



PhUSE 2009, Basel

ClinicalTrials.gov – a programmer's perspective

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Agenda

- ClinicalTrials.gov
- “Basic Results” disclosure
- Initial process
- Future process
- Summary



ClinicalTrials.gov – History

- Launched in Feb 2000
 - Key summary protocol information
- FDA Amendment Act (FDAAA) 801 in 2007
 - Registry expanded
 - Results database added
- Results section enabled on 27 Sep 2007
- Trial registration required by public law from Dec 2007
- Results reporting required from Sep 2008
- Adverse event disclosure from Sep 2009
- “Expansion” foreseen in Sep 2010

ClinicalTrials.gov – Statistics I

<i>(Trials as of 09/28/2009)</i>	<u>Number</u>	<u>Percent</u>
Total registered	79,347	100%
Type of trial		
Observational	12,921	16%
Interventional	66,105	83%
International sites (171 countries)		
USA	42,849	54%
Europe	18,841	24%
Data provider		
US Federal (incl. NIH)	18,824	24%
Industry	32,140	41%
University, Other	40,822	51%

ClinicalTrials.gov – Statistics II

(Trials as of 09/28/2009)

	<u>Number</u>	<u>Percent</u>
Total with results	824	100%
Type of trial		
Observational	41	5%
Interventional	783	95%
International sites		
USA	393	48%
Europe	168	20%
Data provider		
US Federal (incl. NIH)	29	4%
Industry	710	86%
University, Other	110	13%

Results Disclosure on ClinicalTrials.gov

- Registration and results reporting via Web-based Protocol Registration System (PRS)
 - “Basic results” required for “applicable” clinical trials, i.e.
 - Phase 2 to 4 interventional studies*
 - Studies involving drugs, biological products or medical devices approved and regulated by FDA
 - Studies with sites in US or studies conducted under NDA
 - Studies initiated or ongoing as of SEP 27, 2007 or later
- * Self-commitment by PhRMA: Phase 1 to 4 studies involving patients

Timelines for ClinicalTrials.gov

- Generally, submission of results within 12 months of the earlier of the estimated or actual trial completion date
- Delayed submission of results
 - Seeking initial approval
 - Seeking approval for a new use
 - Extensions for “good cause”



Prohibited Acts and Penalties

Prohibited Acts

- Failure to submit a certification
- Knowingly submitting a false certification
- Failure to submit required clinical trial information
- Submission of false or misleading clinical trial information



Penalties

- Penalty for a violation is up to \$10,000
- If the violation is not fixed after 30 days, the penalty can be up to \$10,000 per day until the violation is fixed



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Basic Results Information

- **Scientific information**

- Participants flow (Disposition) – by treatment arm
- Baseline characteristics – overall and by treatment arm
- Primary and secondary outcome measures, statistical analyses – by treatment arm
- Adverse events – by treatment arm



- **Administrative information**

- Point of contact (for scientific information)
- Certain agreements (restrictions on PI to discuss or publish results after trial completion date)



Adverse Events

- **Serious Adverse Events**

- Table of anticipated and unanticipated serious adverse events
- Grouped by organ system class
- Number and frequency of events in each clinical trial arm

- **Frequent (other) Adverse Events**

- Table of anticipated and unanticipated non-serious adverse events
- Exceed a frequency of 5 percent within any trial arm
- Number and frequency of events in each clinical trial arm



The Website ClinicalTrials.gov



Home - ClinicalTrials.gov - Microsoft Internet Explorer

Datei Bearbeiten Ansicht Favoriten Extras ?

Zurück Suchen Favoriten

Adresse <http://www.clinicaltrials.gov/> Wechseln zu

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Home **Search** Study Topics

ClinicalTrials.gov is a registry of federally and privately supported clinical trials conducted in the United States and around the world. ClinicalTrials.gov gives you information about a trial's purpose, who may participate, locations, and phone numbers for more details. This information should be used in conjunction with advice from health care professionals. [Read more...](#)

► **Search for Clinical Trials**

Find trials for a specific medical condition or other criteria in the ClinicalTrials.gov registry. ClinicalTrials.gov currently has **79,285 trials** with locations in **171 countries**.

► **Investigator Instructions**

Get instructions for clinical trial investigators/sponsors about how to register trials in ClinicalTrials.gov. Learn about mandatory registration and results reporting requirements and US Public Law 110-85 (FDAAA).

► **Background Information**

Learn about clinical trials and how to use ClinicalTrials.gov, or access other consumer health information from the US National Institutes of Health.

Resources:

- [Understanding Clinical Trials](#)
- [What's New](#)
- [Glossary](#)

Study Topics:

- [List studies by Condition](#)
- [List studies by Drug Intervention](#)
- [List studies by Sponsor](#)
- [List studies by Location](#)

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Results – Participant flow

Reporting Groups

	Description
Arm 1: VAQTA™	Hepatitis A vaccine, inactivated
Arm 2: VAQTA™ +ProQuad™	Hepatitis A vaccine, inactivated + measles, mumps, rubella, and varicella vaccine live

Participant Flow: Overall Study

	Arm 1: VAQTA™	Arm 2: VAQTA™ +ProQuad™
STARTED	1453	347
Vaccination 1 + Safety Follow-up	1453	347
Postvaccination 1 Post-Safety Follow-up	1393	325
Vaccination 2 + Safety Follow-up	1301	292
Postvaccination 2 Post-Safety Follow-up	1265	271
COMPLETED	1253	264
NOT COMPLETED	200	83
Lost to Follow-up	104	56
Protocol Violation	6	3
Withdrawal by Subject	35	7
Subject Moved	7	4
Unspecified	47	13
Adverse Event	1	0

Results – Baseline Measures

Reporting Groups

	Description
Vytorin	Ezetimibe 10 mg/Simvastatin 20 mg
Atorvastatin	Atorvastatin 10 mg

Baseline Measures

	Vytorin	Atorvastatin	Total
Number of Participants [units: participants]	108	95	203
Age [units: years] Mean $\pm$ Standard Deviation	58.4 $\pm$ 10.7	58.7 $\pm$ 8.7	58.5 $\pm$ 9.8
Gender [units: participants]			
Female	57	56	113
Male	51	39	90
Baseline Low Density Lipoprotein Cholesterol (LDL-C) Strata [units: Participants]			
<130 mg/dl	2	3	5
$\geq$ 130 to <160 mg/dl	45	32	77
$\geq$ 160 to <190 mg/dl	41	43	84
$\geq$ 190 mg/dl	20	17	37
Body Mass Index [units: kg/m ²] Mean $\pm$ Standard Deviation	25.3 $\pm$ 2.9	25 $\pm$ 2.8	25.2 $\pm$ 2.8

Results – Outcome Measures I

4. Secondary Outcome Measure: Maternal Satisfaction With Perineal Pain Management

[Hide these results.](#)

Measure Type	Secondary
Measure Name	Maternal Satisfaction With Perineal Pain Management
Measure Description	5 point Likert scale asking for agreement with the statement "I was satisfied with my pain relief for the pain in my bottom during the first day after delivery". Scale ranged from strongly disagree to strongly agree.
Time Frame	at 24 hours postpartum
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.

No text entered.

Reporting Groups

	Description
Epidural Morphine	2.5 mg dose of epidural morphine given within one hour following vaginal delivery
Placebo	5 ml of epidural preservative-free saline given within one hour following vaginal delivery

Measured Values

	Epidural Morphine	Placebo
Number of Participants Analyzed [units: participants]	113	115
Maternal Satisfaction With Perineal Pain Management [units: participants]		
Strongly Disagree	1	3
Disagree	9	11
Not sure	6	8
Agree	43	38
Strongly Agree	45	45
Missing information	9	10

Results – Outcome Measures II

Reporting Groups

	Description
ER Niacin/Laropiprant	Extended Release (ER) Niacin 2 g/Laropiprant 40 mg once daily for 7 days
ER Niacin	ER Niacin 2 g once daily for 7 days
Laropiprant	Laropiprant 40 mg once daily for 7 days
Placebo	Placebo once daily for 7 days

Measured Values

	ER Niacin/Laropiprant	ER Niacin	Laropiprant	Placebo
Number of Participants Analyzed [units: participants]	22	21	22	22
Urinary 11-Dehydrothromboxane B2 (11-dTxB2) [units: pg/mg creatinine] Least Squares Mean (95% Confidence Interval)	525.3 (423.8 to 651.1)	540.8 (435.0 to 672.3)	585.3 (472.2 to 725.4)	625.1 (504.3 to 774.8)

Statistical Analysis 1 for Urinary 11-Dehydrothromboxane B2 (11-dTxB2)

Groups ^[1]	ER Niacin/Laropiprant vs. ER Niacin
Non-Inferiority/Equivalence Test ^[2]	Yes
Geometric least-squares mean ratio ^[3]	0.97
90% Confidence Interval	(0.8 to 1.18)

[1] Additional details about the analysis, such as null hypothesis and power calculation:

The endpoint is the urine levels of 11-dTxB2 on Day 7 following a 7 day course of daily dosing in the overall 24 hour collection interval. The point estimate and 90% confidence intervals (CIs) were calculated for the geometric mean ratio (GMR) [Treatment A/B] of the urine levels of 11-dTxB2 on Day 7.

[2] Details of power calculation, definition of non-inferiority margin, and other key parameters:

Two treatments are comparable if the geometric mean ratio (GMR) is contained within the interval [0.50-2.00].

[3] Other relevant estimation information:

No test entered.

Results – Serious Adverse Events

Reported Adverse Events

Reporting Groups

	Description
Liquid Palivizumab	Liquid Palivizumab, 15 mg/kg IM q30 days X 5
Lyophilized Palivizumab	Lyophilized Palivizumab, 15 mg/kg IM q30 days X 5

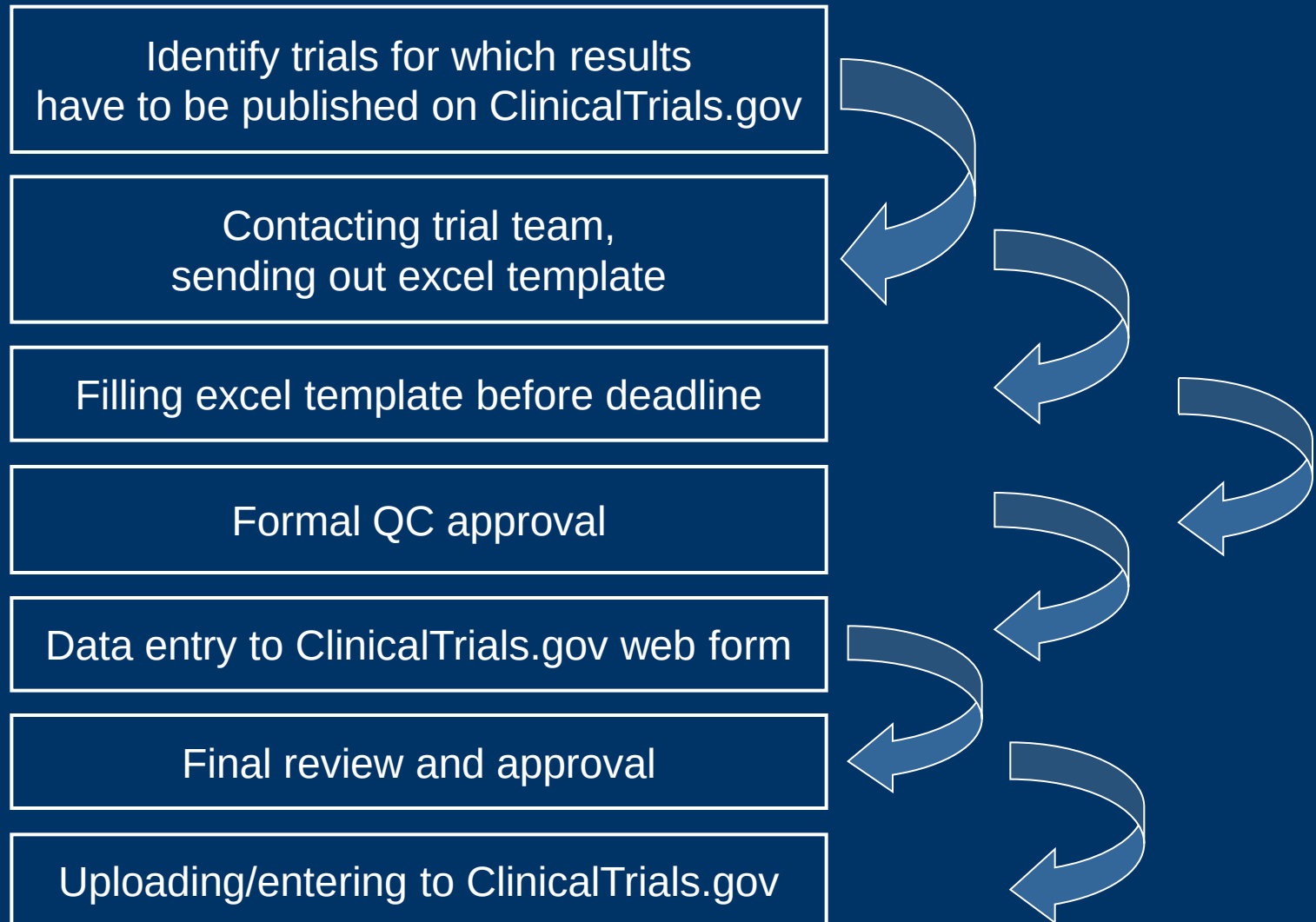
Serious Adverse Events

	Liquid Palivizumab	Lyophilized Palivizumab
Total, serious adverse events		
number of participants affected	18	12
Blood and lymphatic system disorders		
Lymphadenitis †		
number of participants at risk	211	202
number of events	1	0
number of participants affected	1	0
Congenital, familial and genetic disorders		
Cleft Lip †		
number of participants at risk	211	202
number of events	1	1
number of participants affected	1	1
Gastrointestinal disorders		
Anal Fissure †		
number of participants at risk	211	202
number of events	1	0
number of participants affected	1	0
Gastroesophageal Reflux Disease †		
number of participants at risk	211	202
number of events	1	0
number of participants affected	1	0
Inguinal Hernia †		
number of participants at risk	211	202
number of events	1	1
number of participants affected	1	1
Umbilical Hernia †		
number of participants at risk	211	202
number of events	1	0
number of participants affected	1	0
Occult Blood Positive †		
number of participants at risk	211	202
number of events	0	1
number of participants affected	0	1

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Current Process Description



Problems and Issues

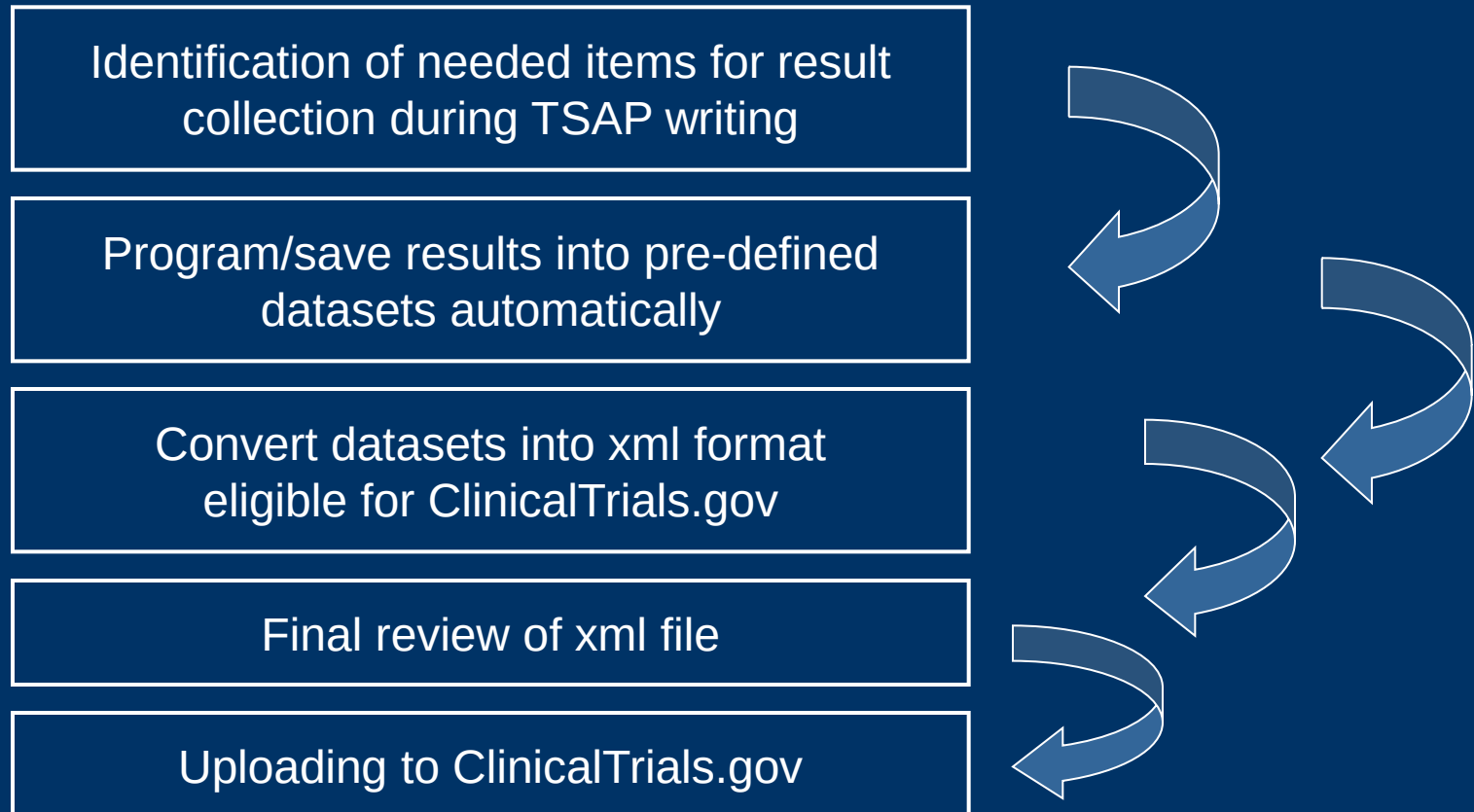
- Mainly manually driven process
- Entering and copying of information vulnerable to errors
- Validation and Quality Check are time-consuming
- Trial teams are often not familiar with ClinicalTrials.gov



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Future Process



The statistician's responsibility

- During writing of Analysis Plan
 - Specify information which should be disclosed
 - Identify tables of CTR with information for disclosure
 - Define specifications for programming
 - Keep track of changes

The programmer's responsibility

- During table creation for Clinical Trial Report (CTR)
 - Extract information needed for ClinicalTrials.gov
 - Save information in dataset (“Disclosure Data Set”)
 - Use validated macro code
 - Transform final dataset into xml format
 - Validation during standard program validation

Advantages

- Information is collected when it is produced anyway
- Manual data entry minimized
- Accuracy of data ensured within current standard processes
- Disclosure data are available early before official deadline
- Minor additional workload



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Summary

- Additional workload due to legal requirements to disclose on ClinicalTrials.gov necessary
- First process
 - Data entry and copy manually
 - Vulnerable to errors
- Future process
 - Needed information is produced automatically
 - Only minor additional workload
 - Use of validated tools

