Systematic reviews of trial data

Catrin Tudur Smith
Department of Biostatistics
University of Liverpool
cat1@liv.ac.uk

MRC Hubs for Trials Methodology Research
North West Hub

UNIVERSITY OF LIVERPOOL

Systematic Review

- Attempts to identify, appraise and synthesise all the empirical evidence that meets pre-specified eligibility criteria to answer a given research question

- Use of explicit methods
  - minimise bias
  - produce more reliable findings that can be used to inform decision making

Meta-analysis

‘the statistical analysis of a large collection of analysis results from individual studies for the purpose of integrating the findings‘

Glass (1976)

- Should be a component of a systematic review

Aggregate Data

Table 4. Summary of Efficacy Results: Overall Survival and Progression-Free Survival

	No. of Patients	% GemCis	% Gem	HR	Log-Rank *P*
Median OS					
All patients	190	7.5	6.0	0.80	.15
Locally advanced	39	10.3	10.4	0.68	.29
Metastatic	151	7.2	4.7	0.82	.23
KPS 70%-80%	76	4.9	4.8	1.13	.64
KPS 90%-100%	84	10.7	6.9	0.62	.051*
6-month survival		59.0	50.5		.45
12-month survival		25.3	24.7		.21
Median PFS					
All patients	190	5.3	3.1	0.75	.053
Locally advanced	39	8.6	3.2	0.30	.0053
Metastatic	151	4.2	3.1	0.84	.31
KPS 70%-80%	76	2.8	2.9	0.91	.69
KPS 90%-100%	84	7.7	2.8	0.54	.013†

Abbreviations: GemCis, gemcitabine plus cisplatin; Gem, gemcitabine alone; HR, hazard ratio; OS, overall survival; KPS, Karnofsky performance status; PFS, progression-free survival.
*Peto-Wilcoxon-Test $P = .0079$.
†Peto-Wilcoxon-Test $P = .0020$.

Journal of clinical oncology 2006, *24:3946-3952.*

Individual participant data (IPD)

Patient Number	Treatment	Survival Time (Days)	Status	Age	Sex	Stage
1	E	44	Dead	67	m	IV
2	E	54	Dead	64	m	III
3	E	67	Alive	55	f	III
4	C	43	Dead	79	f	IV
5	C	70	Alive	62	m	IV
6	E	88	Dead	60	f	IV
7	C	99	Alive	57	m	III
8	C	45	Dead	66	m	III
9	E	90	Alive	59	f	III
10	C	23	Dead	53	m	IV

Why IPD ?

Reinstate patients into the analysis who were originally excluded

- Tierney and Stewart (2005) IPD meta-analysis in soft tissue sarcoma
- 99% of the 344 patients that had been excluded from published individual trial analyses were recovered

Meta-analysis with exclusions:	HR=0.85 (p=0.06)
Meta-analysis reinstating all exclusions:	HR=0.90 (p=0.16)

Why IPD ?

Overcome outcome reporting bias (ORB)

– Definition: Selection of a subset of the original recorded outcomes, on the basis of the results, for inclusion in publication

The impact of outcome reporting bias in randomised controlled trials on a cohort of systematic reviews

Jamie J Kirkham,[1] Kerry M Dwan,[1] Douglas G Altman,[2] Carrol Gamble,[1] Susanna Dodd,[1] Rebecca Smyth,[3] Paula R Williamson[1]

- ORB suspected in at least one trial in 34% of 283 Cochrane reviews
- 42 significant meta-analyses
  - 8 (19%) would not have remained significant
  - 11 (26%) would have overestimated the treatment effect by > 20%

BMJ (2010); **340**:c356

Why IPD ?

Detailed exploration of participant level covariates' influence on treatment effect

- Meta-analysis of 5 RCTs of anti-lymphocyte antibody induction therapy vs control for renal transplant patients **(Berlin et al., 2002)**
- Difference in treatment effect between patients with elevated antibodies compared to non-elevated?
  - Aggregate Data to estimate across-trials interaction:
    estimated difference in log odds ratio between elevated and non-elevated patients = -0.01 (p = 0.68)
  - IPD to estimate the pooled within-study interaction:
    estimated difference in log odds ratio between elevated and non-elevated patients = - 1.33 (p = 0.01)

Why IPD ?

Detailed exploration of participant level covariates influence on treatment effect

- **Lambert et al., 2004** simulated 1000 meta-analyses, each with 5 trials and treatment effective for high risk patients but ineffective for low risk patients
- Each meta-analysis analysed first using IPD, and then using meta-regression; treatment-covariate interactions estimated in both cases
  - IPD approach has a power of 90.8% to detect interactions
  - AD approach (meta-regression) has a power of 10.8% detect interactions

Why IPD?

General disadvantages

- Time consuming
- More costly
- May not be able to obtain all IPD – retrieval bias

THE COCHRANE COLLABORATION®

The Cochrane Collaboration Supports Free Access to all Data from all Clinical Trials

To ensure that all data from all clinical trials become publicly available, without undue delay, The Cochrane Collaboration calls for:

- All randomised clinical trials to be registered at their inception, before recruitment of the first participant
- All data from all randomised clinical trials, including raw anonymised individual participant data that do not allow identification of individual participants, and the corresponding trial protocols, to become publicly available free of charge and in easily accessible electronic formats;
- Governments to consider introducing legislation that makes it a requirement to provide these data from all trials to the public within 12 months from the end of the randomised phase of the trial, in accordance with most international calls for data sharing;
- Governments also to consider punitive measures for non-compliance; a requirement to continue to hold and make available core data indefinitely, or to pass such data to a central and accessible repository; and a recognition that ownership of trial data should be shared between sponsors, investigators and trial participants.

http://www.cochrane.org/about-us/our-policies/support-free-access-to-all-data-from-all-clinical-trials

STATEMENT IS CURRENTLY UNDER REVIEW

EMA policy – observation 1

Respect for the boundaries of patients' informed consent: Patients participate in clinical drug trials in the hope that their data will support the development and assessment of a particular medicine that is useful for the treatment of their disease, and will benefit the advancement of science and public health. The Agency takes the view that any other use of patient data oversteps the boundaries of patients' informed consent, and shall not be enabled by the policy.

- What might the definition of 'any other use of patient data' be?
- How would decisions be reached about whether 'any other use' oversteps the boundaries?
- What about methodological research?

EMA policy – observation 2

4.1.2. Category 2

CT data/documents *without protection of personal data (PPD) concerns*: all documents where PPD is not an issue for concern. The lack of concern for PPD may result from the fact that:

- the document does not contain personal data in the first place (e.g. summary tables presenting only aggregated data), or;
- any personal data in the document have been adequately de-identified, or;
- there are public-health reasons why personal data can be made public, overriding considerations of PPD (Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data; and Regulation (EC) 45/2001on the protection of individuals with regard to the processing of personal data by the Community institutions and bodies and on the free movement of such data). This is the case with personal data of CT personnel.

- Category 2 data are ‘open’ access, available as downloads from Agency’s website

EMA policy – observation 2

- Yes ‘open’ access in principle
  - least burdensome and bureaucratic
  - best way to facilitate research

But

- Should the Agency collect some basic information about who and where these data are being downloaded to?
- Should the Agency request an ‘agreement’ with data downloader?

EMA policy – observation 3

155 **4.1.3. Category 3**

156 *CT data/documents with PPD concerns*: all documents, data and information contained in a Clinical
157 Study Report (see Annex II) that do not fall under Category 2. These are essentially 'raw CT data' (see
158 definition above).

162 **Therefore, all CT data with PPD concerns are 'controlled access' (designated 'C' in Annex II).**

163 Two complementing levels of protection are foreseen to provide best-possible assurance against
164 retroactive patient identification.

165 1. Appropriate de-identification:

176 2. Controlled access:

- Recall that “appropriately de-identified data” are category 2 data
- Therefore, could category 3 data be classified as category 2 i.e. ‘open access’???

EMA policy – observation 4

1. Appropriate de-identification:

Adequately de-identified data can be valuable, and de-identifying the data does not necessarily compromise the analytical utility of the data.

The data to be made available may include all the data sets or a relevant subset (e.g. the main analysis set, containing a limited number of indirect identifiers, so that the risk of compromising subjects' identity in case of wide publication of those data is considered to be absent or sufficiently low, while preserving the ability to replicate the main analysis).

- Gives an opportunity to ‘omit’ data items
- Potential for bias ?
- This will not help researchers undertaking systematic reviews!!

EMA policy – observation 5

2. Controlled access:

'Controlled access' shall mean that access to 'C' data will only be granted after the requester has fulfilled the following requirements:

- requester has identified themselves, and the Agency has verified the identity of the requester;
- requester, whether a natural or legal person, is established in the EU;

- How are requester details “verified”?
- Why only “EU established”??
  - Completely contradicts earlier statements
  - Some patient data may be from outside EU?
  - Could potentially be a barrier to collaborative research

EMA policy – observation 6

- requester has agreed, by way of legally binding data-sharing agreement, to:
  - access controlled data for the sole purpose of addressing a question or conducting analyses that are in the interest of public health, in line with the spirit of informed consent; this may include, inter-alia, meta-analyses, re-analysis, or exploratory analyses for additional hypothesis generation. An exhaustive and detailed list of the aims of accessing the data shall be submitted at the time of the request (though not necessarily a statistical analysis plan; see below),
  - refrain from any attempt to retroactively identify patients in CTs; this includes linkage of CT data accessed with other databases or programs that could result in the identification of patients,
  - refrain from using CT data accessed for any purposes that are deemed outside the boundaries of patients' informed consent,

- Should apply to <u>all</u> data not just those classified as ‘C’ data?

EMA policy – observation 7

The Agency will not immediately disclose any information about the requester, but will publish the identity (name, affiliation and contact details provided), the list of the aims of accessing the data provided, and any uploaded documents (statistical analysis plan and/or others), or the requester's decision to decline to upload documents (as applicable):

- one year after the date of accessing the data, or;
- upon publication, in whatever format or medium, of results, conclusions, or other communications that resulted from the requester accessing 'C' data, or;
- in case of an urgent public-health need, or;
- upon court order,

whichever comes first.

- Increase potential for duplicate research?
- Why not disclose information immediately for all requesters for full transparency?

EMA policy – observation 8

- Mechanism for giving appropriate recognition to the original research team?
- An important component of IPD meta-analysis is the open communication with original researchers

  -Obvious resource implications but would be good to consider how this might be facilitated

Concluding remarks

- IPD provides significant advantages for meta-analysis eg
  - More complete meta-analysis
  - Overcome bias
  - Essential to make advancements in ‘Personalised medicine’
- EMA policy is extremely good news for scientific research
  - Better quality reviews, better quality evidence for health care decision making
  - Benefit to patients

Concluding remarks

- But, limited of course to CTIMPs used for marketing approvals in Europe so may be many years before tangible benefits
- Will hopefully set a precedence for other initiatives
- Systematic review community will need to consider implications:
  - Training reviewers and statisticians
  - Additional resources

Thank you

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