CTTI WS-3

Members of WS-3 Working Group

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- Margaret McLaughlin (Pfizer)
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- Lynda Szczech – Workstream Lead (Duke)
- Leonard Sacks (FDA)
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CTTI CLINICAL TRIALS TRANSFORMATION INITIATIVE

Purpose of the Study

- **The primary objective of this study is to compare current practices with an alternative approach for notifying investigators of unexpected SAEs.**
- **This study will collect self-reported data from each respondent using a paper survey.**
- **The survey is 2 pages and is expected to require 15 minutes to complete. It asks for objective information on time required to complete activities. It does not ask for opinions or other subjective information.**

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Data collection

- Participants in this survey will be clinical investigators conducting multi-center trials utilizing either Rapamune (sirolimus, Wyeth) or lapatinib (GSK).
- Wyeth and GSK have received waivers from FDA to use an aggregate reporting system similar to that which is authorized by the European Commission instead of the standard approach of reporting individual events as they occur.
- Potential survey respondents will be identified by Wyeth and GSK, respectively.
- A letter of introduction along with the survey will be provided to each of the pharmaceutical companies. They will each distribute the survey to the investigators currently participating in clinical trials utilizing the aggregate reporting system.
- Respondents will be instructed to fax their completed survey to Lynda Szczech without a cover sheet or other identifying information.

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Comparator study

- Each site was asked to choose a comparator study from among the studies that they were currently involved in.
- Similar information was collected on this comparator study against which to gauge the values that were provided for the studies utilizing the aggregate reporting system.

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Statistical analysis

- **Descriptive statistics (#, %, range, average, median, mode) will be calculated for each of the four groups of studies (lapatinib, lapatinib comparator study, rapamune, and rapamune comparator study).**
- **The summary statistics for lapatinib and rapamune will be compared to each of their respective comparator studies.**

CLINICAL TRIALS TRANSFORMATION INITIATIVE

I. Characteristics of each study under observation
1. Total number of subjects anticipated for enrollment at all sites:
2. Total number of anticipated sites:
3. Length of subject participation in trial: (months or specify other unit of time)
4. Length of study drug exposure in trial: (days or specify other unit of time)

II. Volume of SUSARs for each study:
1. How many SUSARs did you receive during that time period (including both initial and follow up)? •While, the Rapamune trial had only one aggregate report, how many SUSARs were detailed?
2. How many of the SUSARs suggested a “red flag” i.e. several similar events reported recently that have been unexpected or described a new event for this product seen with similar class compounds?
3. How many SUSARs resulted in a change to the study procedures/treatment?
4. How many SUSARs resulted in a study amendment?
5. How many SUSARs resulted in a change to the informed consent document?
6. For how many SUSARs was it essential that the information from the sponsor be provided immediately to an IRB?
7. How many SUSARs required “no action”?

III. Estimate of “person-power” required to log and triage each SUSAR
1. Time estimate in minutes for each report (1 aggregate for Rapamune trial vs. each individual report for comparator trial.).
A. Read each report
B. Produce compilation report
C. Review with members of the study team
D. Distribute to appropriate staff
E. Prepare submission to IRB
F. Plan and implement changes to informed consent form and process and/or protocol changes
2) Of the time spent “dealing” with the reports what percent of the total time (100%) is spent by
a. Secretarial or administrative staff
b. Professional support staff (nurses/counselors, etc..)
c. Physician staff

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Number of respondents

- **9 respondents studying lapatinib providing data on**
  - 9 lapatinib studies
  - 9 paired comparator studies
- **9 respondents studying rapamune providing data on**
  - 9 rapamune studies
  - 9 paired comparator studies

CLINICAL TRIALS TRANSFORMATION INITIATIVE

Characteristics of each study under observation

	Lapatinib				Comparator			
	n	Mean	SD	Median	n	Mean	SD	Median
Number of subjects to be enrolled at all sites	9	1004.4	1496.70	6.00	9	141.11	226.88	6.00
Number of anticipated sites	7	59.29	152.01	1.00	8	32.25	69.44	3.00
Length of subject participation in trial (months)	7	60.86	56.12	36.0	6	35.50	46.65	13.5
Length of study drug exposure in trial (days)	6	334.33	74.63	365.0	7	332.29	331.85	270.0

	Rapamune				Comparator			
	n	Mean	SD	Median	n	Mean	SD	Median
Number of subjects to be enrolled at all sites	9	279.44	150.55	375.0	9	279.67	199.15	302.0
Number of anticipated sites	9	36.89	20.48	45.00	8	41.50	30.41	50.00
Length of subject participation in trial (months)	9	13.72	5.84	14.00	9	12.89	4.68	12.00
Length of study drug exposure in trial (days)	9	338.67	152.92	364.0	9	294.89	200.14	365.0

CLINICAL TRIALS TRANSFORMATION INITIATIVE

Volume of SUSARs: LAPATINIB

	Lapatinib				Comparator			
Volume of SUSARs	n	Mean	SD	Median	n	Mean	SD	Median
Number of events received	9	165.33	156.06	165.00	9	82.11	124.40	33.00
Number of events suggesting a "red flag“ (several similar events recently reported)	9	3.89	9.84	0.00	9	4.22	9.76	0.00
How many events resulted in a change to the study treatment?	9	0.11	0.33	0.00	9	0.11	0.33	0.00
How many events resulted in a study amendment?	9	0.11	0.33	0.00	9	0.11	0.33	0.00
How many events resulted in a change to the informed consent document?	9	0.11	0.33	0.00	9	0.22	0.44	0.00
How many events were reported to your IRB?	9	0.22	0.67	0.00	9	0.67	1.12	0.00
How many events required "no action“?	9	160.33	156.79	120.00	8	90.38	129.32	33.00

CLINICAL TRIALS TRANSFORMATION INITIATIVE

Volume of SUSARs: RAPAMUNE

	Rapamune				Comparator			
	n	Mean	SD	Median	n	Mean	SD	Median
Number of events received	9	21.22	47.42	4.00	9	34.22	69.75	10.00
Number of events suggesting a "red flag“ (several similar events recently reported)	9	0.11	0.33	0.00	9	0.44	0.88	0.00
How many events resulted in a change to the study treatment?	9	0.11	0.33	0.00	9	0.22	0.67	0.00
How many events resulted in a study amendment?	9	0.22	0.44	0.00	9	0.22	0.67	0.00
How many events resulted in a change to the informed consent document?	9	0.22	0.44	0.00	9	0.78	1.39	0.00
How many events were reported to your IRB?	9	17.00	48.78	0.00	9	24.89	72.05	1.00
How many events required "no action“?	7	23.57	54.70	0.00	7	34.71	80.91	0.00

CLINICAL TRIALS TRANSFORMATION INITIATIVE

Estimate of “person-power”: LAPATINIB

	Lapatinib				Comparator			
Time estimate in minutes (1 aggregate for each trial vs. each individual report for comparator trial)	**n**	**Mean**	**SD**	**Median**	**n**	**Mean**	**SD**	**Median**
Reading each report	**9**	**22.33**	**31.25**	**5.00**	**9**	**25.56**	**39.88**	**5.00**
Producing compilation report	**7**	**3.71**	**3.64**	**5.00**	**7**	**14.29**	**16.94**	**10.00**
Review with members of the study team	**9**	**6.00**	**4.77**	**5.00**	**8**	**7.88**	**4.82**	**10.00**
Distribute to appropriate staff	**8**	**4.50**	**2.83**	**5.00**	**8**	**8.25**	**6.34**	**10.00**
Prepare submission to IRB	**7**	**15.29**	**20.18**	**10.00**	**8**	**15.00**	**23.76**	**2.50**
Plan and implement changes to IC form and process changes	**8**	**26.88**	**47.73**	**0.00**	**8**	**26.88**	**47.73**	**0.00**

CLINICAL TRIALS TRANSFORMATION INITIATIVE

Estimate of “person-power”: RAPAMUNE

Time estimate in minutes (1 aggregate for each trial vs. each individual report for comparator trial)	Rapamune				Comparator			
	n	Mean	SD	Median	n	Mean	SD	Median
Reading each report	9	12.11	18.90	4.00	9	6.89	4.37	5.00
Producing compilation report	9	21.11	37.65	10.00	8	48.75	63.96	15.00
Review with members of the study team	8	4.63	5.42	3.00	7	5.71	4.50	5.00
Distribute to appropriate staff	8	7.25	7.63	5.50	7	7.86	7.56	5.00
Prepare submission to IRB	8	30.63	41.01	12.50	8	33.13	40.26	22.50
Plan and implement changes to IC form and process changes	8	48.13	87.67	5.00	8	36.25	83.01	2.50

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Percent of total time(%) spent by….

	Lapatinib				Comparator			
Percent of total time(%) spent by	**n**	**Mean**	**SD**	**Median**	**n**	**Mean**	**SD**	**Median**
Secretarial or administrative staff (%)	**9**	**48.33**	**40.23**	**50.00**	**9**	**51.67**	**43.01**	**75.00**
Professional support staff (%)	**9**	**35.56**	**35.83**	**10.00**	**9**	**25.89**	**34.69**	**5.00**
Physician staff (%)	**9**	**16.11**	**13.18**	**10.00**	**9**	**11.33**	**10.89**	**5.00**

	Rapamune				Comparator			
	n	**Mean**	**SD**	**Median**	**n**	**Mean**	**SD**	**Median**
Secretarial or administrative staff (%)	**8**	**22.25**	**27.68**	**10.00**	**8**	**21.00**	**28.53**	**5.00**
Professional support staff (%)	**9**	**60.89**	**37.89**	**80.00**	**9**	**55.00**	**34.55**	**50.00**
Physician staff (%)	**9**	**9.33**	**7.68**	**10.00**	**9**	**14.11**	**15.36**	**10.00**

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Limitations

- Small numbers of respondents
- Estimate of time is subject to recall bias
- Information to judge representation of sites relative to all investigators is not available.
- Few reportable (i.e. related and unexpected) events to assess how well the most important outcomes (i.e. how well subjects/investigators are informed of safety concerns).

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Summary

- **For these two medications as well as the medications selected by the respondents, only a small proportion of all SAEs meet the criteria for reportability (related and unexpected).**
- **The respondents report a similar amount of time to review one aggregate report as compared to a report of a single event.**

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Conclusions and recommendations

- These data suggest a potential time savings afforded to investigators by aggregate reporting.
- In the setting of continued communication of all SAEs to sites, consideration should be given toward the examination of how the aggregate reporting system affects time to communication of a potential safety signal, consent form change, procedural changes to reflect safety measures in a protocol.

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