Figure 1. Screening form for literature

RAND EPC EPHEDRA PROJECT **SCREENER FORM**

1. Article ID: _____

2. First Author: _____
   (LAST NAME OF FIRST AUTHOR)

3. Reviewer: _____

4. Research topic: **CHECK ALL THAT APPLY**
   - Ephedra ..... ☐
   - Ephedrine ..... ☐
   - Pseudoephedrine ..... ☐ **(STOP)**
   - Unclear ..... ☐
   - Other (_____) .. ☐ **(STOP)**

5. Subject of article: **CHECK ALL THAT APPLY**
   - Weight Loss ..... ☐
   - Athletic Performance ..... ☐
   - Adverse Events ..... ☐
   - Other (_____) .. ☐ **(STOP)**

6. Study population: **CHECK ALL THAT APPLY**
   - Human ..... ☐
   - Animal ..... ☐ **(STOP)**
   - Unclear ..... ☐
   - Other (specify: _____) .. ☐ **(STOP)**

7. Study design: **CHECK ALL THAT APPLY**
   - Descriptive (historical, editorial etc.) ☐
   - Review/meta-analysis..... ☐
   - Randomized Clinical Trial..... ☐
   - Controlled Clinical Trial..... ☐
   - Case Series ..... ☐
   - Case Report: medical literature... ☐
   - Case Report: popular literature ... ☐
   - Other (specify: _____) .. ☐

8. Does the intervention contain caffeine or caffeine-containing herbs? **CIRCLE ONE**
   - Yes..... 1
   - No 2
   - Unclear 7
   - Not applicable..... 8

9. Language of article: **CIRCLE ONE**
   - English..... 1
   - Chinese..... 2
   - Japanese 3
   - Other (specify: _____) ... 4

Notes:

Figure 2. Quality review form for literature

RAND EPC EPHEDRA PROJECT **QUALITY REVIEW FORM**

Article ID:_____ Reviewer:_____

First Author: _____
(Last Name Only)

Study Number: ___of____Description:_____
(Enter '1 of 1' if only one) (If more than one study)

1. Design: **CIRCLE ONE**
   - RCT 1
   - CCT 2
   - Other ..... 3 **(STOP)**

(IF NOT RCT OR CCT, CHANGE STUDY DESIGN ON COVER SHEET AND STOP)

2. Were any adverse events mentioned?

	CHECK ALL THAT APPLY	
	CHECK OR CODE	**CHECK IF SERIOUS**
Cardiovascular	☐ (01)	☐
Death	☐ (02)	☐
Endocrine	☐ (03)	☐
Neurologic	☐ (04)	☐
Psychiatric	☐ (05)	☐
Pulmonary	☐ (06)	☐
Renal	☐ (07)	☐
Other:	(___ ___, ____ ___, ____ ____)	
No adverse events	☐ (96)	
None mentioned	☐ (97)	
Mentioned but not described	☐ (98)	

3. For articles on weight loss, is there a follow up of at least 8 weeks?
   CIRCLE ONE
   - Yes 1
   - No ..... 2 **(STOP)**
   - Not applicable 9

4. Is the study described as randomized? **CIRCLE ONE**
   - Yes 1
   - No 2

5. If the study was randomized, was method of randomization appropriate?
   CIRCLE ONE
   - Yes 1
   - No 2
   - Method not described 8
   - Not applicable 9

Figure 2. Quality review form for literature (continued)
RAND EPC EPHEDRA PROJECT **QUALITY REVIEW FORM**

6. Is the study described as: **CIRCLE ONE**
   Double blind 1
   Single blind, patient 2
   Single blind, outcome assessment 3
   Open 4
   Blinding not described 8
   Not applicable 9

7. If reported, was the method of double blinding appropriate?
   CIRCLE ONE
   Yes 1
   No 2
   Double blinding method not described 8
   Not applicable 9

8. If study was randomized, did the method of randomization provide for concealment of allocation? **CIRCLE ONE**
   Yes 1
   No 2
   Concealment not described 8
   Not applicable 9

9. Are withdrawals (W) and dropouts (D) described?
   CIRCLE ONE
   Yes, reason described for **all** W and D 1
   Yes, reason described for **some** W and D 2
   Not described 8
   Not applicable 9

10. Is this a cross-over study design? **CIRCLE ONE**
    Yes 1
    No 2
    Not described 8

11. Are outcome data reported separately for or primarily on over 75% of any of the following populations? **CHECK ALL THAT APPLY**
    Race:
    - African-Americans ..... ☐ (01)
    - Hispanic ..... ☐ (02)
    - Asian ..... ☐ (03)

    Gender:
    - Male ..... ☐ (04)
    - Female ..... ☐ (05)

    Age:
    - Adolescents (12-17) ..... ☐ (06)
    - Children (0-11) ..... ☐ (07)

    Misc.:
    - Athletes ..... ☐ (08)
    - Military ..... ☐ (09)

    Other:
    (Enter code: ____ ____, ____ ____, ____ ___, ____ ____)

Figure 2. Quality review form for literature (continued)
RAND EPC EPHEDRA PROJECT **QUALITY REVIEW FORM**

12. What types of comorbidities are described in the groups?

CHECK ALL THAT APPLY

Overweight/ Obesity (BMI > 27) ..... ☐ (01)
Coronary Artery Disease ..... ☐ (02)
Hypertension..... ☐ (03)
Neurological..... ☐ (04)
Psychiatric ..... ☐ (05)
Asthma..... ☐ (06)
Gastrointestinal..... ☐ (07)
Diabetes..... ☐ (08)
Renal ..... ☐ (09)
Other:
(Enter code: ____ ____, ____ ____, ____ ____, ____ ____)

Not described ..... ☐ (98)

Figure 2. Quality review form for literature (continued)
RAND EPC EPHEDRA PROJECT **QUALITY REVIEW FORM**

Arm ___ of ___ Description _____

If the study has a control/usual care arm, enter that data in arm 1.
Otherwise, enter data for the groups in order of first mention.

13. What type of arm is this? **CIRCLE ONE**
    Placebo.....1
    Usual care.....2
    Primary intervention.....3
    Other active treatment.....4

14. Is there a significant co-intervention?
    CHECK ALL THAT APPLY OR ENTER CODE
    Diet ..... ☐ (01)
    Exercise ..... ☐ (02)
    Education ..... ☐ (03)
    Other: (enter code ___ ___, ___ ___, ___ ___)
    No co-interventions..... ☐ (97)

15. What was the sample size in this arm?

    ___ ___ ___ , ___ ___ ___ Entering ___ ___ ___ , ___ ___ ___ Completing

    (ENTER 999,999 IF NOT REPORTED.)

16. What is the common, proprietary, and/or scientific (genus, genus/species) name of the product?
    ENTER CODE OR CIRCLE ONE OF THE BELOW
    Code: ____ ____
    None 97
    Not described 98
    Not applicable..... 99

17. Of which main constituents is the product made?
    ENTER CODE OR CIRCLE ONE OF THE BELOW
    Code: ____ ____, ____ ____, ____ ____
    None 97
    Not described 98
    Not applicable..... 99

18. Was chemical analysis performed on ephedrine alkaloids?
    CIRCLE ONE
    Yes..... 1
    No 2
    Not described 8
    Not applicable..... 9

Figure 2. Quality review form for literature (continued)
RAND EPC EPHEDRA PROJECT **QUALITY REVIEW FORM**

19. Intervention:

INTERVENTION	TOTAL DAILY DOSE	AMOUNT PER DOSE	UNITS	ROUTE OF ADMINISTRATION	DURATION	UNITS	EPHEDRINE ALKALOIDS
1 ____	_____	_____	_____	_____	_____	____	_____
2 ____	_____	_____	_____	_____	_____	____	_____
3 ____	_____	_____	_____	_____	_____	____	_____
4 ____	_____	_____	_____	_____	_____	____	_____
Enter code	Enter a number 998. ND 999. NA	Enter a number 998. ND 999. NA	1. μg 2. mg 3. gm 4. mg kg^{-1} 8. ND 9. NA	1. PO 2. IV 8. ND 9. NA	Enter a number 998. ND 999. NA	1. Hour 2. Day 3. Week 8. ND 9. NA	1. Included in total ephedrine alkaloids 2. In addition to ephedrine alkaloids 3. Unclear 8. ND 9. NA

20. Type of outcomes measured:

ENTER THE CODE FOR EACH OUTCOME MEASURED

____ ____
____ ____
____ ____

21. When, relative to the start of the intervention, were outcomes reported?

ENTER THE NUMBER AND LETTERS IN THE APPROPRIATE BOX

	NUMBER	UNIT
1st follow-up		
2nd follow-up		
3rd follow-up		
4th follow-up		
5th follow-up		
6th follow-up		
Additional follow-ups:		

Use the following abbreviations for units:

MI	minute
HR	hour
DY	day
WK	week
MO	month
YR	year
ND	not described
NA	not applicable

END

Figure 3a. Adverse events analysis form for death, MI, stroke cases

RAND EPC EPHEDRA PROJECT **ADVERSE EVENTS ANALYSIS FORM**

Article ID:_____ Reviewer:_____

FDA Case Number: _____

Form Number: _____of_____(Fill out one form for each subject)

1. Does adverse event form report on ephedra or ephedrine?

CIRCLE ONE

Yes..... 1
No/ Unsure.....2 **(STOP)**

(IF NOT EPHEDRA/EPHEDRINE THEN STOP)

2. Are there adequate data available to analyze this report?

CIRCLE ONE

Yes..... 1
No .....2 **(STOP)**

(IF NOT ADEQUATE DATA THEN STOP-
MUST BE A SERIOUS ADVERSE EVENT AND PRODUCT SPECIFICALLY IDENTIFIED)

3. What additional sources of data are available?

CHECK ALL THAT APPLY AND/OR ENTER CODE

FDA affidavit ..... ☐ (01)
Medical records ..... ☐ (02)
Legal documents ..... ☐ (03)
Labels ..... ☐ (04)
Other (_____)☐ (96)
None of the above ..... ☐ (97)

4. What was the adverse event? **CHECK ALL THAT APPLY AND/OR ENTER CODE**

(Start codes at 40)

Death ..... ☐ (01)
MI..... ☐ (02)
CVA ..... ☐ (03)
Other serious adverse event (enter code: _____)
Other (_____)☐ (96)
None of the above ..... ☐ (97) **(STOP)**

5. IF MI, what procedures were done? **CHECK ALL THAT APPLY**

Coronary angiography..... ☐ (01)
Revascularization ..... ☐ (02)

6. IF MI, what was(were) the outcome of the procedure(s)?

No significant CAD ..... ☐ (01)
< 3V CAD..... ☐ (02)
3V or LMD..... ☐ (03)
Low LVEF (≤ 40%) ..... ☐ (04)

Figure 3a. Adverse events analysis form for death, MI, stroke cases (continued)
RAND EPC EPHEDRA PROJECT ADVERSE EVENTS ANALYSIS FORM

7. IF STROKE, what is the outcome? **CIRCLE ONE**
   - Complete resolution 1
   - Minimally affected (still able to work) 2
   - Moderately affected (more than one limb) 3
   - Severely affected 4
   - Not described 8

8. Who completed the adverse events form? **CIRCLE ONE**
   - Physician / Health care provider 1
   - Subject 2
   - Subject surrogate 3
   - Government agency 4

9. What was the age of the subject on the date report was made?

   Enter number: _____ _____

10. What is the gender of the subject? **CIRCLE ONE**
    - Male 1
    - Female 2
    - Not described 8

11. Why was the subject taking the product?
    CHECK ALL THAT APPLY AND/OR ENTER CODE
    (Start codes at 4)
    - Weight loss ..... ☐ (01)
    - Improved athletic performance ..... ☐ (02)
    - Psychological effect ..... ☐ (03)
    - Other: … (enter code _____ , _____ , _____)
    - Not described ..... ☐ (98)

12. What was the source of the product? **CIRCLE ONE**
    - Retail market 1
    - Multi-level marketing/ out of home 2
    - Direct from manufacturer 3
    - Health care provider 4
    - Other (_____) 6
    - Not described 8

13. Was the product specifically identified? **CIRCLE ONE**
    - Yes 1
    - No 2

    (IF NO THEN SKIP TO QUESTION 18)

14. What is the common, proprietary, and/or scientific (genus, genus/species) name of the product? **ENTER CODE OR CIRCLE ONE OF THE BELOW**
    Code:_____
    - None 97
    - Not described 98
    - Not applicable 99

Figure 3a. Adverse events analysis form for death, MI, stroke cases (continued)
RAND EPC EPHEDRA PROJECT ADVERSE EVENTS ANALYSIS FORM

15. Of which main constituents is the product made?

ENTER CODE FOR EACH OR CIRCLE ONE OF THE BELOW

Code: _____ _____, _____ _____ , _____ , _____

None 97
Not described 98
Not applicable 99

16. Was chemical analysis on ephedra alkaloids data presented?

CIRCLE ONE

Yes 1
No 2
Not described 8
Not applicable 9

17. Please fill in the following information on dosage data.
This information is from **analysis: (ENTER THE NUMBER AND CODES IN THE APPROPRIATE BOXES.)**

Dosage data	Number	Unit (code)
Total daily dose of ephedrine alkaloids		
Single dose of ephedrine alkaloids		
Total daily dose of caffeine		
Ratio caffeine/ephedrine alkaloids	:	

Codes for units:

µg	1
mg	2
gm	3
$mgkg^{-1}$	4
ND	8
NA	9

18. Please fill in the following information on dosage data.
This information is from **label: (ENTER THE NUMBER AND CODES IN THE APPROPRIATE BOXES.)**

Dosage data	Number	Unit (code)
Total daily dose of ephedrine alkaloids		
Single dose of ephedrine alkaloids		
Total daily dose of caffeine		
Ratio caffeine/ephedrine alkaloids	:	

Codes for units:

µg	1
mg	2
gm	3
$mgkg^{-1}$	4
ND	8
NA	9

19. What was the duration of ephedrine use? **CIRCLE ONE**

<48 hours 1
2-13 days 2
14-60 days (acute) 3
>60 days (chronic) 4
Not described 8

Figure 3a. Adverse events analysis form for death, MI, stroke cases (continued)
RAND EPC EPHEDRA PROJECT ADVERSE EVENTS ANALYSIS FORM

20. What was the timing of the last ephedrine dose? **CIRCLE ONE**
    <6 hours 1
    6-24 hours 2
    >24 hours 3
    Not described 8

21. Was the product used again after first adverse event? **CIRCLE ONE**
    Yes 1
    No 2
    Not described 8
    Not applicable 9

22. If product was used again after first adverse event, did the adverse event reoccur? **CIRCLE ONE**
    Yes 1
    No 2
    Not described 8
    Not applicable 9

23. Was the subject actively involved in exercise at or immediately before the occurrence of the adverse event? **CIRCLE ONE**
    Yes 1
    No 2
    Not described 8
    Not applicable 9

24. Did form report on use of any other substances? **(CHECK ALL THAT APPLY AND ENTER CODE)**
    Caffeine (in addition to product) ..... ☐
    Illicit drugs: ..... ☐
    Code: _____ , _____ , _____ , _____ ,
    _____ , _____ , _____ , _____
    Other Herbs: ..... ☐
    Code: _____ , _____ , _____ , _____ ,
    _____ , _____ , _____ , _____
    Prescribed or OTC medication: ..... ☐
    Code: _____ , _____ , _____ , _____ ,
    _____ , _____ , _____ , _____
    Other substance: ..... ☐
    Code: _____ , _____ , _____ , _____ ,
    _____ , _____ , _____ , _____
    Not described ..... ☐
    None ..... ☐

Figure 3a. Adverse events analysis form for death, MI, stroke cases (continued)
RAND EPC EPHEDRA PROJECT ADVERSE EVENTS ANALYSIS FORM

25. Which of the following conditions were evaluated?

CHECK ALL THAT APPLY AND/OR ENTER CODE
(Start codes at 15)

Pre-existing condition:	PRESENT	EXCLUDED
Asthma	☐	☐
CAD	☐	☐
DM	☐	☐
HTN	☐	☐
Obesity	☐	☐
Renal disease	☐	☐
Substance abuse	☐	☐
Syncope	☐	☐
Thyroid condition	☐	☐
TIA History	☐	☐
Other vascular disease (_____)	☐	☐
Rheumatological diseases	☐	☐
Other (Enter code: _____)	☐	☐
Other (Enter code: _____)	☐	☐
Other (Enter code: _____)	☐	☐
Other (Enter code: _____)	☐	☐
Other (Enter code: _____)	☐	☐
Other (Enter code: _____)	☐	☐

26. Was a drug screen performed? **(CIRCLE ONE)**
Yes.....1
No .....2 **(STOP)**

27. Results of **URINE** screen:
(start codes at 03) **(CHECK ALL THAT APPLY)**
No substance found..... ☐ (01)
Substance(s) found and identified: (Enter code(s)):

(_____ , _____ , _____ , _____ , _____ , _____)

Not described ..... ☐ (98)

28. Results of **BLOOD** screen:
(start codes at 03) **(CHECK ALL THAT APPLY)**
No substance found..... ☐ (01)
Substance(s) found and identified: (Enter code(s) below)
(_____ , _____ , _____ , _____ , _____ , _____)

Not described ..... ☐ (98)

END

Figure 3b. Adverse events analysis form for seizure cases

RAND EPC EPHEDRA PROJECT **ADVERSE EVENTS ANALYSIS FORM**

ID/ FDA Case Number:_____ Reviewer:_____

First Author: _____
(Last Name Only)

Form Number: _____of_____(Fill out one form for each subject)

1. Does this adverse event report use of ephedra or ephedrine?

CIRCLE ONE

Ephedra only 1
No/ Unsure ..... 2 **(STOP)**
Ephedrine only 3
Ephedra and Ephedrine 4

(IF NOT EPHEDRA/ OR EPHEDRINE THEN STOP)

2. Is a generalized (tonic-clonic) seizure reported as an adverse event (synonym = grandmal seizure)? **CIRCLE ONE**

Yes 1
No, another type of seizure is reported .... 2 **(STOP)**
No, seizure unspecified is reported ..... 3 **(STOP)**
No, seizure is not reported as an adverse event ..... 9 **(STOP)**

(IF NO SEIZURE REPORTED THEN STOP)

3. For which evaluations are results reported as part of the evaluation of the seizure? **CHECK ALL THAT APPLY**

Serum electrolytes (must include Na) ..... ☐
Calcium ..... ☐
Magnesium ..... ☐
Glucose ..... ☐
CT/ MRI of head ..... ☐
EEG ..... ☐
Temperature ..... ☐

4. Were the following pre-existing conditions specifically mentioned as present or excluded?

Pre-existing condition:	NOT DESCRIBED	PRESENT	EXCLUDED
Alcoholism	☐	☐	☐
Substance Abuse	☐	☐	☐
Seizure Disorder	☐	☐	☐

5. What was the age of the subject on the date the report was made?

Enter number: _____ _____ (No Data = 99)

6. What is the gender of the subject?

Male 1
Female 2
Not described 8

Figure 3b. Adverse events analysis form for seizure cases (continued)
RAND EPC EPHEDRA PROJECT ADVERSE EVENTS ANALYSIS FORM

7. Why was the subject taking the product? .....
(Start codes at 04) **(CHECK ALL THAT APPLY AND/OR ENTER CODE)**
Weight loss..... ☐ (01)
Improved athletic performance ..... ☐ (02)
Psychological effect ..... ☐ (03)
Other:……. (enter code _____ , _____ , _____)
Not described ..... ☐ (98)

Figure 3b. Adverse events analysis form for seizure cases (continued)
RAND EPC EPHEDRA PROJECT **ADVERSE EVENTS ANALYSIS FORM**

Product: _____ of _____

Description:_____

8. What is the common, proprietary, and/or scientific (genus, genus/species) name of the product? **(ENTER CODE OR CIRCLE ONE OF THE BELOW)**

Code:_____
None.....97
Not applicable 99

.

9. Of which main constituents is the product made?
(ENTER CODE FOR EACH OR CIRCLE ONE OF THE BELOW)

Code: _____ , _____ , _____ , _____ , _____

_____ , _____ , _____ , _____ , _____
None.....97
Not applicable 99

10. Was chemical analysis on ephedra alkaloids data presented?
(CIRCLE ONE)

Yes 1
No.....2
Ordered but not reported 3
Not described 8
Not applicable 9

11. Please fill in the following information on dosage data.
This information is from **analysis: (ENTER THE NUMBER AND CODES IN THE APPROPRIATE BOXES.)**

Dosage data	Number	Unit (code)
Total daily dose of ephedrine alkaloids		
Single dose of ephedrine alkaloids		
Total daily dose of caffeine		
Ratio caffeine/ephedrine alkaloids	:	

Codes for units:

µg	1
mg	2
gm	3
$mgkg^{-1}$	4
ND	8
NA	9

12. Please fill in the following information on dosage data.
This information is from **label: (ENTER THE NUMBER AND CODES IN THE APPROPRIATE BOXES.)**

Dosage data	Number	Unit (code)
Total daily dose of ephedrine alkaloids		
Single dose of ephedrine alkaloids		
Total daily dose of caffeine		
Ratio caffeine/ephedrine alkaloids	:	

Codes for units:

µg	1
mg	2
gm	3
$mgkg^{-1}$	4
ND	8
NA	9

Figure 3b. Adverse events analysis form for seizure cases (continued)
RAND EPC EPHEDRA PROJECT ADVERSE EVENTS ANALYSIS FORM

13. What was the duration of ephedrine use? **(CIRCLE ONE)**
    - <48 hours 1
    - 2-13 days 2
    - 14-60 days (acute) 3
    - >60 days (chronic) 4
    - Not described 8

14. What was the timing of the last ephedrine dose? **(CIRCLE ONE)**
    - <6 hours 1
    - 6-24 hours 2
    - >24 hours 3
    - Not described 8

15. Was/were the product(s) discontinued after problematic symptoms emerged? **(CIRCLE ONE)**
    - Yes 1
    - No 2
    - Not described 8
    - Not applicable 9

16. If product(s) was/were used again after discontinuation, did the problematic symptoms reoccur? **(CIRCLE ONE)**
    - Yes 1
    - No 2
    - Not described 8
    - Not applicable 9

17. Did form report on use of any other substances? **(ENTER CODE OR CIRCLE)**

    Code: _____ , _____ , _____ , _____ , _____

    _____ , _____ , _____ , _____ , _____
    - None 97
    - Not described 98
    - Not applicable 99

18. Which of the following conditions were evaluated?
    (Start codes at 15) **(CHECK ALL THAT APPLY AND/OR ENTER CODE)**

Pre-existing condition:	PRESENT	EXCLUDED
Asthma	☐	☐
CAD	☐	☐
DM	☐	☐
HTN	☐	☐
Obesity	☐	☐
Prior psychiatric history	☐	☐
Renal disease	☐	☐
Syncope	☐	☐
Thyroid condition	☐	☐
TIA History	☐	☐
Other vascular disease (_____)	☐	☐
Rheumatological diseases	☐	☐
Not described	☐ (98)	

Figure 3b. Adverse events analysis form for seizure cases (continued)
RAND EPC EPHEDRA PROJECT **ADVERSE EVENTS ANALYSIS FORM**

19. Was a drug screen performed? **(CIRCLE ONE)**
    Yes 1
    No ..... 2 **(STOP)**

20. Results of **URINE** screen:
    (start codes at 03) **(CHECK ALL THAT APPLY)**
    No substance found ..... ☐ (01)
    Substance(s) found and identified: (Enter code(s)):

    (_____ , _____ , _____ , _____ , _____ , _____)

    Not described ..... ☐ (98)

21. Results of **BLOOD** screen:
    (start codes at 03) **(CHECK ALL THAT APPLY)**
    No substance found ..... ☐ (01)

    Substance(s) found and identified: (Enter code(s) below)

    (_____ , _____ , _____ , _____ , _____ , _____)

    Not described ..... ☐ (98)

END

Figure 3c. Adverse events analysis form for psychiatric cases

RAND EPC EPHEDRA PROJECT **ADVERSE EVENTS ANALYSIS FORM**

ID/ FDA Case Number:_____ Reviewer:_____

First Author: _____
(Last Name Only)

Form Number: _____of_____(Fill out one form for each subject)

1. Does this adverse event report use of ephedra or ephedrine?
(**CIRCLE ONE**)
Ephedra only 1
No/ Unsure ..... 2 **(STOP)**
Ephedrine only 3
Ephedra and Ephedrine 4
(IF NOT EPHEDRA/ OR EPHEDRINE THEN STOP)

2. Is there an adverse event? (**CIRCLE ONE**)
Yes 1
No ..... 2 **(STOP)**
(IF NO ADVERSE EVENT THEN STOP)

3. Was the product specifically identified? (**CIRCLE ONE**)
Yes 1
No ..... 2 **(STOP)**
(MUST BE A SERIOUS ADVERSE EVENT AND PRODUCT SPECIFICALLY IDENTIFIED OR STOP)

4. What was the adverse event? (**CHECK ALL THAT APPLY AND/OR ENTER TEXT**)
Psychosis ..... ☐ (06)
Mania or severe agitation ..... ☐ (07)
Severe depression ..... ☐ (08)
Suicidal ideation ..... ☐ (09)
Suicide attempt/ Suicide ..... ☐ (146)
Hallucinations ..... ☐ (138)
Other serious psychiatric events: (enter below)
_____ ..... ☐ (.)
_____ ..... ☐ (.)
_____ ..... ☐ (.)
_____ ..... ☐ (.)

Other non-serious event: _____) ..... ☐ (96) **(STOP)**
None of the above ..... ☐ (97) **(STOP)**

Figure 3c. Adverse events analysis form for psychiatric cases (continued)
RAND EPC EPHEDRA PROJECT ADVERSE EVENTS ANALYSIS FORM

5. Is there a presence or history of the following conditions?

(CHECK ALL THAT APPLY AND/OR ENTER TEXT)

	PRESENCE	HISTORY	(CODES)
Psychosis	☐	☐	(01)
Mania or severe agitation	☐	☐	(02)
Hallucinations	☐	☐	(03)
Severe depression	☐	☐	(04)
Suicide attempt	☐	☐	(05)
Suicide ideation	☐	☐	(06)
Schizophrenia	☐	☐	(07)
Acute confusion	☐	☐	(08)
Delusions	☐	☐	(09)
Aggression/threatened violence	☐	☐	(10)
Substance abuse	☐	☐	(11)
Other conditions:			
_____	☐	☐	( )
_____	☐	☐	( )
_____	☐	☐	( )
_____	☐	☐	( )
_____	☐	☐	( )
_____	☐	☐	( )
_____	☐	☐	( )
_____	☐	☐	( )
None described		☐	(98)

6. What was the outcome of the event? (CHECK ALL THAT APPLY)

- Death ☐
- Harm to self/others ☐
- Hospitalization ☐
- ER Visit ☐
- On-going adverse event/disability ☐
- Resolved ☐
- Other:_____ ☐
- Not described ☐

Figure 3c. Adverse events analysis form for psychiatric cases (continued)
RAND EPC EPHEDRA PROJECT ADVERSE EVENTS ANALYSIS FORM

7. What was intervention was prescribed after adverse event occurred?
(CHECK ALL THAT APPLY)

No procedure ☐
Discontinue Ephedra ☐
Change existing medication ☐

New medication ☐
Initiate/change frequency/intensity of outpatient visits ☐
Hospitalization ☐

Involuntary hospitalization ☐
Legal action ☐
Not described ☐
Not applicable ☐

8. What was the age of the subject on the date report was made?

Enter number: _____ _____ (No Data=99)

9. What is the gender of the subject? (CIRCLE ONE)

Male 1
Female 2
Not described 8

10. Why was the subject taking the product? (CHECK ALL THAT APPLY)

Weight loss ☐
Improved athletic performance ☐
Psychological effect ☐
Addiction ☐

Other:_____ ☐
Not described ☐

11. Did report describe the use of any other substances or medications taken prior to/or during the event?

_____ ( )

_____ ( )

_____ ( )

_____ ( )

_____ ( )

None described ☐ 98

Figure 3c. Adverse events analysis form for psychiatric cases (continued)
RAND EPC EPHEDRA PROJECT ADVERSE EVENTS ANALYSIS FORM

12. What is the common, proprietary, and/or scientific (genus, genus/species) name of the product? (ENTER TEXT OR CIRCLE ONE BELOW)

Name:_____( )
None....97
Not described....98
Not applicable....99

13. Of which main constituents is the product made?
(Enter text or circle one below)

_____( )

_____( )

_____( )

_____( )

_____( )

_____( )

_____( )

_____( )

None....97
Not described....98
Not applicable....99

14. Was chemical analysis on ephedra alkaloids data presented?
(CIRCLE ONE)

Yes....1
No....2
Ordered but not presented....3
Not described....8
Not applicable....9

Figure 3c. Adverse events analysis form for psychiatric cases (continued)
RAND EPC EPHEDRA PROJECT ADVERSE EVENTS ANALYSIS FORM

15. Please fill in the following information on dosage data.
This information is from **analysis:** (ENTER THE NUMBER AND UNITS IN THE APPROPRIATE BOXES.)

Dosage data	Number	Unit	Unit Code
Total daily dose of ephedrine alkaloids			
Single dose of ephedrine alkaloids			
Total daily dose of caffeine			
Ratio caffeine/ephedrine alkaloids	:		

Codes for units:

µg	1
mg	2
gm	3
$mgkg^{-1}$	4
ND	8
NA	9

16. This information is from **label**: (ENTER THE NUMBER AND UNITS IN THE APPROPRIATE BOXES.)

Dosage data	Number	Unit	Unit Code
Total daily dose of ephedrine alkaloids			
Single dose of ephedrine alkaloids			
Total daily dose of caffeine			
Ratio caffeine/ephedrine alkaloids	:		

Codes for units:

µg	1
mg	2
gm	3
$mgkg^{-1}$	4
ND	8
NA	9

17. What was the duration of ephedra/ephedrine use? (CIRCLE ONE)
<48 hour 1
2-13 days 2
14-60 days (acute) 3
>60 days (chronic) 4
60 days to 1 year 5
Over 1 year 6
Not described 8

18. What was the timing of the last ephedra/ephedrine dose?(CIRCLE ONE)
<6 hours 1
6-24 hours 2
>24 hours 3
Not described 8

19. Was/were the product(s) discontinued after problematic symptoms emerged? (CIRCLE ONE)
Yes 1
No 2
Not described 8
Not applicable 9

Figure 3c. Adverse events analysis form for psychiatric cases (continued)
RAND EPC EPHEDRA PROJECT ADVERSE EVENTS ANALYSIS FORM

20. If product(s) was/were used again after discontinuation, did the problematic symptoms reoccur? (CIRCLE ONE)
    Yes 1
    No 2
    Not described 8
    Not applicable 9

21. Was autopsy performed? (CIRCLE ONE)
    Yes 1
    No 2
    Not Applicable 9

22. Was drug screen performed? (CIRCLE ONE)
    Yes 1
    No ..... 2 (STOP)

23. Results of URINE screen: (CHECK ALL THAT APPLY AND/OR ENTER TEXT)
    No substance found ..... ☐ (01)
    Substance(s) found and identified:

    _____..... ( )

    _____..... ( )

    _____..... ( )

    _____..... ( )

    _____..... ( )

    _____..... ( )

    Not described ..... ☐ (98)

21. Results of **BLOOD** screen:(check all that apply and/or enter text)
    No substance found ..... ☐ (01)
    Substance(s) found and identified:

    _____..... ( )

    _____..... ( )

    _____..... ( )

    _____..... ( )

    _____..... ( )

    _____..... ( )

    Not described ..... ☐ (98)

END

Figure 4. Brief data collection form for case reports

RAND EPC EPHEDRA PROJECT **BRIEF FORM FOR CASE REPORTS**

Article ID:_____ Reviewer:_____

FDA Case Number:_____

Form Number: _____of _____ (Fill out one form for each subject)

1. Does adverse event form report on ephedra or ephedrine?

CIRCLE ONE

Yes 1
No/ Unsure ..... 2 **(STOP)**

(IF NOT EPHEDRA/EPHEDRINE THEN STOP)

2. What was the adverse event? **CHECK ALL THAT APPLY**

Death…… ☐ (01)

Cardiovascular:
- Heart rate, >120 *or* <50 ☐ (02)
- Hypertension, Systolic >180 *or* Diastolic >105 ☐ (03)
- MI ☐ (04)
- Ventricular tachycardia/ fibrillation ☐ (05)
- Cardiac arrest ☐ (06)

Pulmonary:
- Respiratory arrest ☐ (07)

Neurological:
- TIA ☐ (08)
- CVA ☐ (09)
- Brain Hemorrhage, not CVA ☐ (10)
- Fainting / Loss of consciousness ☐ (11)
- Coma ☐ (12)
- Seizure ☐ (13)
- Paralysis ☐ (14)

Psychiatric:
- Severe depression ☐ (15)
- Hallucinations ☐ (16)
- Mania or severe agitation ☐ (17)
- Psychosis ☐ (18)
- Suicide ☐ (19)

Other adverse events:
- Changes in glucose <40 *or* >400 ☐ (20)
- Liver failure ALT/AST >200 ☐ (21)
- Rhabdomyolysis CPK >400 ☐ (22)
- Miscarriage ☐ (23)
- Serious renal event ☐ (25)
- Autonomic Hyperactivity ☐ (26)

None of the above ☐ (24)

Figure 5. Examples of MIPER Files
5a. Email record of a telephone conversation

From: Redacted
Posted At: Monday, November 29, 1999 8:23 AM
Conversation: Redacted menstrual irreg
Posted To: Medical Group

Subject: Redacted menstrual irreg

Sensitivity: Private

Categories: Menstrual Irregularity

Redacted
27 yrs 210 lbs
customer reports taking 1 1/2 caps tid ac for 1 month - eats adequate, drinks qs - now experiencing menstrual irreg an is 5 days late for her cycle
recommended contact gyn and discuss whether to continue taking- may be able to just decrease to 1 or 1 1/2 caps a day or may need to completely stop- be sure to continue to eat 3 healthy high protein meals qd and drink 64 oz of water

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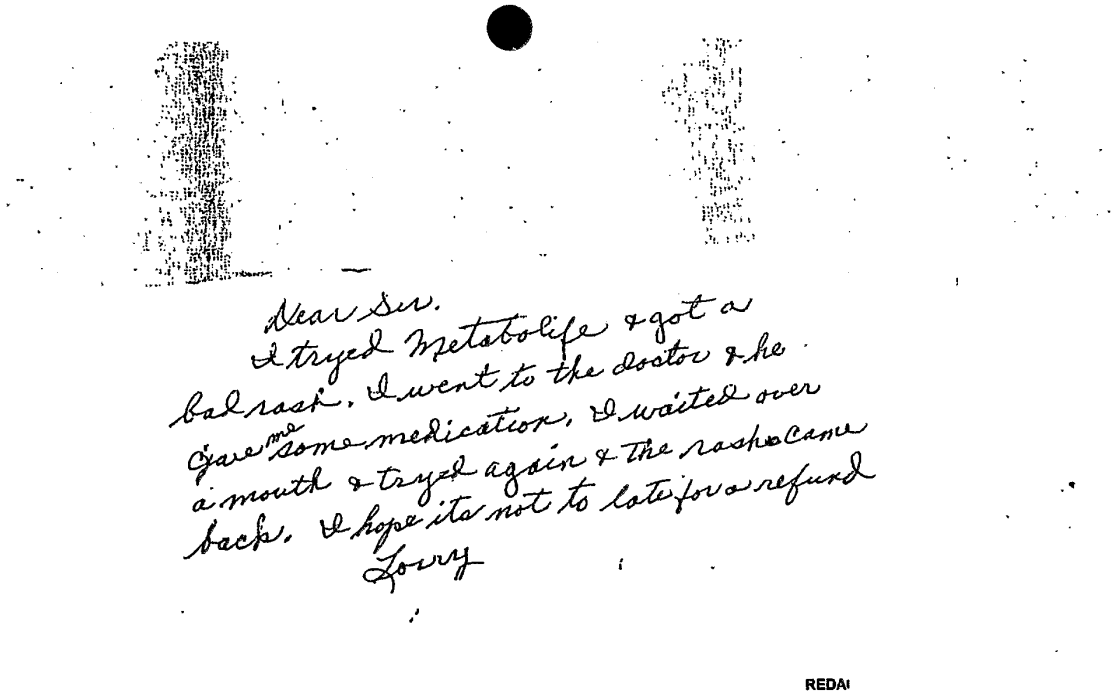
Figure 5. Examples of MIPER Files (continued)
5b. Typed or handwritten letter from the consumer to the company



Dear Sir.
I tryed Metabolife & got a
bad rash. I went to the doctor & he
gave me some medication. I waited over
a month & tryed again & the rash came
back. I hope its not to late for a refund
Lowry

REDA

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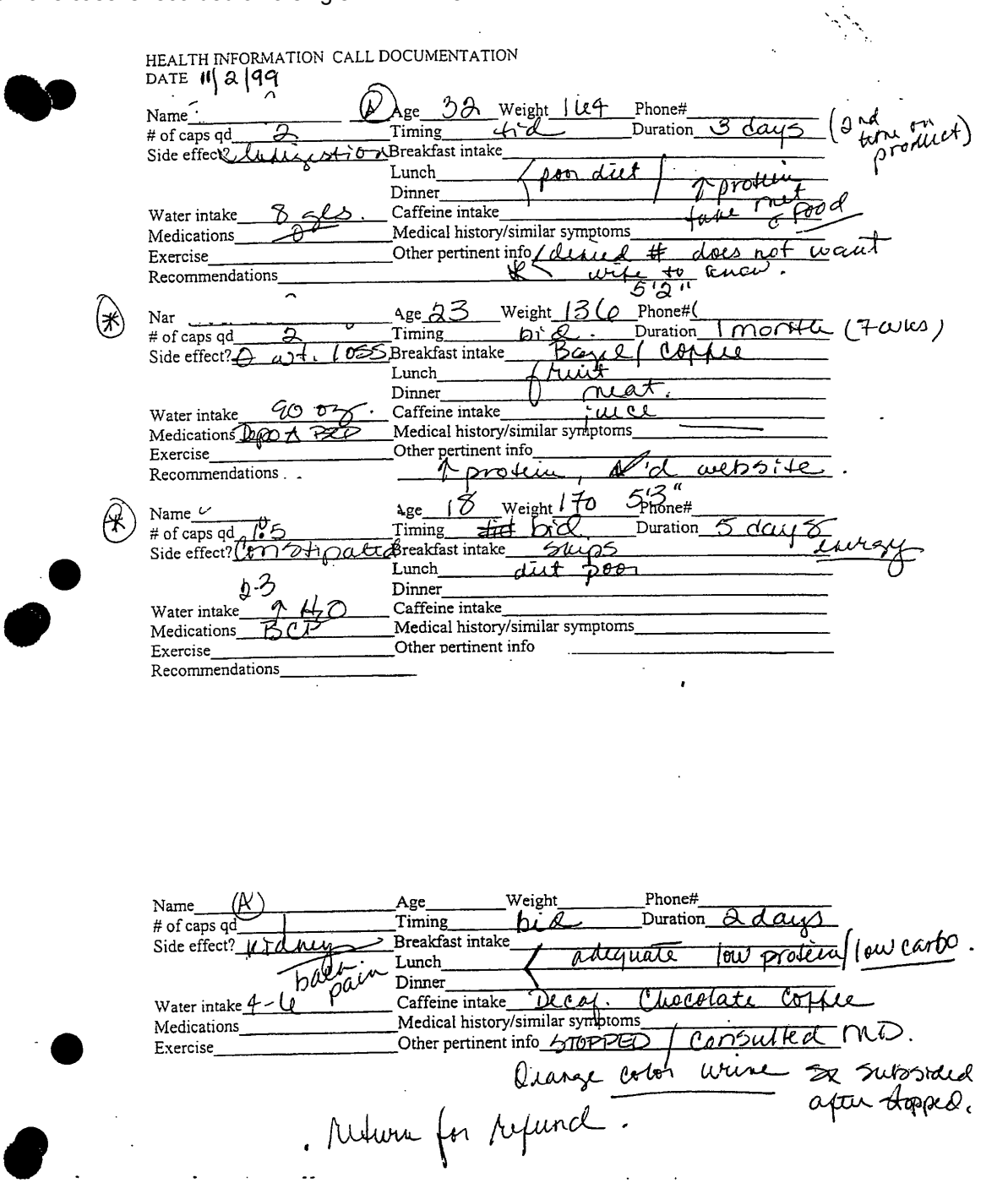
MIPER020990

Figure 5. Examples of MIPER Files (continued)
5c. Handwritten note of telephone conversation with consumer written on a rudimentary form. Note more than one case is recorded on a single MIPER file.



HEALTH INFORMATION CALL DOCUMENTATION
DATE 11/2/99

Name _____ (R) Age 32 Weight 164 Phone# _____
# of caps qd 2 Timing tid Duration 3 days (2nd time on product)
Side effect? indigestion Breakfast intake _____
Lunch poor diet
Dinner
Water intake 8 qts. Caffeine intake
Medications 0 Medical history/similar symptoms
Exercise Other pertinent info desired # does not want
Recommendations wife to know.
5'2"

(*) Nar _____ Age 23 Weight 136 Phone#(
# of caps qd 2 Timing bid Duration 1 month (7 wks)
Side effect? 0 wt. loss Breakfast intake Bagel / coffee
Lunch fruit
Dinner meat.
Water intake 90 oz. Caffeine intake juice
Medications Dyaz PRN Medical history/similar symptoms
Exercise Other pertinent info
Recommendations ↑ protein, d/c website.

(*) Name _____ Age 18 Weight 170 5'3" Phone# _____
# of caps qd 10 5 Timing ~~tid~~ bid Duration 5 days
Side effect? constipated Breakfast intake skips energy
Lunch diet poor
Dinner
Water intake ↑ H2O Caffeine intake
Medications BCP Medical history/similar symptoms
Exercise Other pertinent info
Recommendations

Name (R) Age Weight Phone# _____
# of caps qd 1 Timing bid Duration 2 days
Side effect? kidney pain Breakfast intake
Lunch adequate low protein / low carbo.
Dinner
Water intake 4-6 Caffeine intake Decaf. Chocolate Coffee
Medications Medical history/similar symptoms
Exercise Other pertinent info STOPPED / consulted MD.
Orange color urine ~~x~~ subsided after stopped.
Return for refund.

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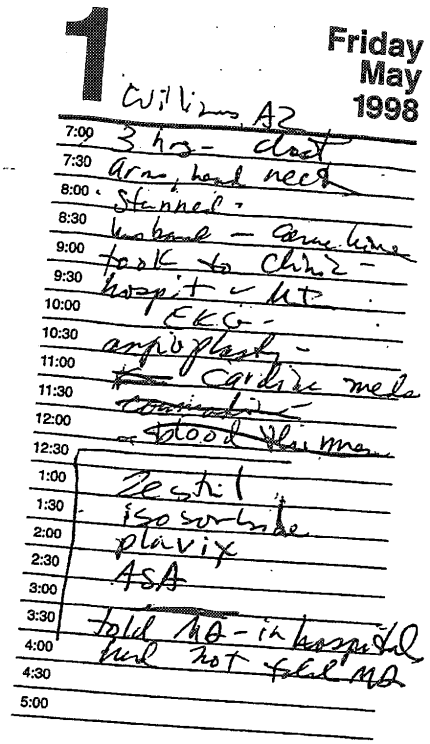
CONFIDENTIAL & NON RESPONSIVE REDACTION

MIPER022677

Figure 5. Examples of MIPER Files (continued)
5d. Handwritten note of telephone conversation with consumer written on a piece of paper



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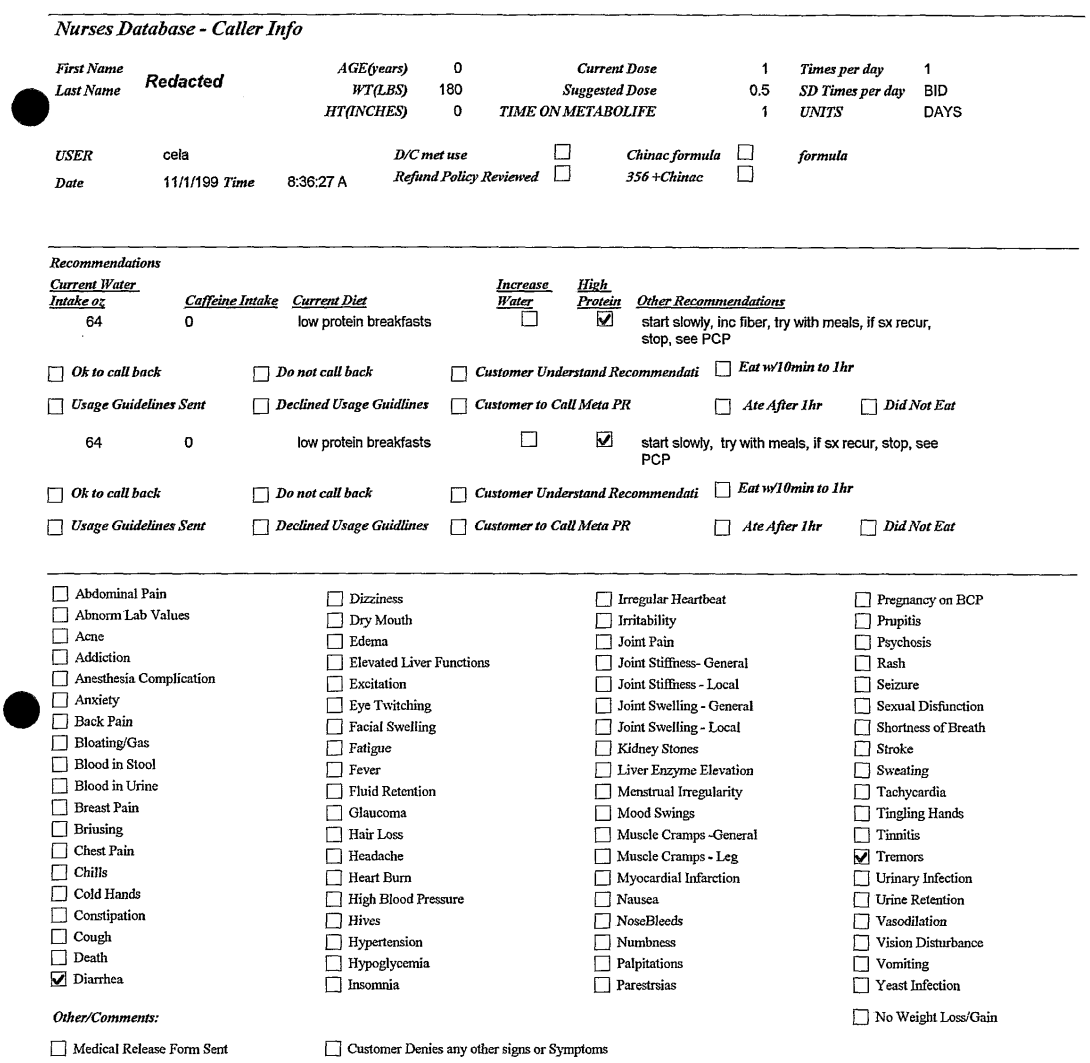
REDACTED

MIPER024166

Figure 5. Examples of MIPER Files (continued)

5e. A form developed for systematically collecting information about possible adverse events



Nurses Database - Caller Info

First Name		*AGE(years)*	0	*Current Dose*	1	*Times per day*	1
Last Name	**Redacted**	*WT(LBS)*	180	*Suggested Dose*	0.5	*SD Times per day*	BID
		HT(INCHES)	0	*TIME ON METABOLIFE*	1	*UNITS*	DAYS

USER cela *D/C met use* ☐ *Chinac formula* ☐ *formula*

Date 11/1/199 *Time* 8:36:27 A *Refund Policy Reviewed* ☐ *356 +Chinac* ☐

Recommendations

Current Water Intake oz	*Caffeine Intake*	*Current Diet*	*Increase Water*	*High Protein*	*Other Recommendations*
64	0	low protein breakfasts	☐	☑	start slowly, inc fiber, try with meals, if sx recur, stop, see PCP

☐ *Ok to call back* ☐ *Do not call back* ☐ *Customer Understand Recommendati* ☐ *Eat w/10min to 1hr*

☐ *Usage Guidelines Sent* ☐ *Declined Usage Guidlines* ☐ *Customer to Call Meta PR* ☐ *Ate After 1hr* ☐ *Did Not Eat*

64	0	low protein breakfasts	☐	☑	start slowly, try with meals, if sx recur, stop, see PCP

☐ *Ok to call back* ☐ *Do not call back* ☐ *Customer Understand Recommendati* ☐ *Eat w/10min to 1hr*

☐ *Usage Guidelines Sent* ☐ *Declined Usage Guidlines* ☐ *Customer to Call Meta PR* ☐ *Ate After 1hr* ☐ *Did Not Eat*

☐ Abdominal Pain	☐ Dizziness	☐ Irregular Heartbeat	☐ Pregnancy on BCP
☐ Abnorm Lab Values	☐ Dry Mouth	☐ Irritability	☐ Prupitis
☐ Acne	☐ Edema	☐ Joint Pain	☐ Psychosis
☐ Addiction	☐ Elevated Liver Functions	☐ Joint Stiffness- General	☐ Rash
☐ Anesthesia Complication	☐ Excitation	☐ Joint Stiffness - Local	☐ Seizure
☐ Anxiety	☐ Eye Twitching	☐ Joint Swelling - General	☐ Sexual Disfunction
☐ Back Pain	☐ Facial Swelling	☐ Joint Swelling - Local	☐ Shortness of Breath
☐ Bloating/Gas	☐ Fatigue	☐ Kidney Stones	☐ Stroke
☐ Blood in Stool	☐ Fever	☐ Liver Enzyme Elevation	☐ Sweating
☐ Blood in Urine	☐ Fluid Retention	☐ Menstrual Irregularity	☐ Tachycardia
☐ Breast Pain	☐ Glaucoma	☐ Mood Swings	☐ Tingling Hands
☐ Briusing	☐ Hair Loss	☐ Muscle Cramps -General	☐ Tinnitis
☐ Chest Pain	☐ Headache	☐ Muscle Cramps - Leg	☑ Tremors
☐ Chills	☐ Heart Burn	☐ Myocardial Infarction	☐ Urinary Infection
☐ Cold Hands	☐ High Blood Pressure	☐ Nausea	☐ Urine Retention
☐ Constipation	☐ Hives	☐ NoseBleeds	☐ Vasodilation
☐ Cough	☐ Hypertension	☐ Numbness	☐ Vision Disturbance
☐ Death	☐ Hypoglycemia	☐ Palpitations	☐ Vomiting
☑ Diarrhea	☐ Insomnia	☐ Parestrsias	☐ Yeast Infection

Other/Comments: ☐ No Weight Loss/Gain

☐ Medical Release Form Sent ☐ Customer Denies any other signs or Symptoms

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Figure 6. Example of duplicate case

From: Cela Nash
Posted At: Thursday, June 03, 1999 11:35 AM
Conversation: REDACTED Seizure
Posted To: Medical Group

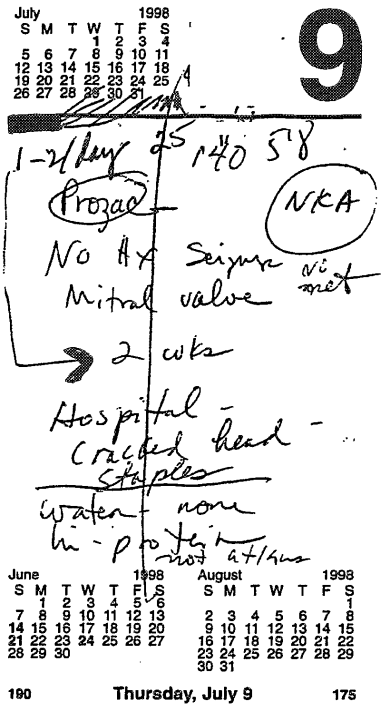
Subject: REDACTED Seizure

Categories: Seizure

25 yr old female, 5'8", 145 lbs, had been taking 1-2 met tabs per day for the last 2 weeks for energy. Had a seizure, fell and injured head, went to hospital, staples and sutures placed in head. No hx epilepsy, or family hx. Has mitral valve prolapse. Nka. Taking prozac daily; had read label, noted that met not to be taken with maos, no mention of ssris. Water, caffeine, protein intake all within guidelines. she is a nutrition/fitness professional, has taken other ephedrine products without problems, but not at the same time as prozac. Has d/c'd met. Inst that met works by stimulating cns, can lower seizure threshhold. Her eeg test is pending.

REDACTED

Figure 6. Example of duplicate case (continued)



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REDACTED

MIPER024209

Figure 7. Metabolife record screener form

Case Number:_____ Reviewer:_____

Form Number: _____of_____(Fill out one form for each subject)

1. Subject's age: _____ (Not Described =999)

2. What is the subject's gender? (**CIRCLE ONE**)
   - Male.....1
   - Female 2
   - Not described/ Not reported.....3

3. What was the adverse event? **(CHECK ALL THAT APPLY)**
   - No adverse event reported .....☐ (01)

   (IF NO ADVERSE EVENT THEN STOP.)
   - Death.....☐ (02)

   Cardiovascular:
   - Heart rate, >120 or <50.....☐ (03)
   - Heart rate, 50-120, or not otherwise unspecified.....☐ (04)
   - Hypertension, Systolic >180 or Diastolic >105 .....☐ (05)
   - Hypertension, Systolic <180 or Diastolic <105, or not otherwise specified .....☐ (06)
   - Myocardial Infarction/ Heart Attack.....☐ (07)
   - Cardiac Dysrythmia, Other/ Palpitations.....☐ (08)
   - Cardiac arrest.....☐ (09)
   - Ventricular Tachycardia/ Fibrillation.....☐ (10)
   - Chest Pain, not specified as MI .....☐ (11)

   Pulmonary:
   - Respiratory arrest.....☐ (12)

   Neurological:
   - Transient Ischemic Attack.....☐ (13)
   - CVA/ Stroke, not known to be hemorrhage .....☐ (14)
   - Brain Hemorrhage.....☐ (15)
   - Fainting / Loss of consciousness .....☐ (16)
   - Coma.....☐ (17)
   - Seizure .....☐ (18)

   Psychiatric:
   - Depression .....☐ (19)
   - Hallucinations.....☐ (20)
   - Mania or severe agitation.....☐ (21)
   - Psychosis .....☐ (22)
   - Suicide attempt .....☐ (23)
   - Autonomic Hyperactivity (includes: tremor, twitching, jitteriness, insomnia, increased sweating, agitation, nervousness, and irritability).....☐ (24)

Figure 7. Metabolife record screener form (continued)

3. What was the adverse event? **(CHECK ALL THAT APPLY)**
(continued)
Other adverse events:
- Changes in glucose <40 or >400 ☐ (25)
- Liver failure ALT/AST >200 ☐ (26)
- Liver abnormality, not otherwise specified ☐ (27)
- Rhabdomyolysis CPK >400 ☐ (28)
- Rhabdomyolysis, not otherwise specified ☐ (29)
- Miscarriage ☐ (30)
- Allergic Reaction ☐ (31)
- Anesthesia complication ☐ (32)
- Fatigue/Fever/ Chills ☐ (33)
- Abnormal lab values, not otherwise specified ☐ (34)

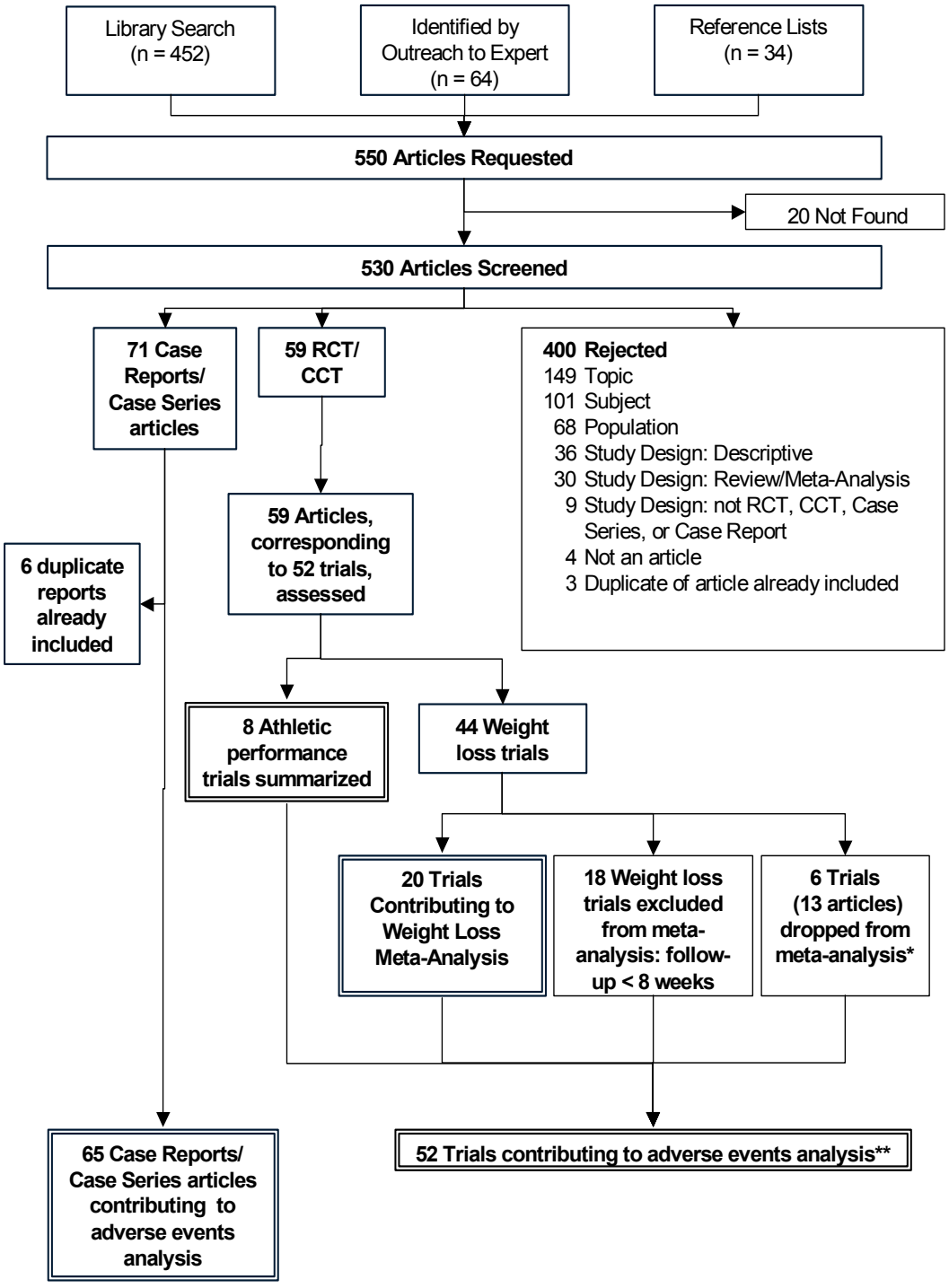
Other adverse events not already specified:
- Ear, Eye, Nose, or Throat ☐ (35)
- Respiratory System ☐ (36)
- Cardiovascular System ☐ (37)
- Gastrointestinal System ☐ (38)
- Hepatobiliary System ☐ (39)
- Musculoskeletal System ☐ (40)
- Genitourinary System ☐ (41)
- Gynecologic (includes breast and menstrual symptoms) ☐ (42)
- Sexual Dysfunction ☐ (43)
- Neurological System (includes headache) ☐ (44)
- Mental Health ☐ (45)
- Skin (includes Pruritis) ☐ (46)
- Hematologic System ☐ (47)
- Oncologic System ☐ (48)
- Other symptoms not specified above ☐ (49)

4. Did the adverse event result in a hospital stay (at least one night; do not include emergency room visits)? **(CIRCLE ONE)**
- Yes 1
- No/ No Data 2

5. Is there additional information (medical records or similar) available for more detailed review regarding past health history, current, problems, toxicology results, etc? **(CIRCLE ONE)**
- Yes 1
- No 2

END

Figure 8. Literature flow



* Various reasons, see table 9.
** Two studies had no placebo group and, therefore, contribute to the power calculations but not to the odds ratio meta-analysis.

Figure 9. Ephedrine versus placebo – forest plot

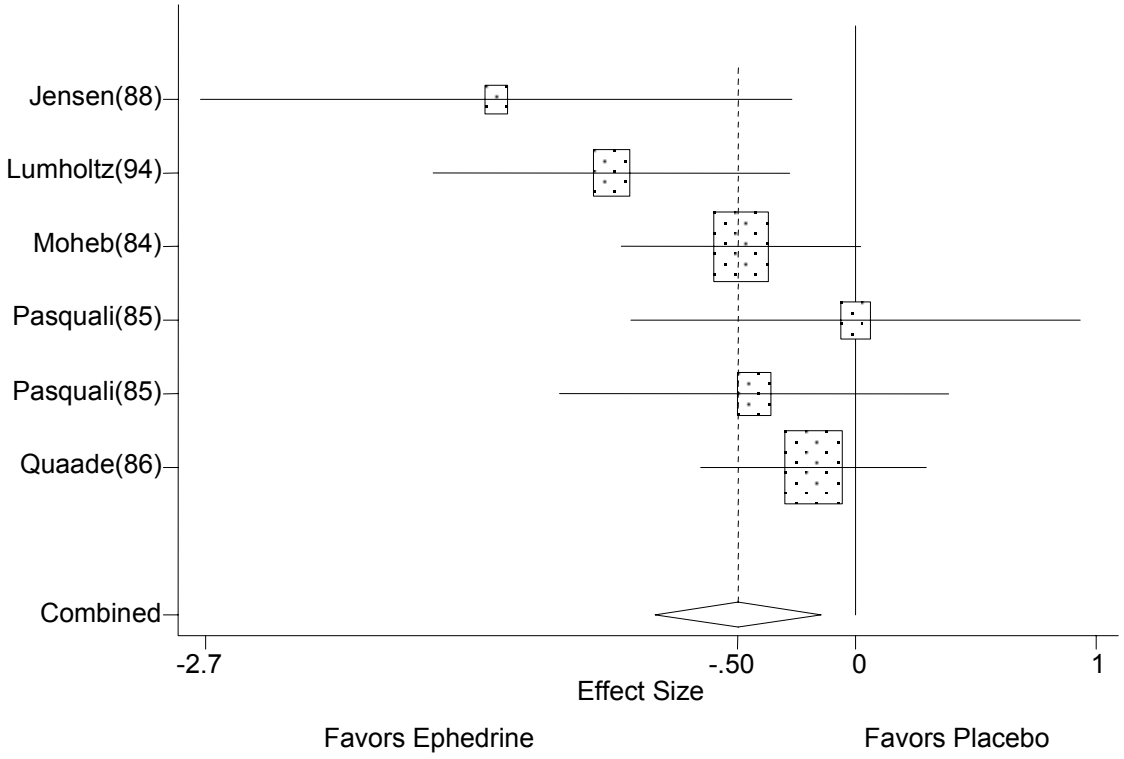


Figure 10. Ephedrine versus placebo – funnel plot

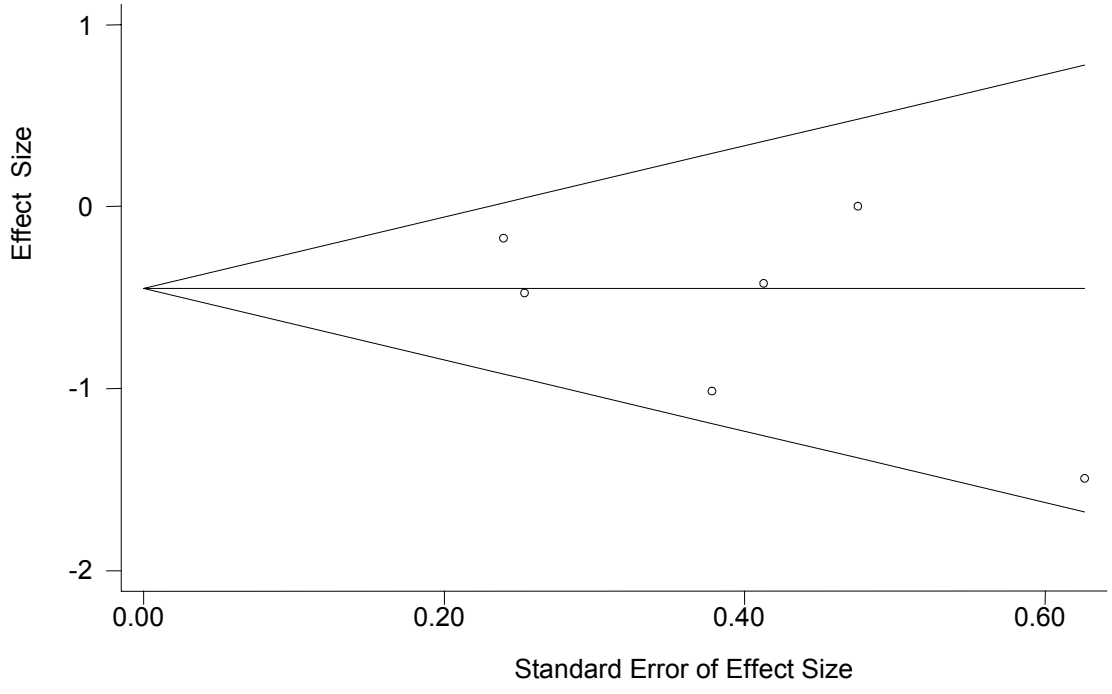


Figure 11. Ephedrine + caffeine versus placebo – forest plot

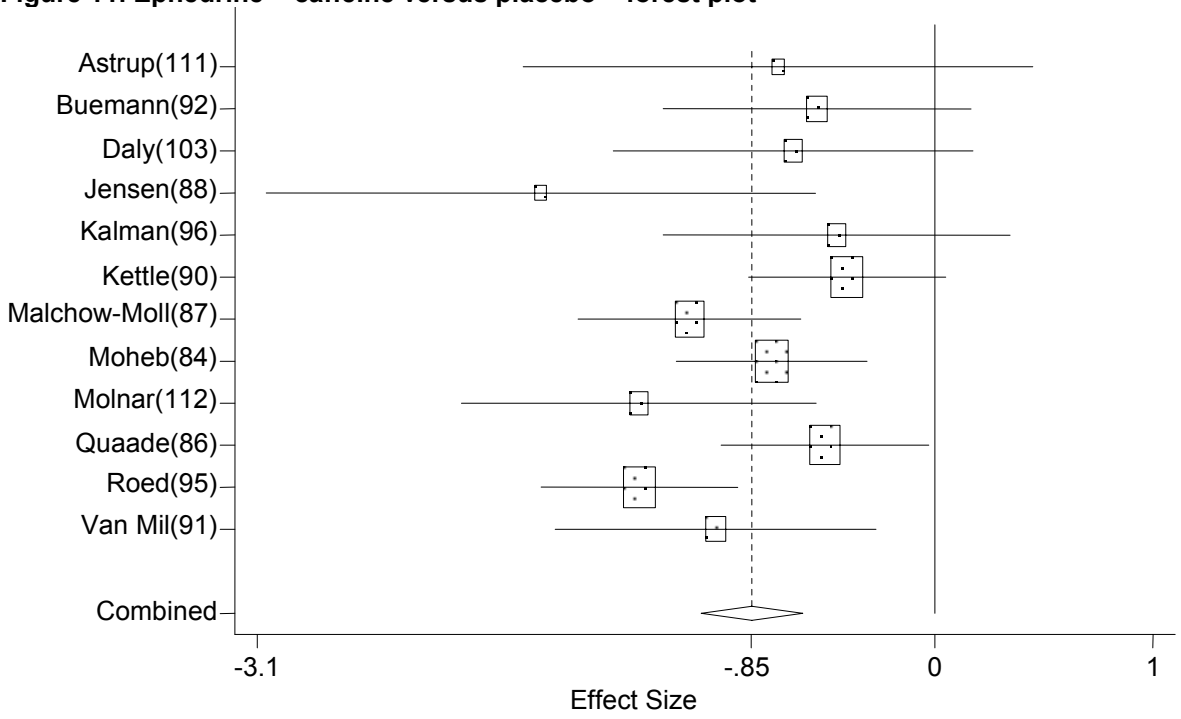


Figure 12. Ephedrine + caffeine versus placebo – funnel plot

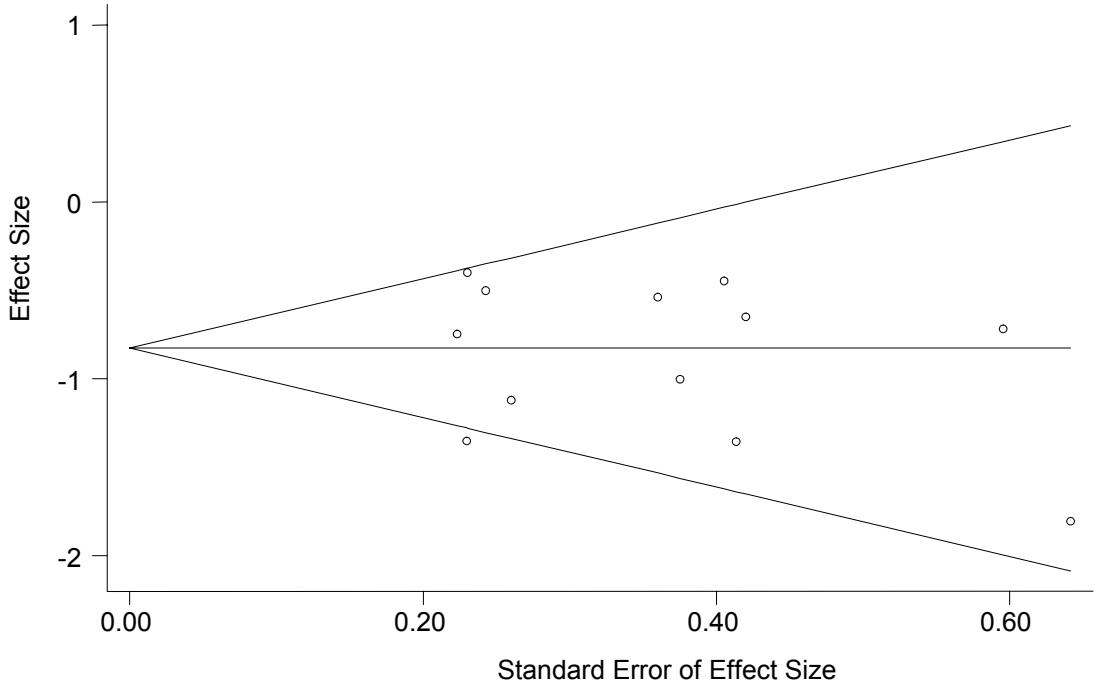


Figure 13. Ephedrine + caffeine versus ephedrine alone – forest plot

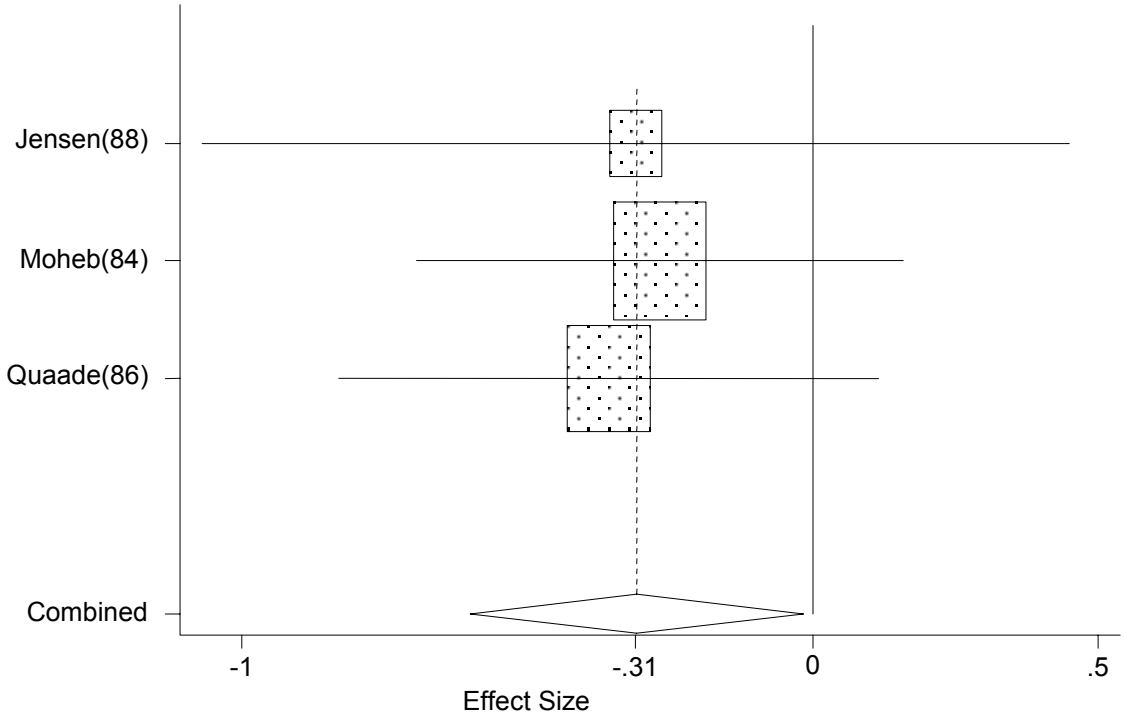


Figure 14. Ephedra + herbs containing caffeine versus placebo – forest plot

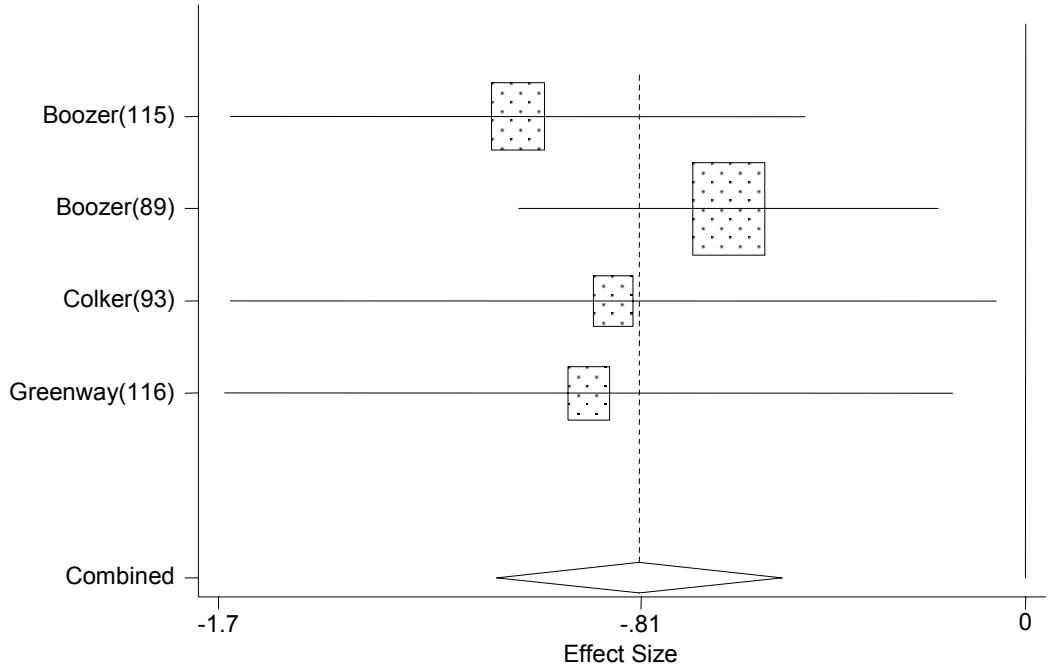


Figure 15. Ephedra + herbs containing caffeine versus placebo – funnel plot

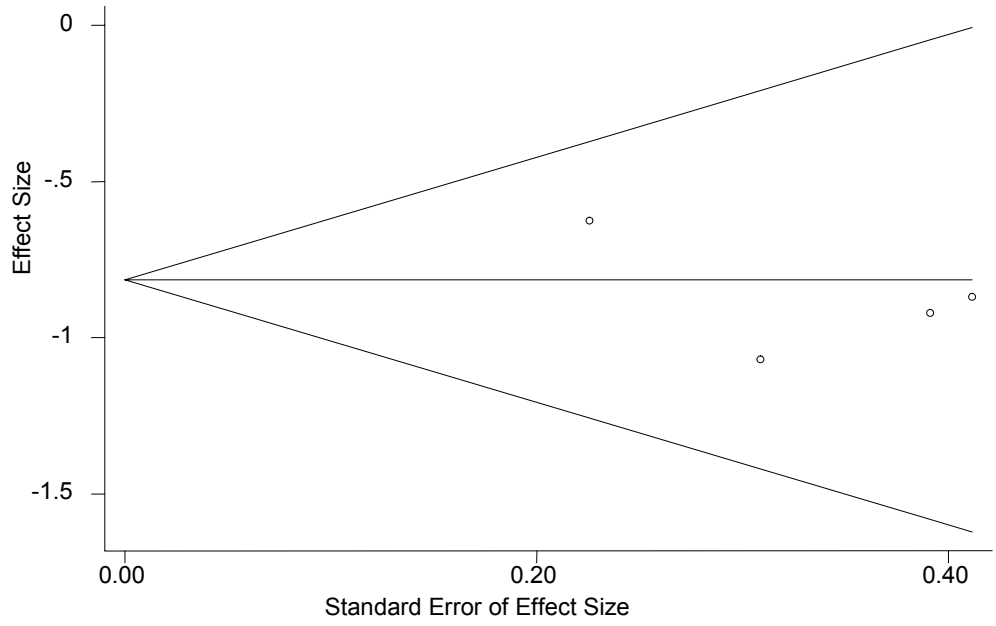


Figure 16. Effect sizes by comparison group

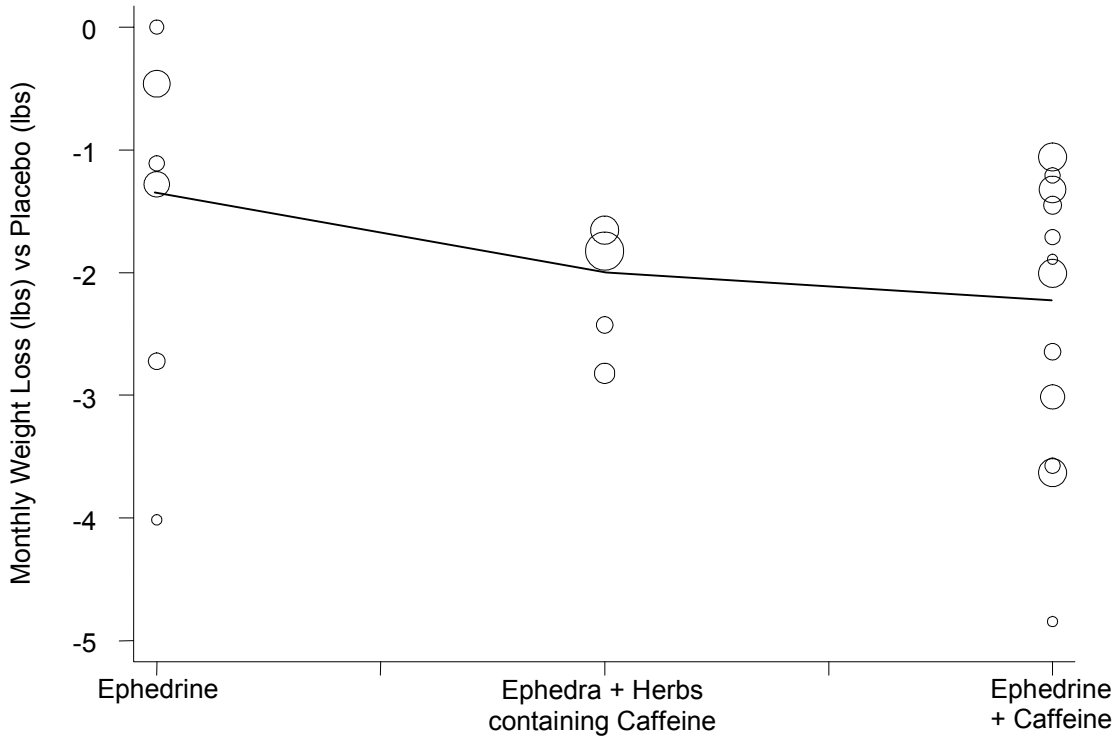


Figure 17a. Flow of evidence for adverse events analysis, part 1

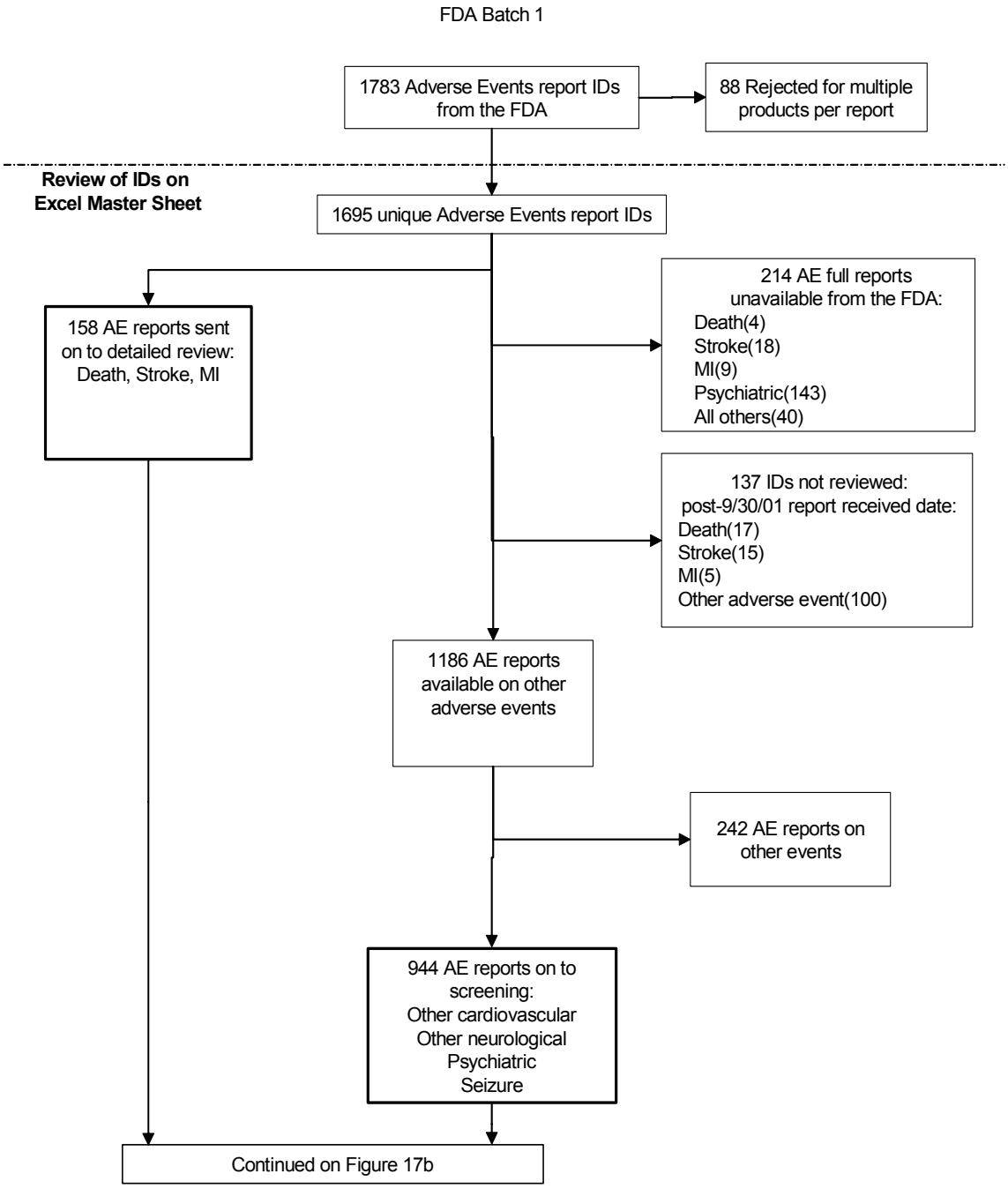


Figure 17b. Flow of evidence for adverse events analysis, part 2

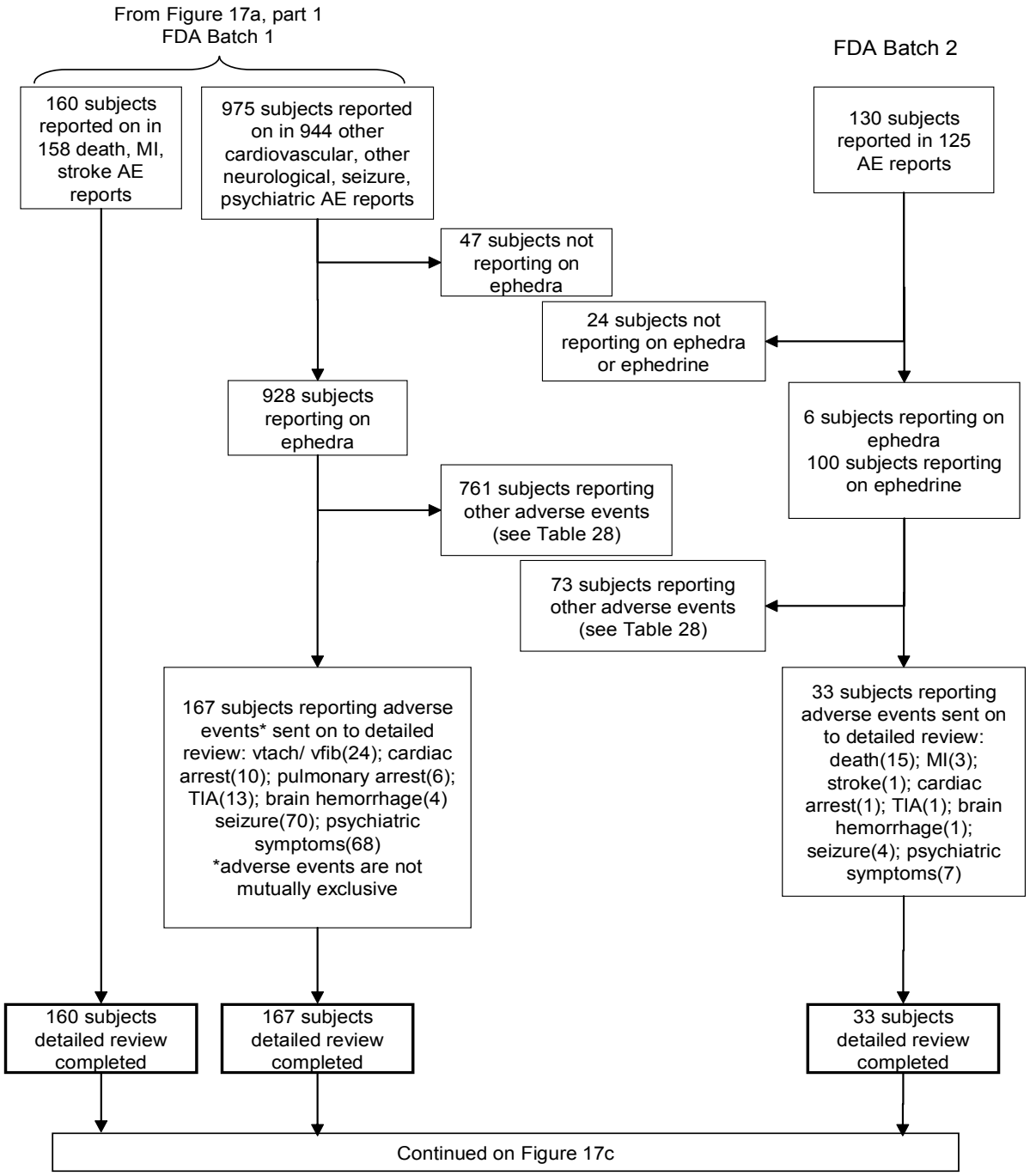


Figure 17c. Flow of evidence for adverse events analysis, part 3

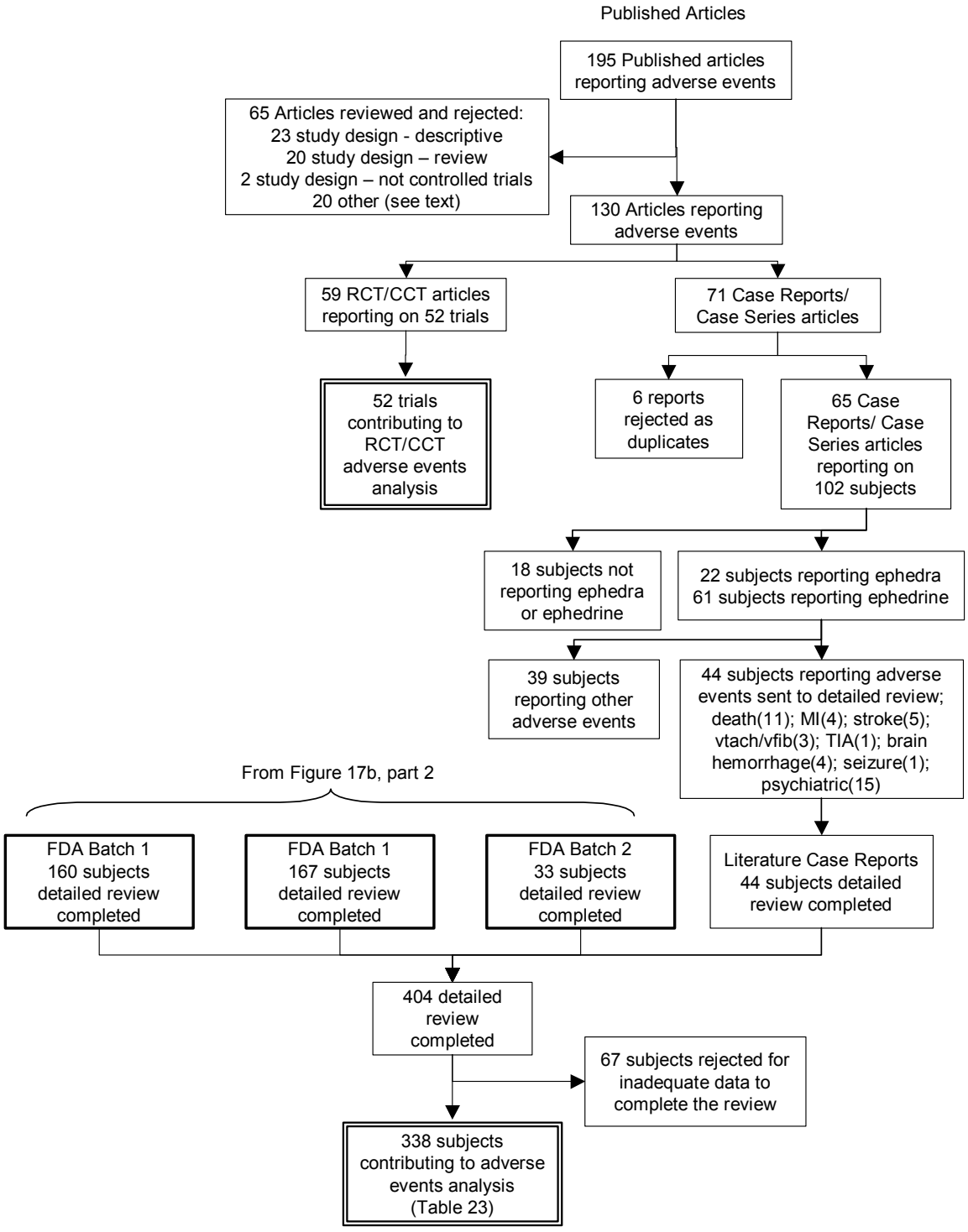


Figure 18. Flow of MIPER ID Numbers