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Johns Hopkins Bloomberg School of Public Health

Navigating the clinical study report (CSR): A road map to the data abstraction of CSRs for systematic reviews

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Trusted evidence.
Informed decisions.
Better health.

Purpose and Structure of this Workshop

- Introduction to Clinical Study Reports (CSRs) and their use in systematic reviews (10 minutes)
- Small group scavenger hunt using excerpts from CSRs (30 minutes)
- Discussion of findings from scavenger hunt (30 minutes)
- Lessons learned from our experiences (10 minutes)
- Evaluation (10 minutes)

What is a clinical study report (CSR)?

"integrated full report of an individual study of any therapeutic, prophylactic or diagnostic agent (referred to herein as drug or treatment) conducted in patients, in which the clinical and statistical description, presentations, and analyses are integrated into a single report"[1]

Example of a CSR: https://industrydocuments.library.ucsf.edu/drug/docs/#id=llgw0217

1. ICH 1995

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What information is in a CSR?

- Study design
- Risk of bias
- Analysis methods
- Results for all outcomes
- All adverse events
- Case report forms
- Individual patient data

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CSR Structure Example

Section Description	Number of Pages
Title page/Synopsis	9
Table of contents	9
List of abbreviations and definitions of terms	2
Ethics	1
Investigators and study administrative structure	1
Introduction	1
Study objectives, plan, and procedures	43
Study subjects	10
Efficacy results	25
Safety results	48
Discussion and overall conclusions	6
Tables, figures, and graphs referred to but not included in the text	1458
Appendix: Study information (e.g., Protocol, Case Report Forms, Statistical Analysis Plan, Publications based on study)	2097
Appendix: Subject data listings	4316

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Individual patient data in CSRs

- Not always available
- Can be extracted into usable format using optical character recognition software

IPD Example

Quetiapine Fumarate 5077US/0049

Listing 12.2.9.3 Height, Weight and BMI

TREATMENT	SUBJECT CODE	WINDOWED VISIT	DATE	DAY	HEIGHT (cm)	WEIGHT (kg)	BMI	CHANGE FROM BASELINE WEIGHT	CHANGE FROM BASELINE BMI
QUETIAPINE 600 MG (BIPOLAR I)	E0019005	SCREEN	[redacted]	-6	163.0	66.0	24.8		
		DAY 57		59		66.0	24.8	0.0	0.0
	E0019015	SCREEN		-14	173.0	81.0	27.1		
		DAY 57		57		80.0	26.7	-1.0	-0.4
	E0020004	SCREEN		-18	170.0	91.0	31.5		
		DAY 43		45		91.0	31.5	0.0	0.0
	E0020010	SCREEN		-8	160.0	64.0	25.0		
		DAY 57		57		66.0	25.8	2.0	0.8
	E0020014	SCREEN		-7	165.0	54.0	19.8		
		DAY 57		56		54.0	19.8	0.0	0.0
	E0020021	SCREEN		-6	173.0	143.0	47.8		
		DAY 57		57		152.0	50.8	9.0	3.0
	E0020023	SCREEN		-8	173.0	99.0	33.1		
		DAY 57		56		99.0	33.1	0.0	0.0
	E0022007	SCREEN		-6	158.0	82.0	32.8		
	E0022010	SCREEN		-7	184.0	80.0	23.6		
		DAY 57		57		81.0	23.9	1.0	0.3
	E0022012	SCREEN		-14	177.0	108.0	34.5		
		DAY 57		57		112.0	35.7	4.0	1.2
	E0022019	SCREEN		-7	181.0	102.0	31.1		
		DAY 57		58		104.0	31.7	2.0	0.6
	E0022025	SCREEN		-20	160.0	72.0	28.1		
		DAY 8		8		72.0	28.1	0.0	0.0

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Benefits of using CSRs in meta-analysis

- Access to unpublished results
  - Whole outcomes (e.g., quality of life)
  - Subgroups (e.g., sex, comorbid conditions)
  - Adverse events
- Standardization of analysis methods
  - Population of analysis
  - Methods for handling missing data

Challenges of using CSRs

- Hard to obtain
- Extremely long
  - Our 8 CSRs: average length 2917 pages, range 1315-8027
- Contradicting information

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Case example: Tamiflu[2, 3]

- Meta-analysis in 2003 showed:
  - Reduced secondary complications and hospital admission
- FDA had different conclusions:
  - Tamiflu did not reduce complications
- Cochrane review of CSRs

2. Jefferson 2012; 3. Doshi 2012

Gains from using CSRs[2, 3]

- Access to trials with delayed or no publication
- Fine details of trial conduct
- Subgroup analysis
- Information about adverse events
- Ability to assess of validity of other data sources

2. Jefferson 2012; 3. Doshi 2012

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Questions?

References

1. ICH E3. Structure and content of clinical study reports. London, UK: International Conference on Harmonisation; 1995.
2. Jefferson T, Jones MA, Doshi P, et al. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. Cochrane Database Syst Rev. 2012;1(1).
3. Doshi P, Jefferson T, Del Mar C. The imperative to share clinical study reports: recommendations from the Tamiflu experience. PLoS medicine. 2012;9(4):e1001201.

Small groups

- Form groups of 2-3
- Each group will extract data from a CSR section
- Each group will have different sections of the CSR
- We will compare groups' findings and discuss the benefits and challenges of using CSRs for systematic reviews

Data Extraction Item 1

What population(s) (e.g., intent-to-treat, all randomized, evaluable, etc.) will be used for the efficacy analyses and how are these populations defined?

Data Extraction Item 2

Which outcomes are identified as "secondary" outcomes?

Data Extraction Item 3

The primary outcome was change from baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) at the end of the study (day 57). What data would you extract for meta-analysis of this outcome?

Follow-up Discussion

- What was difficult?
- What was unexpected?

Lessons Learned

- If the CSR is in PDF format, make sure the text is searchable
- Utilize the “Add note to text” function

Example

A9451008 CONTENTS

All concomitant medications were recorded in the subject's medical record and on the CRFs.

2.2.5 Treatment Compliance

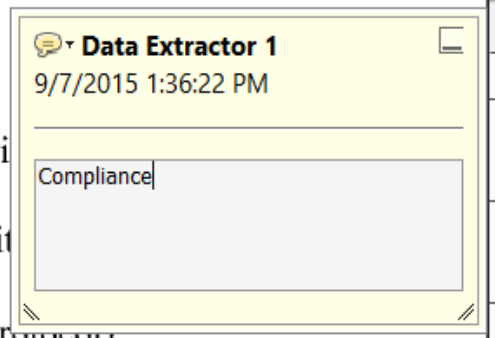
Lack of study compliance was defined as 1 or more of the following:

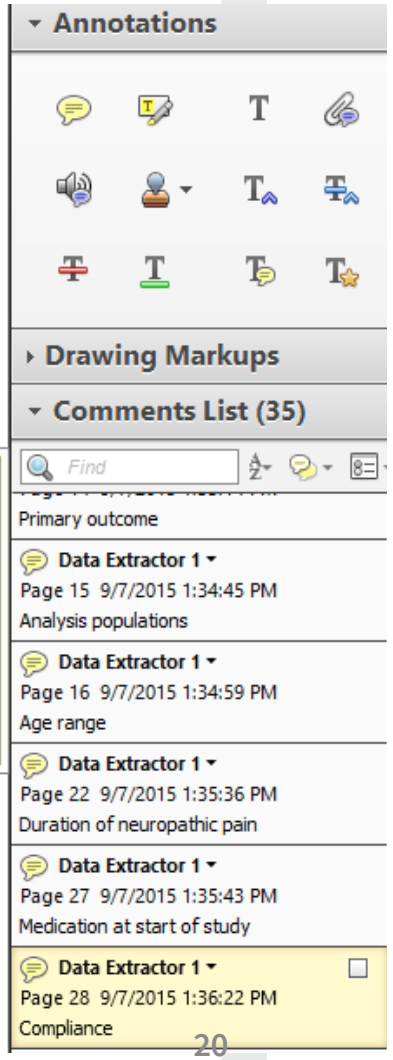
- Missing 3 or more consecutive days of study medication, beginning wi
  placebo lead-in phase of the study.
- Missing >15% of study medication between any 2 visits, beginning wit
- Missing a required visit (as defined in Appendix A of the protocol).
- Starting any prohibited medication (as defined in Appendix C of the protocol).

2.3 Diagnoses and Criteria for Inclusion of Subjects

2.3.1 Inclusion Criteria

1. Males or non-pregnant, non-lactating females not of childbearing potential;





Lessons Learned

- If the CSR is a PDF, make sure the text is searchable
- Utilize the “Add note to text” function
- Make *a priori* rules about which sections you will “trust” when there are discrepancies
- Completely specify outcome
  - Comparing outcomes in CSRs with outcomes in other sources can help identify potential for reporting bias

Wrap-Up

- Remaining questions
- Possible solutions to problems that arise

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