

Posting of the results

A important step toward transparency

Philippe Ravaud



Background

- US Federal law enacted in 2007 mandates **registration and results reporting** at clinicaltrials.gov
- Applicable clinical trials include
 - phase II to IV interventional controlled trials registered after the enactment of the Food and Drug Administration Amendment Act (FDAAA 801) or ongoing at this date
 - involving drugs, biologic agents, or devices after FDA approval for any use
 - regardless of sponsorship
 - involving at least one US site

FDA Amendment Act 801

- Study sponsors or PI are required to report summary results information whether the results are published or not, within 1 year of completing data collection for the prespecified primary outcome
- The law requires for each arm
 - a table of the demographic and baseline data collected
 - a table of values for each of the primary and secondary outcome measures
- Not complying with this requirement could result in civil monetary penalties (up to US\$10,000 a day), and for federally funded studies the withholding of grant funds

Posting Results :

A required template on clinicaltrials.gov

Recruitment Information

Significant events following enrollment, but prior to assignment
 400 participants were screened. 175 did not meet criteria.

Participant Flow: Treatment Initial Randomization (Period 1)

Milestone	Placebo	Drug X, Low Dose	Drug X, High Dose
STARTED	115	110	0
Received Intervention	114	110	0
COMPLETED	104	101	0
NOT COMPLETED	11	9	0
Adverse Event	4	5	0
Lost to Follow-up	4	2	0
Neutropenia	3	2	0

Participant Flow: Treatment Re-Randomization (Period 2)

	Placebo	Drug X, Low Dose	Drug X, High Dose
STARTED	104	51	50
COMPLETED	99	48	45
NOT COMPLETED	5	3	5
Lost to Follow-up	2	2	5
Neutropenia	3	1	0

"Customized" Reason for Non-completion

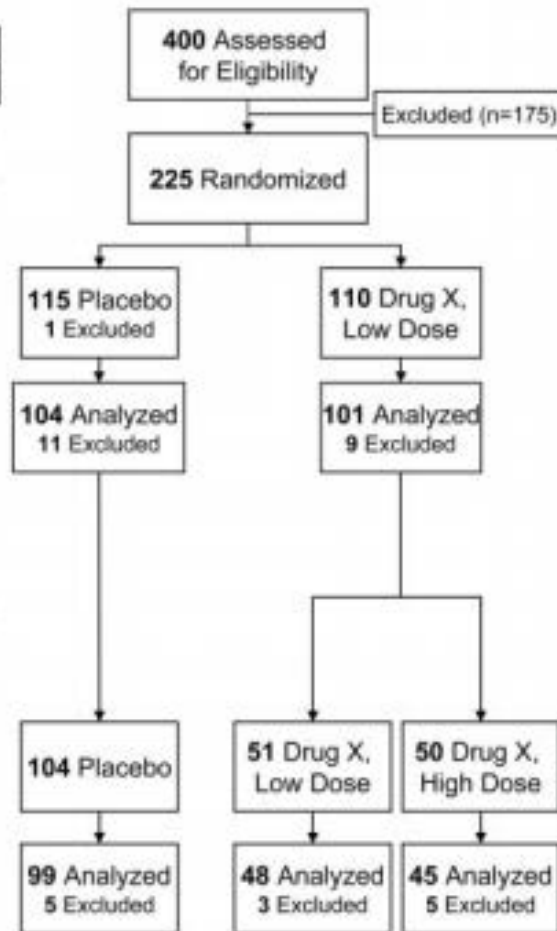


FIGURE 2. Participant flow display in ClinicalTrials.gov (left) and corresponding CONSORT diagram (right).

Outline

- How frequently results are available on CT.gov?
- How complete are results posted compared to published results ?
- Is there any discrepancies between the 2 sources for safety issues ?
- Is it feasible to improve the frequency of posting ?

Public Availability of Results of Trials Assessing Cancer Drugs in the United States

Thi-Anh-Hoa Nguyen, Agnes Dechartres, Soraya Belgherbi, and Philippe Ravaud

- To evaluate to what extent results of completed trials of cancer drugs conducted in the United States falling under the FDAAA are publicly available at ClinicalTrials.gov or are published in journals

Public Availability of Results of Trials Assessing Cancer Drugs in the United States

Thi-Anh-Hoa Nguyen, Agnes Dechartres, Soraya Belgherbi, and Philippe Ravaud

- We searched ClinicalTrials.gov for **cancer trials** governed by the FDAAA: phase II to IV trials assessing drugs in the United States with a primary completion date between December 2007, and May 2010.
- For each trial, we searched PubMed to identify the publication of results.

Public Availability of Results of Trials Assessing Cancer Drugs in the United States

Thi-Anh-Hoa Nguyen, Agnes Dechartres, Soraya Belgherbi, and Philippe Ravaud

- At 24 months after completion, among 646 trials
 - 61% had no results available at ClinicalTrials.gov or published in journals.
 - 17% had results published in journals, but no results posted at ClinicalTrials.gov,
 - 7% had results both posted at ClinicalTrials.gov and published in journals,
 - 15% had results posted at ClinicalTrials.gov but not published

38 % of trials with results publicly available are only available on CT.gov

Timing and Completeness of Trial Results Posted at ClinicalTrials.gov and Published in Journals

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- We aimed to compare the timing and completeness of results publicly posted at ClinicalTrials.gov and in published articles for trials of drug interventions

Timing and Completeness of Trial Results Posted at ClinicalTrials.gov and Published in Journals

Carolina Riveros^{1,2,3}, Agnes Dechartres^{1,2,3*}, Elodie Perrodeau^{1,3}, Romana Haneef^{1,3},
Isabelle Boutron^{1,2,3,4}, Philippe Ravaud^{1,2,3,4,5}

- We searched ClinicalTrials.gov for randomized controlled trials of drugs with posted results
- We searched PubMed for corresponding publications.
- Trials with results both posted and published data were extracted independently from ClinicalTrials.gov and from the published articles

Definition of completeness of reporting (point of view of meta-analysts)

- **Flow of participants**
- **Efficacy results**
 - For binary outcomes:*
Number of events per arm
and Number of patients
analyzed per arm
 - For continuous outcomes:*
Mean or median per arm
and SD or SE or 95%CI or
Q1–Q3 or Effect size with
95% CI
 - For time-to-event outcomes:*
Hazard ratio with 95% CI
- **Adverse events**
Number of adverse events
per arm without restriction
to statistically significant
differences between arms
for all randomized
participants or for those
who received at least one
treatment dose
- **Serious adverse events**
Number of serious adverse
events per arm

Results are more complete at CT.gov than in the published articles

Domain	Percent of Trials with Complete Reporting at ClinicalTrials.gov (n = 202)	Percent of Trials with Complete Reporting in Published Article (n = 202)	p-Value
Flow of participants	64 %	48%	0.001
Efficacy results	79%	69%	0.02
Adverse events	73%	45%	0.001
Serious adverse events	99%	63%	0.001

Comparison of Serious Adverse Events Posted at ClinicalTrials.gov and Published in Corresponding Journal Articles

- To assess whether there are discrepancies in **serious adverse events** reported in ClinicalTrials.gov and corresponding published articles

Methods


- Identification of phase III and IV interventional **trials with at least one serious adverse event posted** at ClinicalTrials.gov
- For a random sample of these trials we searched the published articles by:
 - Using the link within ClinicalTrials.gov to identify article
 - Searching MEDLINE via PubMed using NCT number and keywords



Summary of Results

- Of the random sample of 200 trials, 84 (42%) did not have a corresponding journal article
- Number of Serious Adverse Events(SAEs) per arm is completely reported and match those in ClinicalTrials.gov in only 47% (55) of 116 trials with corresponding published articles
- Types of SAEs are completely reported in only 21% (24) of 116 trials
- Many inconsistencies between posted results and published articles
- Journal articles often report only drug-related and/or most common SAEs
- **Overall, number and details of SAEs were completely reported in only 20 (17%) of 116 trials with corresponding published articles**

Impact of sending email reminders of the legal requirement for posting results on ClinicalTrials.gov: cohort embedded pragmatic randomized controlled trial

 OPEN ACCESS



Annabel Maruani *professor*¹, Isabelle Boutron *professor*¹, Gabriel Baron *statistician*¹, Philippe Ravaud *professor*¹ *director*²

- Approximately 75% of applicable clinical trials do not post basic results
- To evaluate the impact of sending an email to responsible parties of completed trials that do not comply with the Food and Drug Administration Amendments Act 801 legislation, to remind them of the legal requirement to post results.

Methods

- We identified a cohort of all trials registered on ClinicalTrials.gov that did not comply with the FDAAA 801 requirements for posting trial results (no results posted).
- We randomly selected a sample of these trials to receive an intervention.
- This design was similar to the “cohort multiple randomized controlled trial » by Relton
- The proportion of trials with basic results posted at 3 months (Primary Outcome) was assessed for the whole cohort and compared between trials receiving the intervention and the rest of the cohort.

Intervention

- Sending reminders of the FDAAA 801 requirement through personalized emails (title and NCT number of the trial) to responsible parties of the randomly selected trials.
- The emails were constructed as surveys, notifying responsible parties of trials that the primary completion date was over a year old and asking for the reasons why they had not posted results on the register
- The email outlined whether responsible parties were aware of the risk of civil penalties (up to \$10 000 a day) and withholding of grant funds for federally funded trials if they failed to comply with this requirement

Intervention

- This intervention was based on automatically generated reminders (IF This ThenThat (IFTTT) technology)
- Emails were signed by me indicating one American academic affiliation (Mailman School of Public Health, Columbia University, NYC).
- Reminders were systematically sent at day 7 and at two and five months

Results

- We identified 379 that had not posted results according to the FDAAA 801
- A random sample of 190 of these trials was allocated to the intervention group (and 189 did not receive intervention)
- We excluded 48 trials wrongly included because with a “results first received” date that was before our date of randomization
- In fact , there is a delay between the first submission of trial results by responsible parties and their public posting at ClinicalTrials.gov (2 to 3 months)

Results

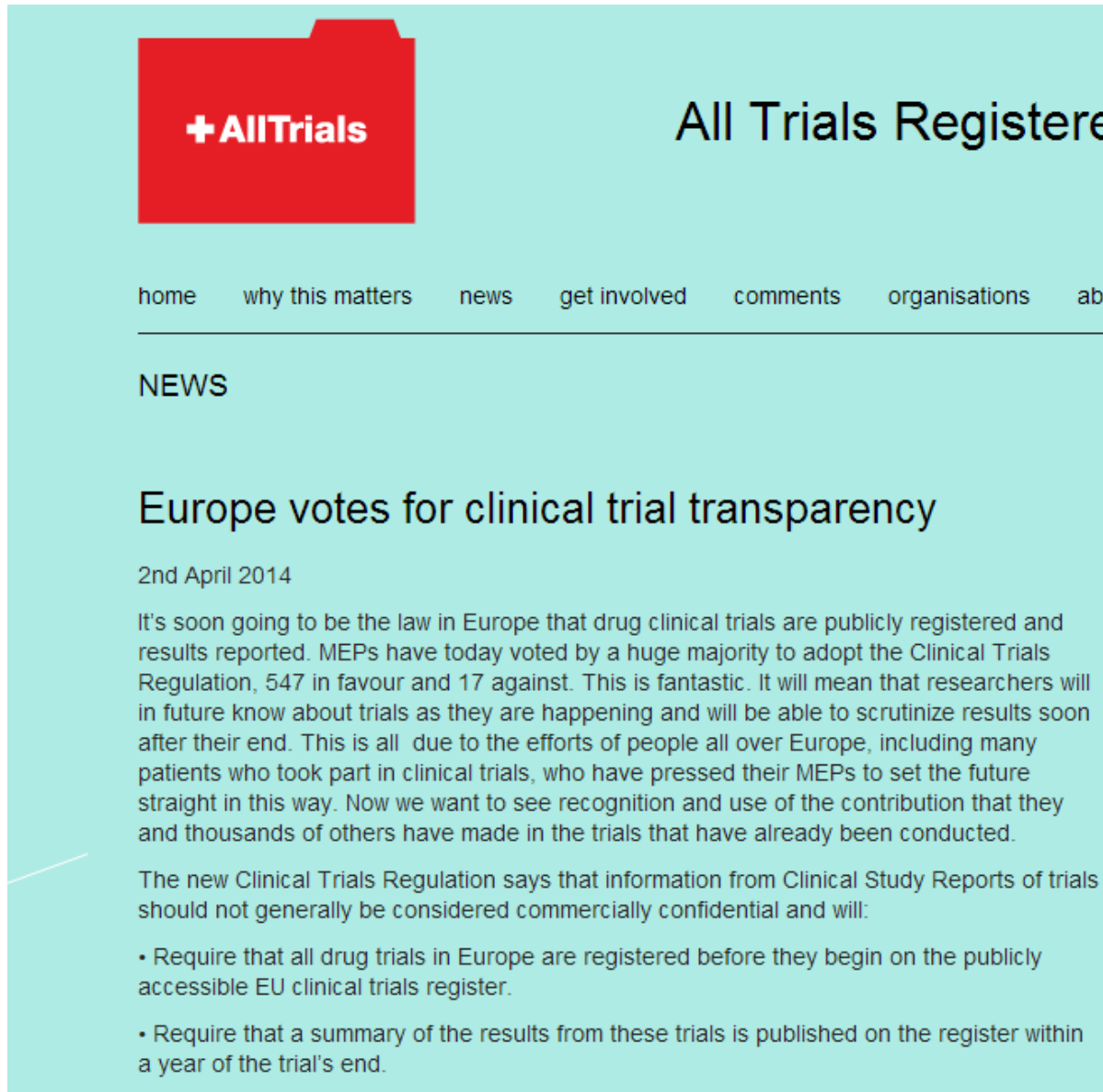
331 trials without results posted at the time of randomization

Analysis	Intervention (n=164)	Control (n= 167)	Risk difference (95% CI)	Relative risk (95% CI)
3 months	10 % (6)	2 %(1)	4.9 (0.9 to 8.9)	5.1 (1.1 to 22.9)
6 months	20 % (12)	5 %(3)	9.2 (3.6 to 14.8)	4.1 (1.6 to 10.6)

Number needed to have an additional posting : 9

email reminders sent to responsible parties of 9 trials led to results posted for one additional trial

New EU Clinical Trials Regulation



The screenshot shows the AllTrials website interface. At the top left is a red logo with a white plus sign and the text '+AllTrials'. To the right of the logo is the text 'All Trials Registered'. Below the logo is a navigation menu with links: 'home', 'why this matters', 'news', 'get involved', 'comments', 'organisations', and 'about'. Below the navigation menu is a section titled 'NEWS'. The main article is titled 'Europe votes for clinical trial transparency' and is dated '2nd April 2014'. The article text discusses the adoption of the Clinical Trials Regulation by MEPs and its implications for clinical trial transparency. At the bottom of the article, there are two bullet points summarizing the key requirements of the regulation.

+AllTrials All Trials Registered

home why this matters news get involved comments organisations about

NEWS

Europe votes for clinical trial transparency

2nd April 2014

It's soon going to be the law in Europe that drug clinical trials are publicly registered and results reported. MEPs have today voted by a huge majority to adopt the Clinical Trials Regulation, 547 in favour and 17 against. This is fantastic. It will mean that researchers will in future know about trials as they are happening and will be able to scrutinize results soon after their end. This is all due to the efforts of people all over Europe, including many patients who took part in clinical trials, who have pressed their MEPs to set the future straight in this way. Now we want to see recognition and use of the contribution that they and thousands of others have made in the trials that have already been conducted.

The new Clinical Trials Regulation says that information from Clinical Study Reports of trials should not generally be considered commercially confidential and will:

- Require that all drug trials in Europe are registered before they begin on the publicly accessible EU clinical trials register.
- Require that a summary of the results from these trials is published on the register within a year of the trial's end.

This new legislation will come into effect in 2016

Requires that a summary of the results from these trials is posted on the register within a year of the trial's end

Conclusion I

- Compliance to the law remains poor in USA : 75% of applicable clinical trials do not post basic results
- When Data are posted, they are
 - sometimes available even if trials are not published
 - more complete than published articles (particularly safety data)
 - Discrepancies are frequent between data published and data posted
- Posting of results must be systematically searched when performing systematic reviews or meta-analyses

Conclusion II

- Posting could be improved through simple and cheap interventions
- Successes of the formats used for the posting should make us wonder about the methods and formats used to report the results in the paper articles
 - verification by humans at clinicaltrials.gov
 - structured template versus narrative results section

Acknowledgements to all the members of my team involved in these research

- Pr Isabelle Boutron
- Pr Annabel Maruani
- Dr. Agnes Dechartres
- Dr. Carolina Riveros
- Elodie Perrodeau
- Romana Haneef
- Soraya Belgherbi
- Thi-Anh-Hoa Nguyen,
- Eve Tang
- Gabriel Baron