted to published data is at risk of publication bias
- Include all relevant trials published & unpublished
- Unpublished trials not peer reviewed, but
  - trial protocol & IPD allows extensive ‘peer review’
  - can clarify proper randomisation, eligibility
  - quality publication does not guarantee quality data
- Proportion of trials published will vary by
  - disease, intervention, over time
- Extent of unpublished data can be considerable

Identification of trials

Chemoradiation for cervical cancer (initiated 2004)



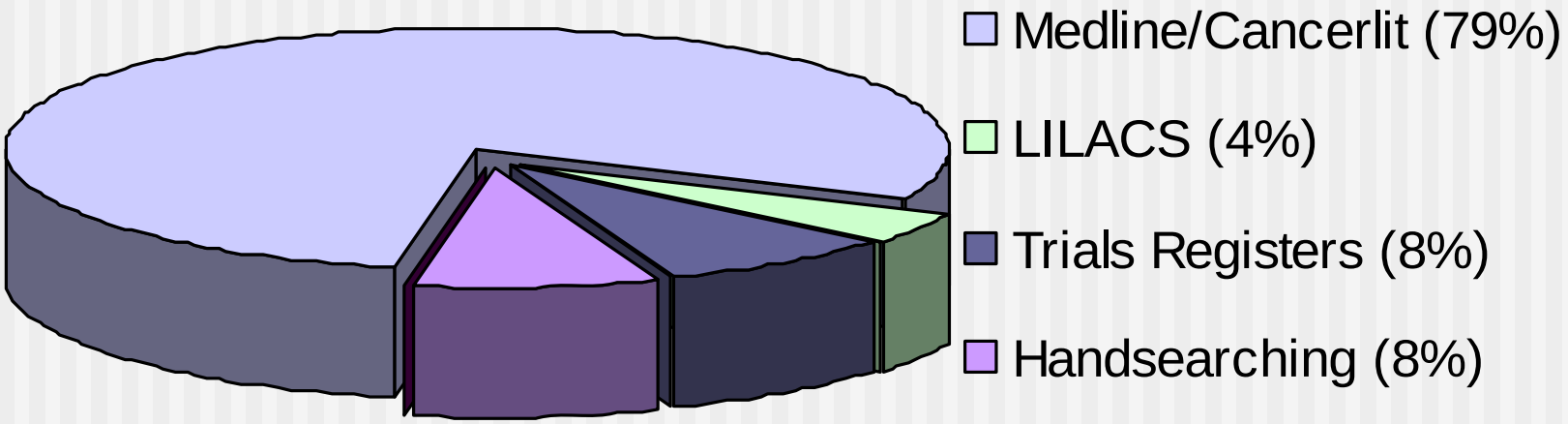
Identification of trials

Chemoradiation for cervical cancer

- Electronic databases
  - Medline, Cancerlit , LILACS
- Trial Registers
  - e.g. Clinicaltrials.gov, PDQ (cancer.gov), metaRegister , CENTRAL
- Hand search
  - reference lists, conference proceedings
- Experts
  - include preliminary trial list in protocol and ask collaborators to supplement it

Identification of trials

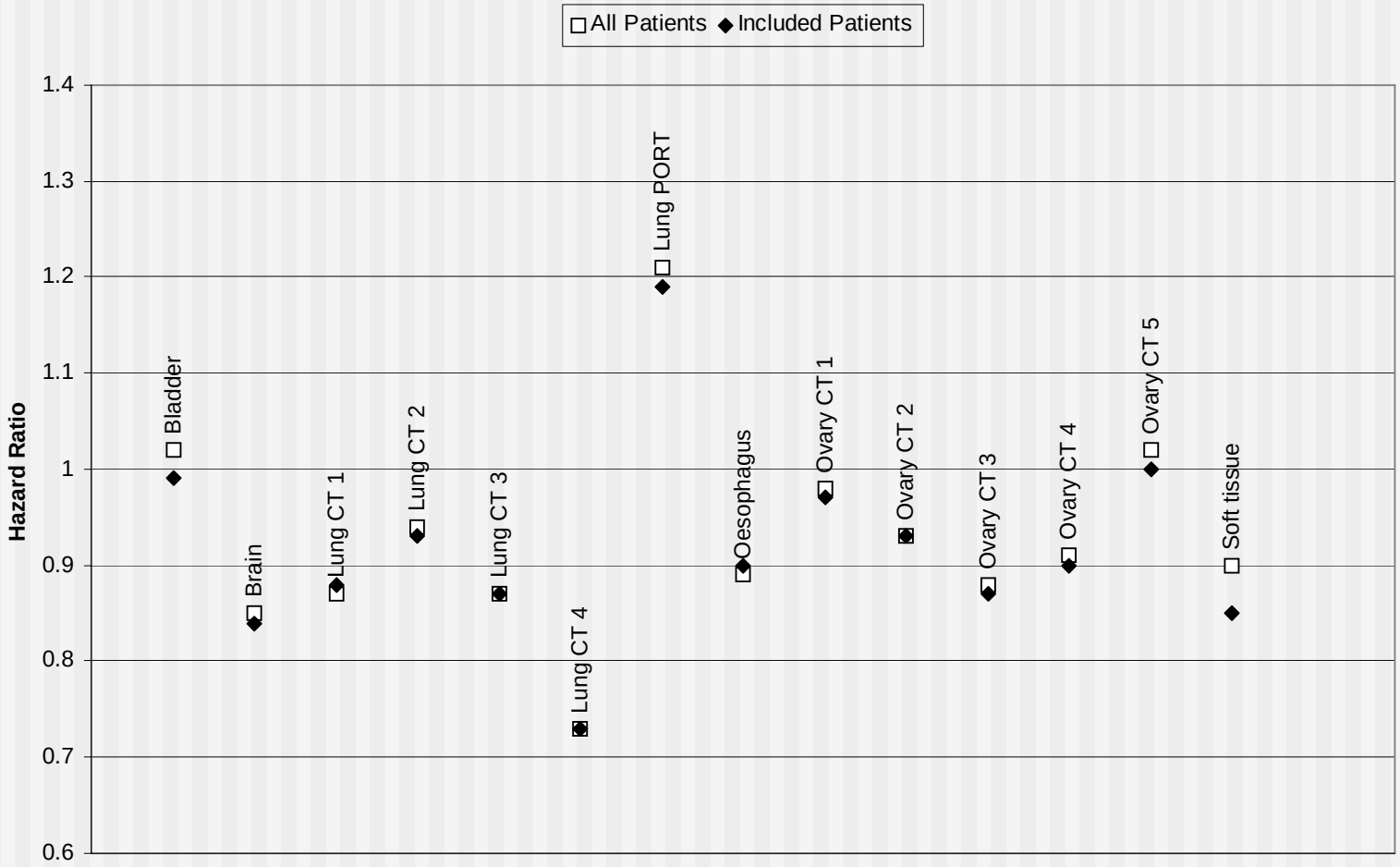
Chemoradiation for cervical cancer



Which IPD to collect: All patients

- Trial investigators frequently exclude patients from trial analyses and reports
  - ineligibility, patient withdrawal, early outcome, lost to follow-up
- Ad hoc exclusion of patients could introduce bias
- Aim to collect data on all randomised patients
- Also useful to collect data on which patients were excluded and the reasons for their exclusion
  - retention of such data may vary by disease and intervention

Which IPD to collect: All patients



Tierney JF, Stewart LA. Investigating exclusion bias in meta-analysis. *Int J Epidemiol* 34:79-87

Which IPD to collect: All patients

Chemotherapy for soft tissue sarcoma

- Obtained data for 14 trials, 1568 patients
- 341 (22%) of these patients excluded from the investigators' analyses

Patients excluded	Events / Patients	Overall Survival	
		HR	P-value
Investigators	553 / 1227	0.85	0.056
None	709 / 1568	0.90	0.157

Which IPD to collect: All patients

Chemotherapy for soft tissue sarcoma

- Pre-specify in the protocol if any patients will be excluded from the analysis
- Assess impact by sensitivity analyses

Patients excluded	Events / Patients	Overall Survival	
		HR	P-value
Locally recurrent <15 years Metastatic Induction CT	597 / 1366	0.91	0.278
None	709 / 1568	0.90	0.157

Which IPD to collect: Variables

- Decision by secretariat in consultation with Advisory Group
- Think about the analyses and work back
- Only want data necessary to carry out these analyses and adequately describe trials
- Publications can indicate
  - which data are feasible (but note there may be more available than reported)

Which IPD to collect: Variables

- Basic identification of patients
  - e.g. anonymous patient ID, centre ID
- Baseline data for descriptive purposes or analyses
  - e.g. age, sex, disease or condition characteristics
- Intervention of interest
  - e.g date of randomisation, treatment allocated
- Outcomes of interest
  - e.g. survival, toxicity, maternal death, pre-eclampsia, wound healing
- Information on excluded patients
- Include list of variables in meta-analysis protocol

Which IPD to collect: Variables

Chemoradiation for cervical cancer

Baseline characteristics

- Patient ID
- Centre ID
- Patient date of birth or age
- Tumour histology
- Tumour stage
- Tumour grade
- Lymph node involvement
- Patient performance status
- Allocated treatment
- Date of randomisation

Treatment characteristics

- Surgery
- External beam radiotherapy
- Brachytherapy

Outcomes

- Tumour response
- Loco-regional recurrence status
- Date of loco-regional recurrence
- Distant metastases status
- Date of distant metastases
- Survival status
- Date of death or last follow-up
- Acute toxicity
- Late toxicity

Other

- Cause of death
- Whether excluded from analysis
- Reason for exclusion

IPD variable definitions

- Form the basis of the meta-analysis database
- Define variables in way that is unambiguous and facilitates data collection and analysis
- Publications and protocols can indicate
  - how to collect data

IPD variable definitions

Chemoradiation for cervical cancer

Age

Type numeric
Width 3
Code age in years
unknown = 999

Survival status

Type numeric
Width 1
Code 0 = Alive
1 = Dead

Date of death

Type date
Width -
Code 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

Type numeric
Width 1
Code 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

✓ Onset of labour

1 = spontaneous

2 = induced

3 = pre-labour caesarian

9 = not recorded

✓ Sex of baby

1 = male

2 = female

3 = ambiguous

9 = not recorded

✓ 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

  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

Variable definitions

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

Planning analyses

- Range of possibilities
  - Main analyses of outcomes
  - Subset analyses by trial group
  - Subgroup analyses by patient characteristics (patient treatment interactions)
    - realistically only possible with IPD
  - Sensitivity analyses
  - Exploratory analyses (e.g. prognostic factors, baseline risk etc.)
  - Time-to-event analysis
- Pre-specify all in protocol

Planning analyses

Chemoradiation for cervical cancer

- Main analyses of outcomes
  - survival, local and distant disease-free survival, response, acute and late toxicity
- Subset analyses by
  - chemotherapy type, dose intensity & scheduling
  - radiotherapy dose and duration
- Subgroup analyses by
  - patient age and performance status, tumour histology, stage and grade and lymph node involvement

Planning analyses

Chemoradiation for cervical cancer

- Sensitivity analysis
  - by trial design
- Exploratory analysis of
  - relationship between treatment, haemoglobin levels and outcome

Collecting Data

Initiating collaboration with trialists

- Initial letter inviting collaboration, but not yet asking for data explaining
  - main aims and objectives
  - importance of the collaborative group
  - publication policy
  - collaborative group policy
  - confidentiality of data
- Ask specific questions relating to trial eligibility

Trial level data collection

- Data needed to adequately describe the trial
  - Trial ID and trial title
  - Method of randomisation & allocation concealment
  - Planned treatments
  - Recruitment and stopping information
  - Other information that is not clear from trial report
- Obtaining the trial protocol can also be valuable in describing a trial
- Use to clarify eligibility
  - Establish table of included studies

Trial level data collection

- Principal contact details
- Data contact details
- Up to date trial publication information
- Other trials of relevance
- Whether willing to take part in meta-analysis
- Preferred method of data transfer

- This information can be collected on forms accompanying the meta-analysis protocol

Example form

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

Name: _____ Your trial/protocol number: _____

Name of trial: _____

_____

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 ☐☐ mm ☐☐ yy ☐☐ Date trial closed to accrual: dd ☐☐ mm ☐☐ yy ☐☐

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? _____

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

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 ☐

Example form

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

Name: _____ Address: _____

Telephone: _____

Fax: _____

E-mail: _____

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

Name: _____ Address: _____

Telephone: _____

Fax: _____

E-mail: _____

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	☐	☐

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

Initiating collaboration with trialists

- Barriers
  - Practical (tracing people, language differences)
    - e-mail, web-sites, directories, search engines
  - Unfamiliar with methods
    - protocol, good communication
  - Political (difficult people, powerful groups)
    - protocol, good communication, intermediaries
  - Financial (money for data or preparing data)
    - ???

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 & no crossed wires

Project Status: May 2005

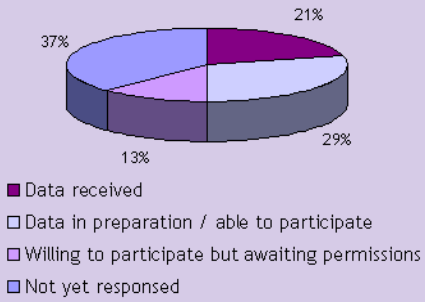
Concomitant chemoradiotherapy for cervical cancer:

A meta-analysis of individual patient data

Meta-analysis progress

Since the last newsletter in February, we have received more responses to our invitation to participate. Fourteen investigators have now replied. Five have already provided their data; seven more are able to participate and some are already preparing their data. Three investigators have replied that they are keen to participate, but will need to have appropriate permissions to supply data to us. We will try to help these investigators wherever we can.

We are now really keen to hear from the remaining investigators. If you have not yet been in touch, please could you let us know if you are able to participate or not. We might be able to help.



Missing Trialists: Can you help?

We still are not sure if we have been able to reach all of the investigators and so they may not have received our previous correspondence. We would therefore like to check whether our contact details for the investigators of the following trials are out of date? Can you help us by letting us know if you have up-to-date contact information for any of the following:

- Wong LC, Choo YS, Choy D, Sham JST, Ma HK. University of Hong Kong (Gynecologic Oncology 1989; 35:159-63)
- Tseng C-J, Chang-Ting C, Chyong-Huey L, Soong Y-K, Hong J-H, Tang SG, et al. Chang Gung Memorial Hospital, Taipei (Gynecologic Oncology 1997; 66:52-8)
- Singh TT, Singh IY, Sharma DT, Singh N. Regional Institute of Medical Sciences, Imphal, Manipur State, India (Indian J. Cancer 2003; 40(3):101-7)
- Ayala Hernandez JR, de la Huerta RS, Canfield FM, Orozco AF. Hospital de Oncologia, CMN, IMSS, Mexico City (Ginecología y Obstetricia De Mexico 1991; 59:238-42)
- Wong LC, Ngan HYS, Cheung ANY, Cheng DKL, Ng TY, Choy DTK. University of Hong Kong (Journal of Clinical Oncology 1999; 17(7): 2055-60)
- Fernandez DJ, Vidyasagar MS, Rao KK, Shenoy A, Kasturi DP. Kasturba Medical College, Manipal, Karnataka State, India (Proc 16th Annual Meeting of the Assoc. Radiation Oncologists of India 1995; Kerala: 97-103.)
- Bulnes R, Rivera R. Hospital San Felipe, Tegucigalpa, Honduras (Prensa Med Argentina 1986; 73(3):100-3.)

Consumer involvement

In this project we will involve women from the UK who have been affected by cervical cancer as Research Partners. They will work with the Meta-analysis Secretariat on a variety of aspects of the project. By working together we might better understand and interpret side effects data; disseminate the findings widely and identify where more research can be done to address issues that are important to women affected by cervical cancer.

On April 1st, the first meeting of our Reference Group for consumer involvement took place. The meeting highlighted that we need to make it clear what we expect the Research Partners to do and think carefully about what support they may need. We have now drafted information and Terms of Reference for the Research Partners, which the Reference Group is currently reviewing.

We have already recruited two women to be Research Partners and hope to recruit 3-4 more. We aim to hold a first meeting of the Research Partners in the next month or so.

Collaborators' Meeting

The results of the meta-analysis will be presented for the first time at a meeting of the Collaborative Group. We are currently looking at potential venues for this meeting, which we aim to hold this the end of 2005.

In order to do this, we need to complete our analyses by late Autumn. For this reason we have set a deadline of **September 2005** for receipt of data.

Please let us know if this deadline may cause you any difficulty.

For further information please contact:
Claire Vale, Meta-analysis group, MRC Clinical Trials Unit, 222 Euston Road, London NW1 2DA, UK
Tel: +44(0)20 7670 4723 Fax: +44(0)20 7670 4816 cv@ctu.mrc.ac.uk

Project Status: October 2001

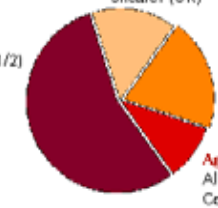
Chemotherapy for locally advanced bladder cancer

A meta-analysis of individual patient data

Status of Data Collection

We are very pleased to report an excellent response to the meta-analysis so far. We have either received or been promised data from 80% of the trials we identified. However, we are still waiting for agreement to collaborate from a further 4 trials. If you can help us to contact the investigators responsible for these trials, we would be very grateful.

Data being prepared
Bassi (Italy)
Cortesi (Italy)
Hall (UK)
Malmstrom (Nordic 1/2)
Raghavan (Australia)
Richards (UK)
Skinner (USA)
Stockle (Germany)
Studer (Switzerland)
Wallace (UK)



Data received
Abol-Enein (Egypt)
Martinez-Piniero (Spain)
Shearer (UK)

Contact not yet established
Bono (Italy)
Einstein (USA)
Freiha (USA)
Natale (USA)

Agreed to collaborate
Allen (USA)
Coppin (Canada)

Since the last newsletter, we have received data from two more trials and would like to thank the responsible investigators. We are currently collating this information to ensure that we represent the data accurately prior to inclusion in the meta-analysis.

Collaborators' Conference

An important feature of all of our individual patient data meta-analyses is that we hold a Collaborators' Conference, where we present and discuss the results for the first time. For this meta-analysis we will be holding the Conference at the Nailcote Hall Hotel, Birmingham, UK on **21-22 February 2002.** This is to coincide with the European Urological Association meeting, which will be taking place from 23-26 February 2002 at the National Exhibition Centre, Birmingham. All of those investigators who provide data for the meta-analysis will be invited to attend.

Nailcote Hall Hotel

The meeting will follow a fairly informal format to allow open and detailed discussion of the results. All collaborators will enjoy spacious, en-suite rooms within the hotel and access to a wide range of leisure facilites. The hotel has a reputation for excellent food and high standards and so we hope will be an ideal venue for our meeting.

Nailcote Hall is a seventeenth century stately home, set amongst 15 acres of countryside. It is just 10 minutes drive from the National Exhibition Centre and Birmingham International Airport. The Meeting will be held in the hotel's conference centre over two days, which will enable us to discuss the results fully whilst giving you time to relax and enjoy the facilities at the hotel.

We would also like to thank those investigators who are currently preparing their data to send to us and urge them to do so **as soon as possible.** Ideally we need to have collected in all of the data by the end of November 2001 to make sure that we have enough time to thoroughly check and verify the data with you before we begin the analyses. **Success of the meta-analysis and Collaborator's Conference relies on your data.** We very much hope to hear from you soon.

Meta-analysis group, MRC Clincial Trials Unit. Tel: +44(0)20 7670 4723 Fax: +44(0)20 7670 4816 cv@ctu.mrc.ac.uk

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
- Security issues
  - request anonymous patient IDs
  - encrypt electronic data
- Accept the trialists coding, secretariat can re-code
  - but suggest data coding
- Offer assistance
  - site visit, financial ??

Data collection: Method of data transfer

- Chemotherapy for ovarian cancer (initiated 1989)
  - 44% on paper, 39% on disk, 17% by e-mail
- Chemotherapy for bladder cancer (initiated 2001)
  - 10% on paper, 10% on disk, 80% by e-mail
- Chemoradiation for cervical cancer (initiated 2004)
  - 10 data sets received so far, 100% by e-mail

Data collection: Time to assemble data

Neoadjuvant chemotherapy for locally advanced cervix cancer

- Protocol and searches
  May 98 - Jan 99
- Invite to collaborate
  Mar 1999
- Collaborators' meeting
  Sep 2000

Neoadjuvant chemotherapy for locally advanced bladder cancer

- Protocol and searches
  Dec 00 - May 01
- Invite to collaborate
  Jun 2001
- Collaborators' meeting
  Feb 2002

Data collection: Managing trial data

- Set up meta-analysis database
- Retain copy of trial data as supplied
- Convert data formats (ASCII, spreadsheet, database, etc.) to database format
  - Excel, Dbase, Access, Foxpro, SPSS, SAS, Stata
  - software more compatible now

Data collection: Managing trial data

- Re-code data to meta-analysis coding
  - calculate or transform derived variables e.g.
    - calculate survival time from date of death / last follow-up and date of randomisation
    - derive disease-free survival from recurrence / progression / metastases and survival variables
- Keep records of all changes to trial data
- Check, query and verify data with trialist
  - improved software automates more tasks
- Then append trial to meta-analysis database

Example individual patient data

Patient ID	Date of randomisation	Treatment allocated	Age	Stage	Grade
001	23 June 1990	Control	46	2b	poor
002	19 Oct 1988	Treatment	39	4	moderate
003	01 Feb 1991	Treatment	51	2a	good
004	09 April 1987	Control	32	3	moderate
203	11 Nov 1989	Control	40	2b	good
204	03 Jan 1990	Treatment	35	2a	poor
205	15 Mar 1992	Control	56	3	moderate

Example individual patient data

PatID	DOR	Arm	Age	Stage	Grade
001	23/06/1990	2	46	4	3
002	19/10/1988	1	39	7	2
003	01/02/1991	1	51	3	1
004	09/04/1987	2	32	5	2
203	11/11/1989	2	40	4	1
204	03/01/1990	1	35	3	3
205	15/03/1992	1	56	5	2

Data checking: Rationale

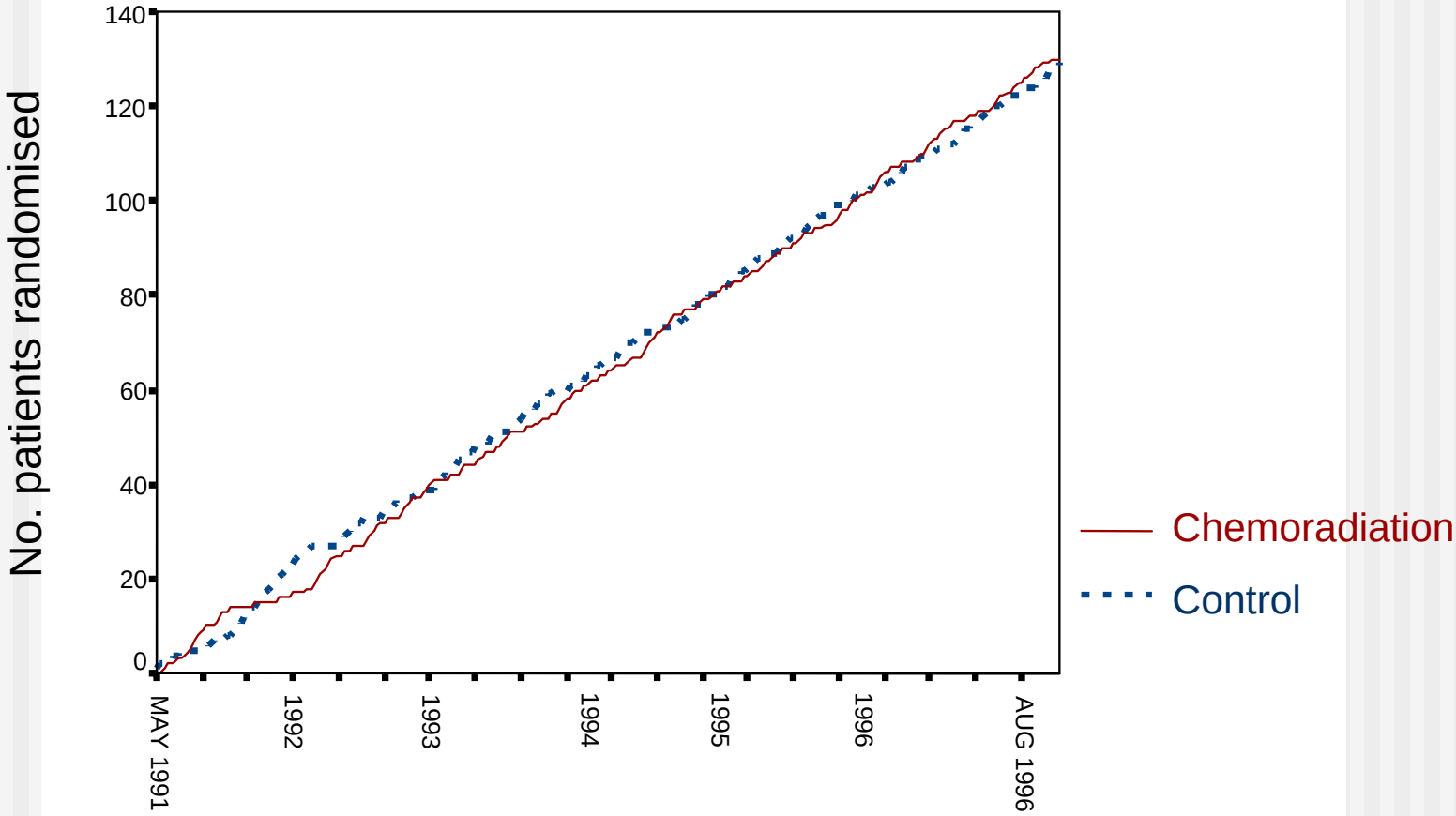
- IPD enables detailed data checking,not easily achieved with any other approach
- Reasons for checking
  - not to centrally police trials or to expose fraud
  - improve accuracy of data
  - improve follow-up
  - ensure appropriate analysis
  - ensure all randomised patients are included
  - ensure no non-randomised patients are included

Data checking: Types

- Standard
  - missing data, excluded patients
  - internal consistency and range checks
  - compare with publication
- Randomisation
  - balance across arms and baseline factors
  - pattern of randomisation
- Follow-up
  - up-to-date and equal across arms
- Verification
  - send tables, data list and trial analysis to trialist

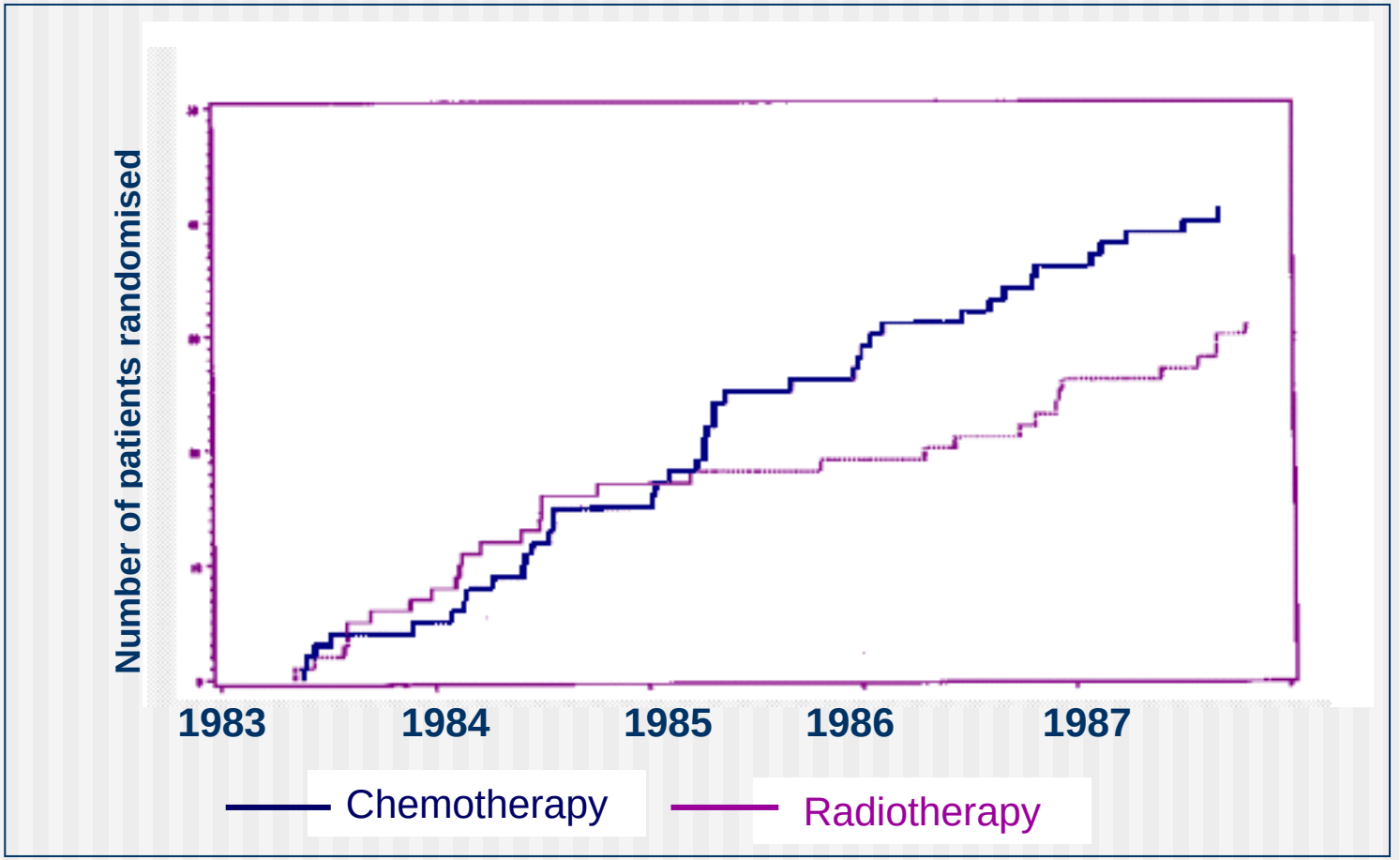
Data checking: Pattern of randomisation

Chemoradiation for cervical cancer



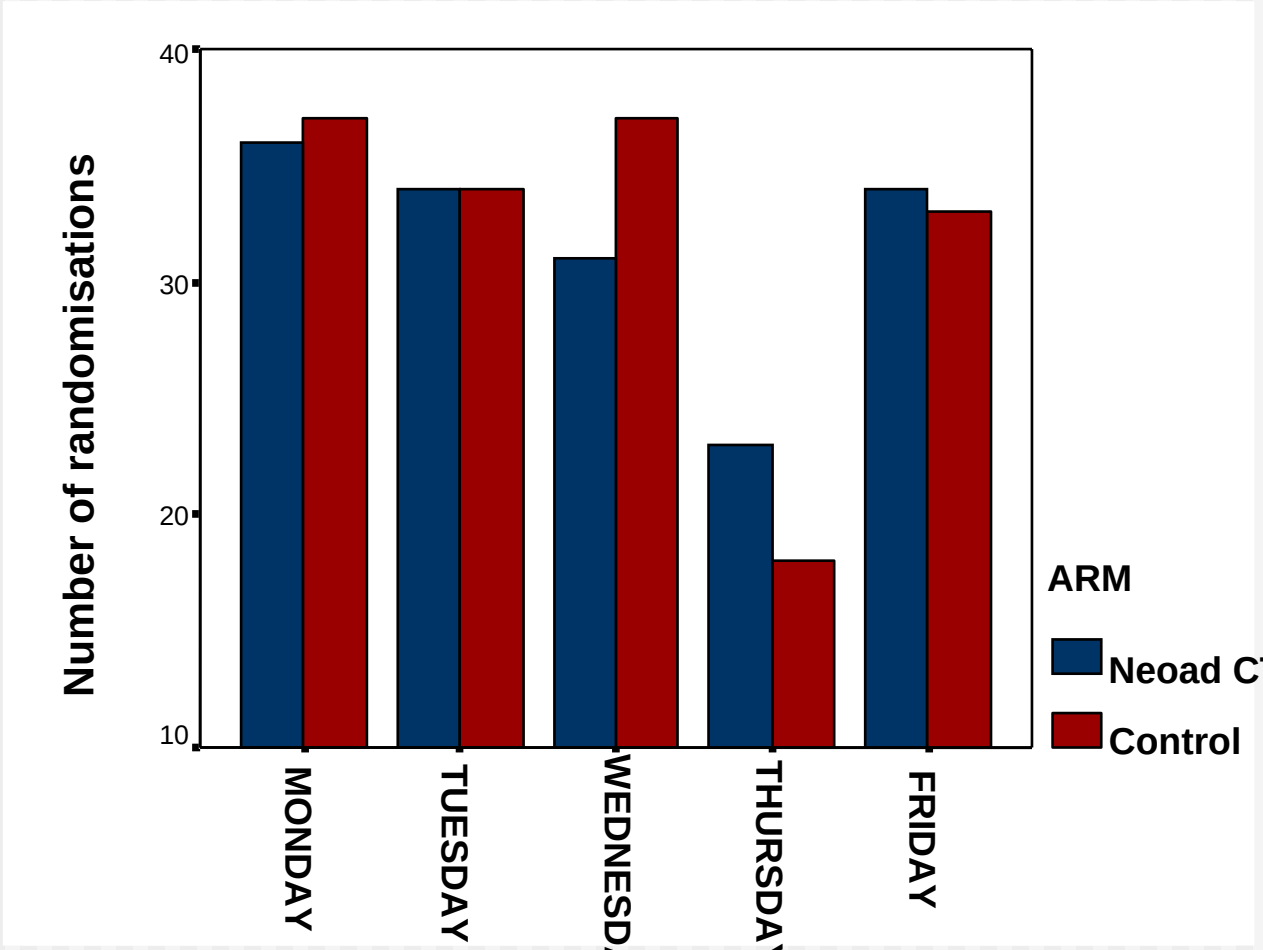
Data checking: Pattern of randomisation

Radiotherapy vs Chemotherapy in Multiple Myeloma



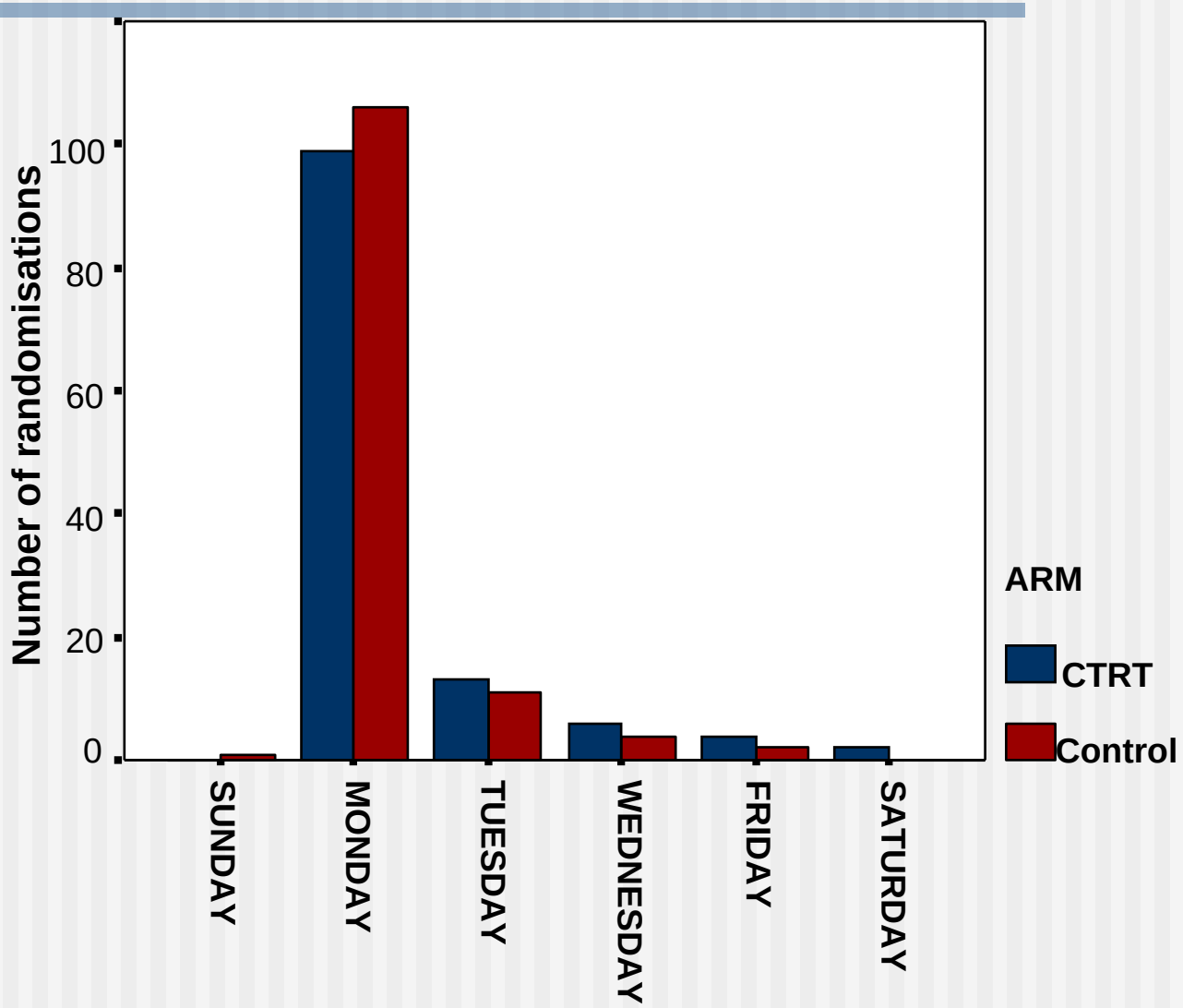
Data checking: Weekday randomised

Chemotherapy for bladder cancer



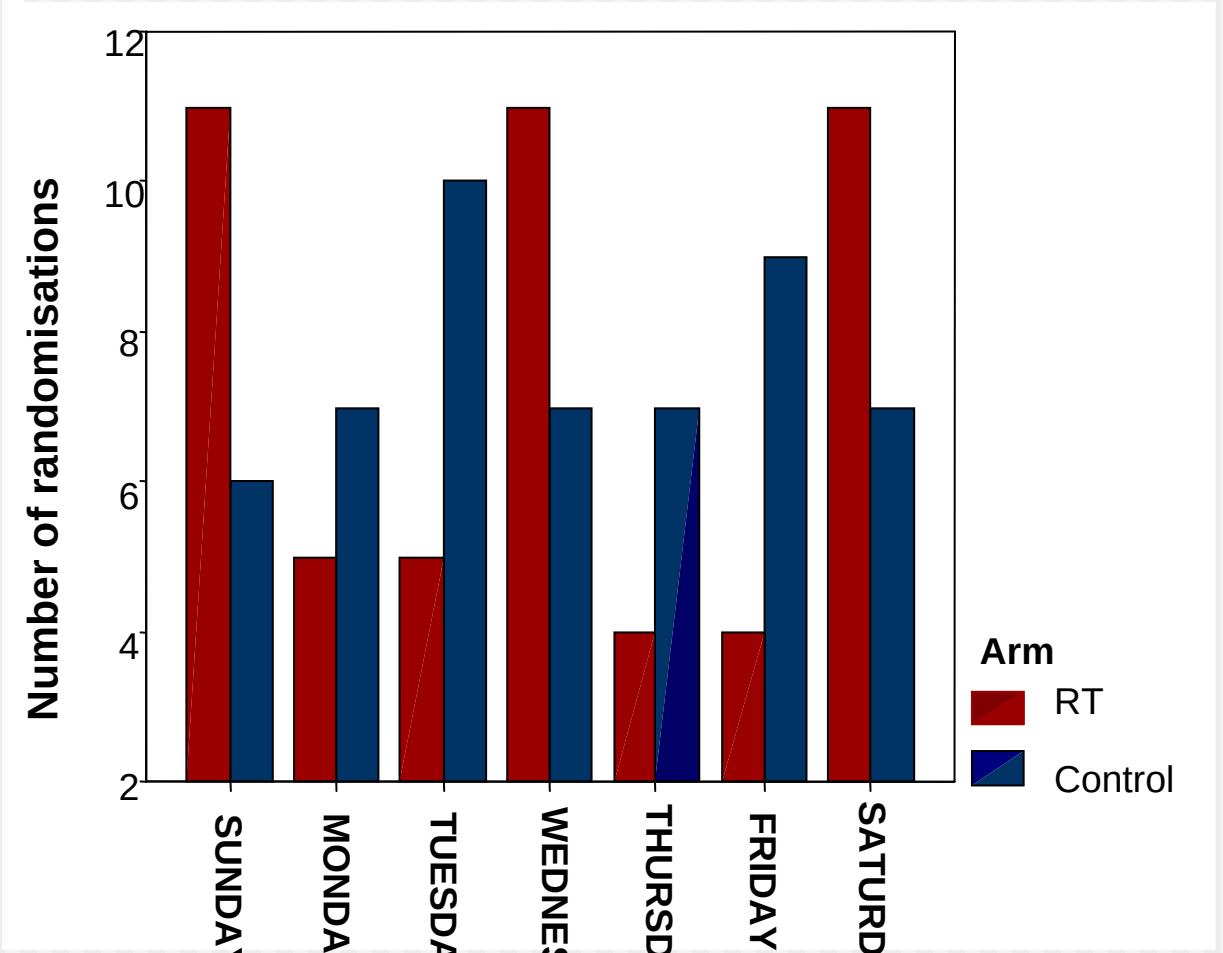
Data checking: Weekday randomised

Chemoradiation for cervical cancer



Data checking: Weekday randomised

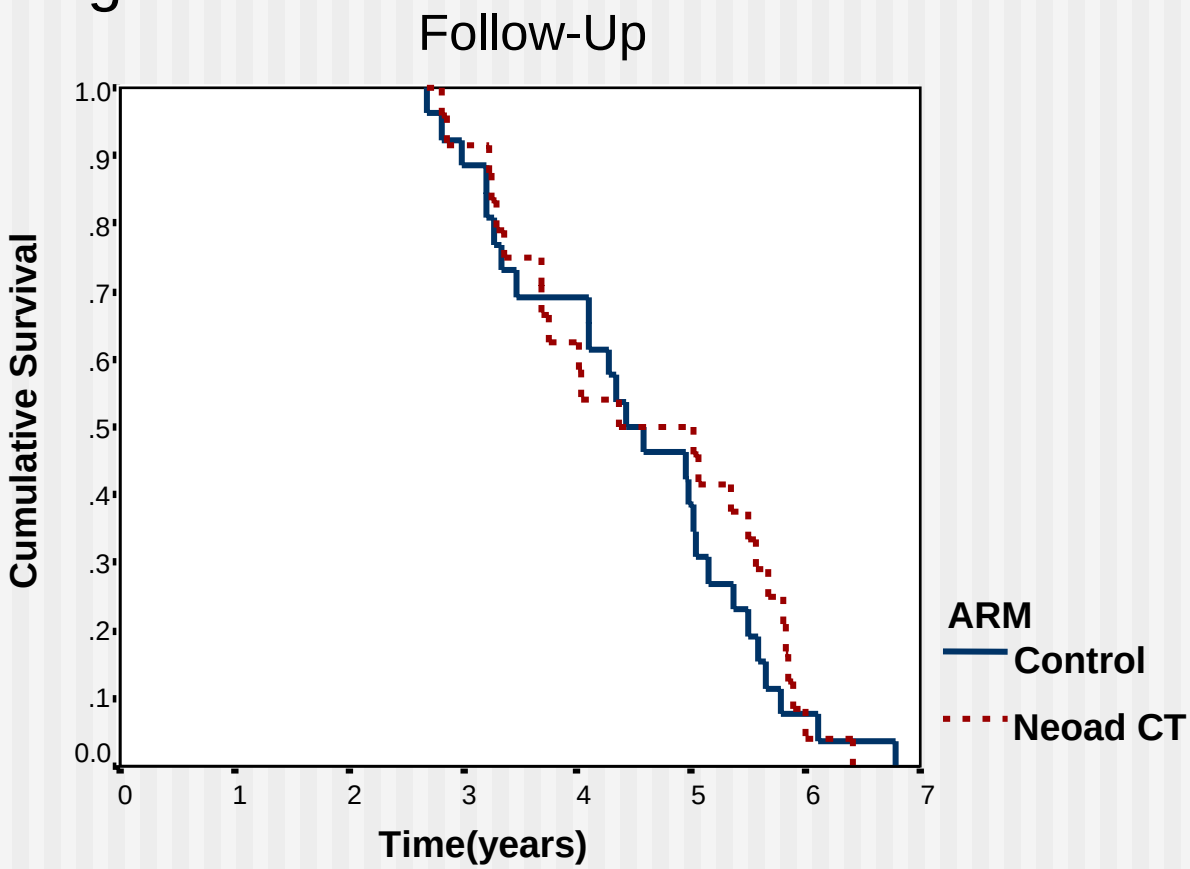
Post-operative radiotherapy in lung cancer



Data checking: Follow up

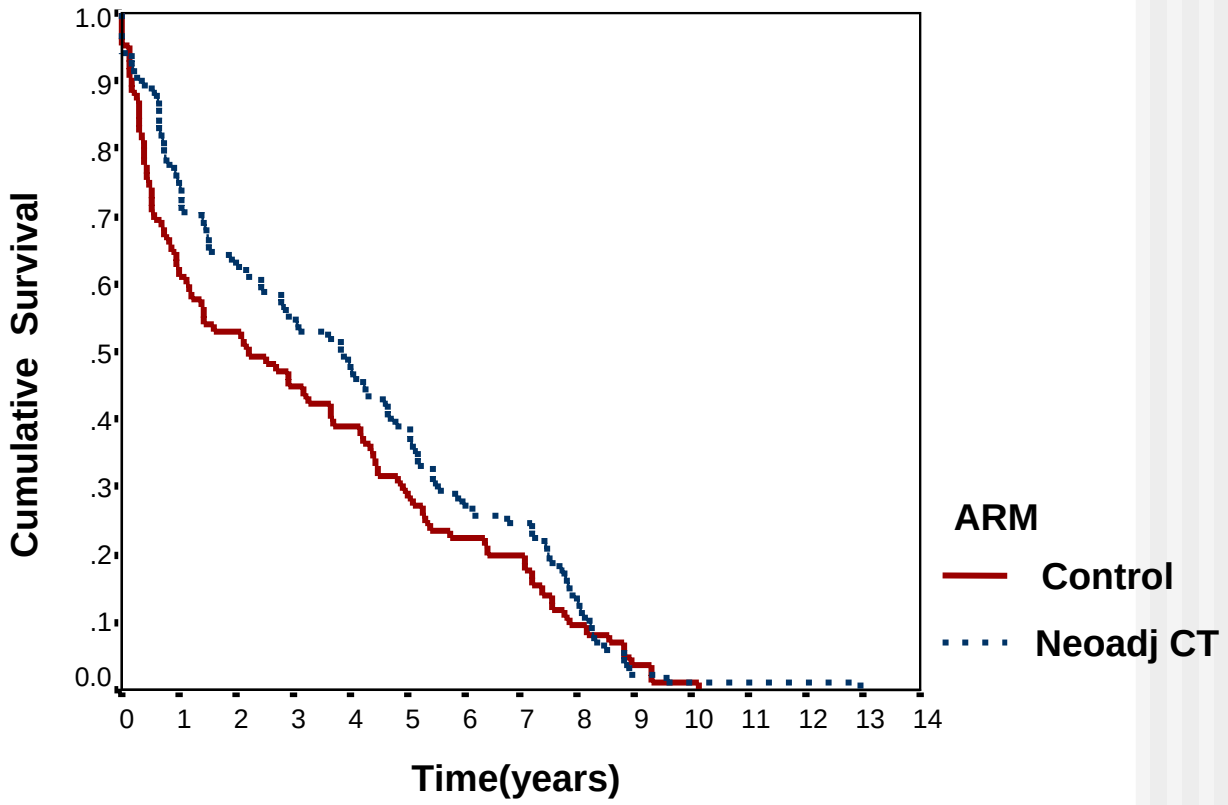
Chemotherapy for bladder cancer

'Reverse' survival curve - take patients event-free, use censoring as event



Data checking: Follow up

Chemotherapy for bladder cancer



Analysing data

Analysis: General principles

- Most commonly, 2-stage analysis
  - same summary statistics used
    - odds ratio, relative risk risk difference, mean difference and standardised mean
  - derived from IPD for each trial
  - combined in meta-analysis, stratified by trial
- Less commonly, 1 stage analysis
  - regression/modelling approach
  - all patients are combined into a single ‘mega’ trial (not appropriate)

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

Benefits of IPD approach to analysis

- IPD can improve analysis quality
- Use the IPD to re-do the analyses from scratch, in the same way in all trials, correcting any problems in original analyses

Benefits of IPD approach to analysis

- E.g Adjuvant bladder cancer - previous systematic reviews based on published data raised concerns about some trials
  - did not use conventional log rank tests to compare treatment and control arms
  - did not conduct intention-to-treat analyses
  - did not clearly define / report outcomes
- Outcomes re-defined from IPD and analyses re-done appropriately

Analysis: Time-to-event

- Major benefit of IPD is that it allows time-to-event analysis, which takes account of
  - whether an event happens
  - the time at which it happens
- For some diseases just the ability to do such an analysis justifies the IPD approach
  - cure is not likely, prolongation of survival
  - time to onset of disease, time free of symptoms

Analysis: Time-to-event

- Individual patient data
  - uses individual times at which each event takes place & takes account of censoring
  - uses log rank O-E & V
  - summarises entire survival experience
  - estimate hazard ratio (HR)
  - allows survival curves

Exploring trial-level differences

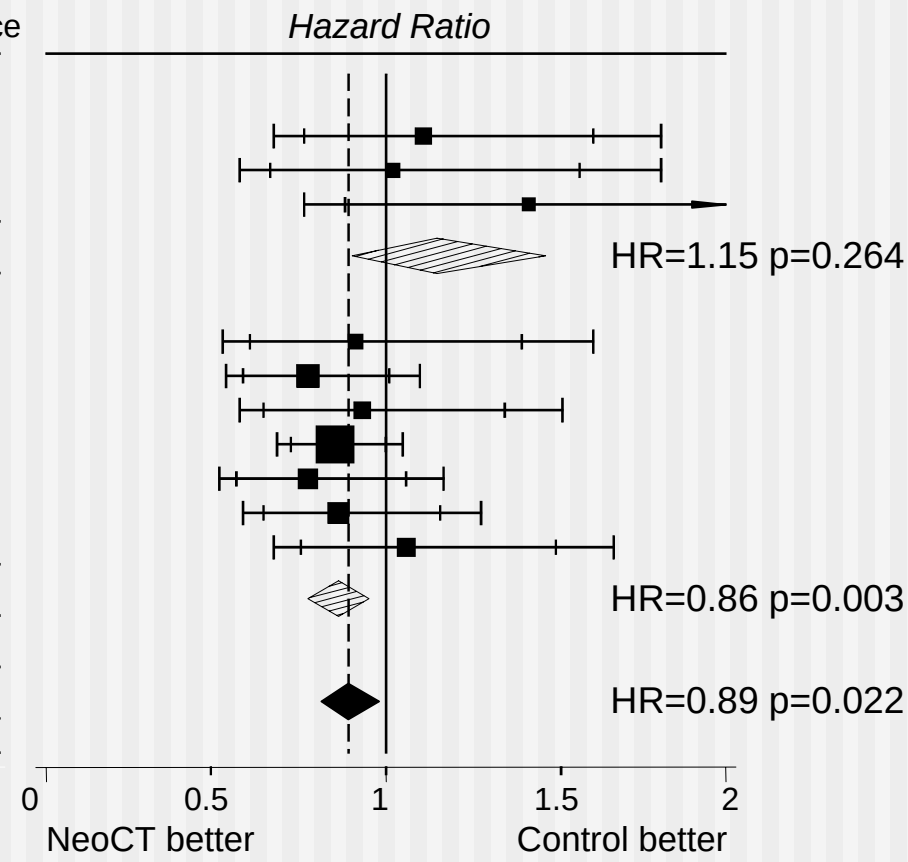
Subset analysis

- Or ‘subgroup’ analysis by trial characteristics
- Group by trial treatments, methodology, quality etc.
  - drug type, treatment scheduling
  - drug dose
- Compares the size of treatment effect on outcome across different trial groups
- Easy to do with published summary data or IPD
- May have more trial level data when collecting IPD

Subset analysis

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 combinaitons				
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

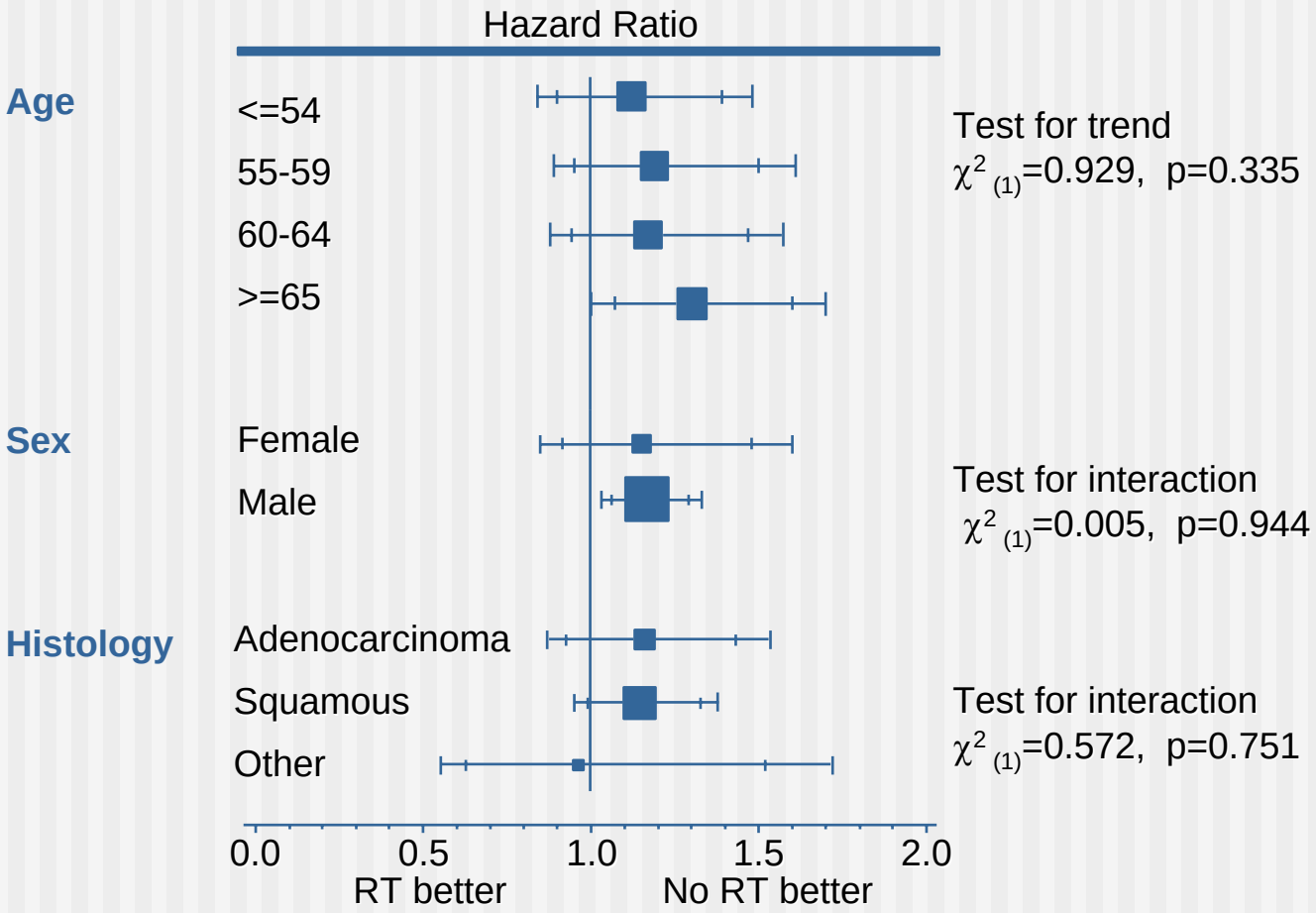
- Group by type of patient
  - age, sex, tumour stage, tumour grade
  - previous hypertensive disorders of pregnancy, previous SGA infant
- Compares size of treatment effect on outcome (not prognosis) across patient subgroups

Exploring patient-level differences

- Difficult to do with published summary data
  - trial-level summaries of patient-level information e.g. mean age
  - rarely report outcome according to patient subgroups
- Easy to do with IPD which allows
  - many combinations of subgroups and outcomes
  - consistent definition of subgroups across trials

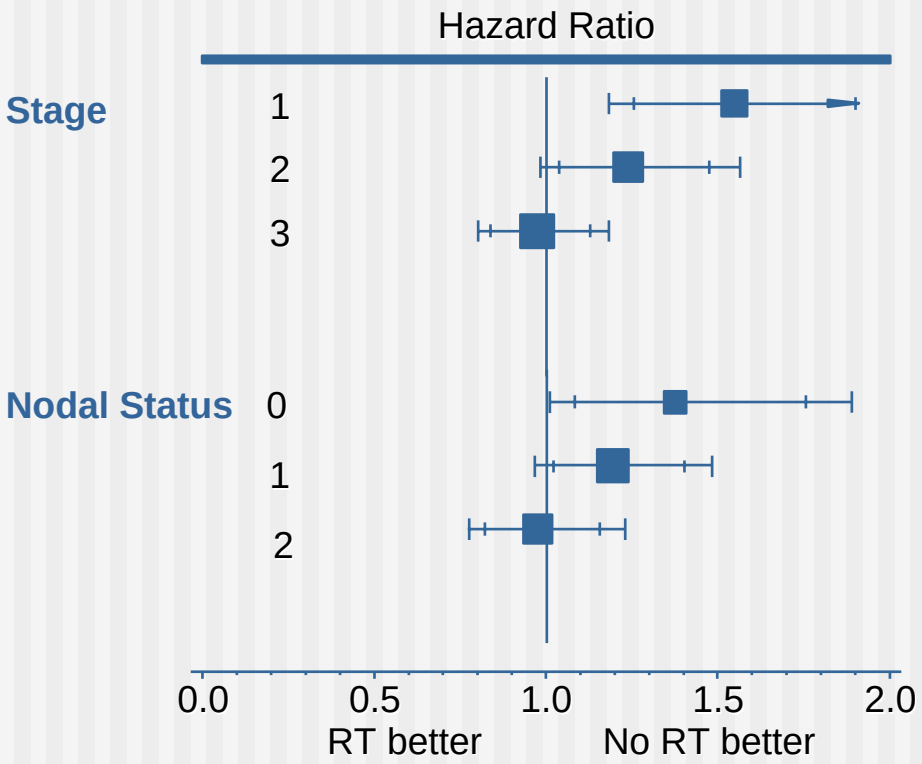
Subgroup analysis

Post-operative radiotherapy for lung cancer



Subgroup analysis

Post-operative radiotherapy for lung cancer



Test for trend
$\chi^2_{(1)}$=13.194, p=0.0003

Test for trend
$\chi^2_{(1)}$=5.780, p=0.016

Analysis: Exploratory/sensitivity

- Assess the robustness of the 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
- Explore additional hypotheses
  - adjustment for imbalances in baseline characteristics
  - prognostic factor analysis

Analysis: Software

- Most IPD groups use own software
  - ours (SCHARP) does 2-stage analyses and produces graphical output for
  - re-developed version available next year
- Input into RevMan
  - primary analysis needs to be done elsewhere
  - for time-to-event outcomes use “IPD” or “generic inverse variance” outcome type
  - for other outcomes use appropriate RevMan outcome types (e.g. “dichotomous” etc)
  - not easy to enter (patient) subgroup analyses

Collaborators' Meeting

- Integral part of IPD approach
- IPD MA a collaborative project
- Incentive to collaborate
- Trialists have opportunity
  - to discuss results
  - to challenge the analysis
  - to discuss interpretation & implication of results
  - Suggest new research
- Sets a deadline to which secretariat and trialists have to work

Resources required

- Likely to be more costly and time-consuming
  - need empirical data
  - but technology advances to cut costs/ time
- But differences between IPD and other types of systematic review may not be so great
- IPD projects can be run concurrently
- Practical / political issues
- Cost of Collaborators' Conference not encountered in other types of review

Getting started

- Contact IPD Meta-analysis Methods Group
  - Administrator: Larysa Rydewska (lhr@ctu.mrc.ac.uk)
  - Website (http://www.ctu.mrc.ac.uk/ukcccr/ipd/home.asp)
    - Database of ongoing and planned IPD reviews
    - Database of methodological projects
    - Reference lists, FAQ,s etc
- Cochrane handbook (to be updated)
- Mentoring - work with someone who has already completed an IPD meta-analysis

To IPD or not to IPD?

- Many benefits particularly
  - improved data and analysis quality
  - improved trial identification, interpretation and dissemination
  - collaboration on further research
- Some benefits possible through collection of additional summary data, but
  - re-doing analyses, re-classifying data etc. may be as much or more work for trialists?
- So why not collect IPD ?