Disponibilité des résultats d'essais: intérêt des registres

Agnès Dechartres
agnes.dechartres@htd.aphp.fr

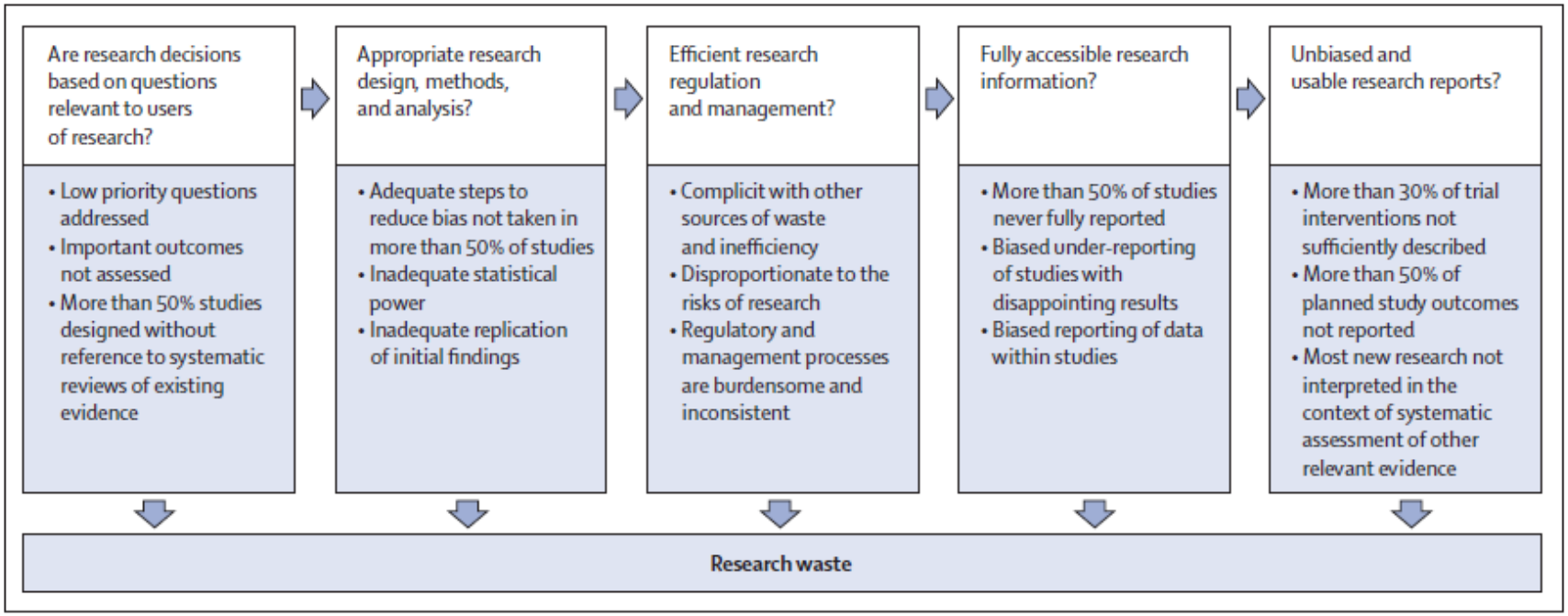
INSERM U1153
Centre de Recherche Epidemiologie et Statistique Sorbonne Paris Cité

THE LANCET

Biomedical research: increasing value, reducing waste

"Without accessible and usable reports, research cannot help patients and their clinicians."

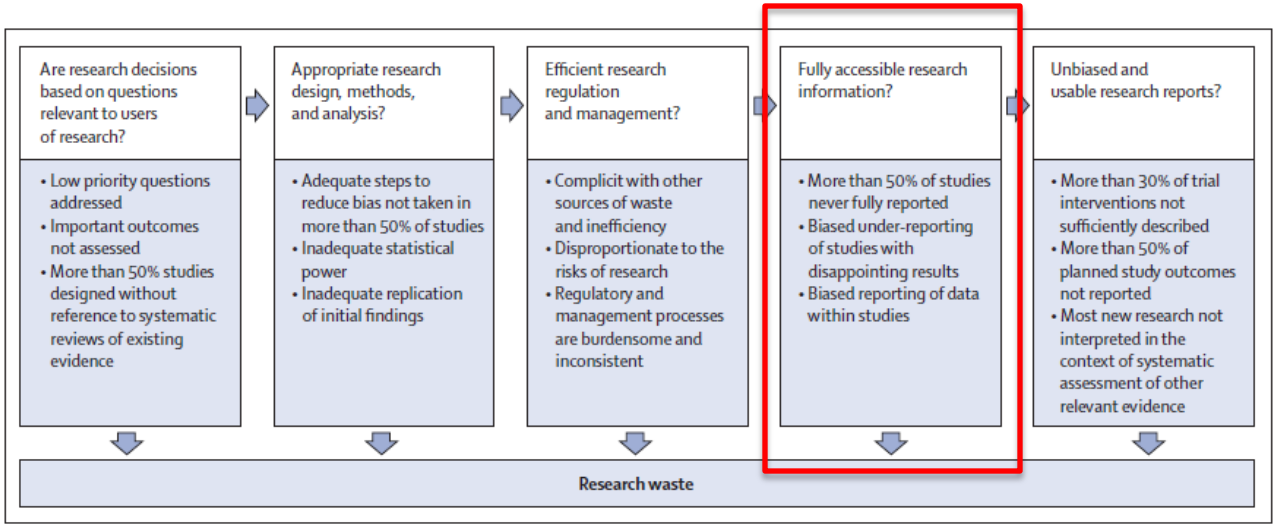
Chalmers et Glasziou., *Lancet*, 2009



Macleod et al., *Lancet*, 2014

Underreporting of trial results

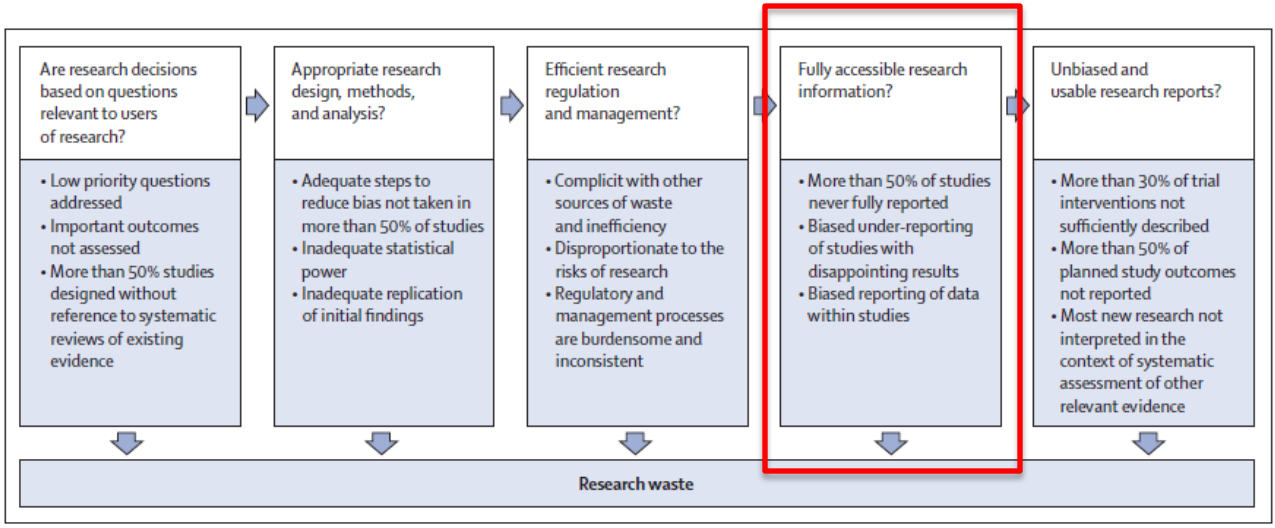
- Non publication de certains résultats (principalement s'ils sont négatifs)
- Publication retardée de certains résultats (principalement s'ils sont négatifs)
- Présentation sélective des résultats de certains critères de jugement (surtout s'ils sont positifs)
- Résultats incomplètement rapportés dans la publication



Macleod et al., *Lancet*, 2014

Underreporting of trial results

- Non publication de certains résultats (principalement s'ils sont négatifs)
- Publication retardée de certains résultats (principalement s'ils sont négatifs)
- Présentation sélective des résultats de certains critères de jugement (surtout s'ils sont positifs)



Macleod et al., *Lancet*, 2014

- Résultats incomplètement rapportés dans la publication

→ Impossible de combiner les résultats dans une méta-analyse sur données résumées

Données nécessaires pour la méta-analyse

Nombre de patients analysés par bras et:

- Critère de jugement binaire (ex: mortalité à 28 jours)
  - Nombre de patients ayant eu l'évènement dans chaque bras
- Critère de jugement continu (ex: douleur mesurée par EVA)
  - Moyenne (écart-type) dans chaque bras
- Critère de jugement censuré (ex: mortalité)
  - Hazard ratio (IC 95%) ou nombre d'évènements

Exemple : critère binaire

Table 4. Frequency of Fatal Events in 299 Patients with Septic Shock*

Variable	No. (%) Placebo	Steroids	Adjusted OR (95% CI)	*P* Value
		Nonresponders		
No. of patients	115	114		
28-day mortality	73 (63)	60 (53)	0.54 (0.31-0.97)	.04
ICU mortality	81 (70)	66 (58)	0.50 (0.28-0.89)	.02
Hospital mortality	83 (72)	70 (61)	0.53 (0.29-0.96)	.04
1-Year mortality	88 (77)	77 (68)	0.57 (0.31-1.04)	.07
		Responders		
No. of patients	34	36		
28-Day mortality	18 (53)	22 (61)	0.97 (0.32-2.99)	.96
ICU mortality	20 (59)	24 (67)	0.99 (0.31-3.16)	.99
Hospital mortality	20 (59)	25 (69)	1.20 (0.38-3.76)	.75
1-Year mortality	24 (71)	25 (69)	0.70 (0.20-2.40)	.57
		All Patients		
No. of patients	149	150		
28-Day mortality	91 (61)	82 (55)	0.65 (0.39-1.07)	.09
ICU mortality	101 (68)	90 (60)	0.61 (0.37-1.02)	.06
Hospital mortality	103 (69)	95 (63)	0.67 (0.40-1.12)	.12
1-Year mortality	112 (75)	102 (68)	0.62 (0.36-1.05)	.08

Exemple : critère continu

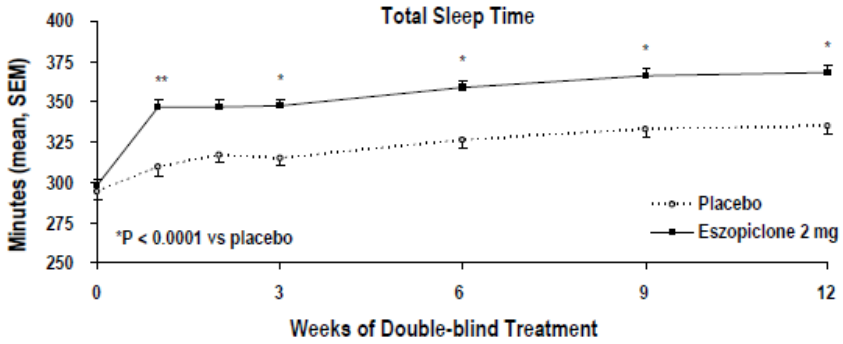
Variable	Valeur initiale (J0)		Mois 6 (M6)				
	Groupe de traitement*		Groupe de traitement*		Analyse statistique		
	IAS (n = 84)	Placebo (n = 78)	IAS (n = 84)	Placebo (n = 78)	Différence inter-groupe finale	p	Intervalle de confian à 95% de la Δ finale
Index algofonctionnel de Lequesne†							
coaxarthrose (n = 50)	9.4 ± 0.4	9.3 ± 0.5	7.5 ± 0.6	9.9 ± 0.7	- 2.5 ± 0.9	< 0.01	[- 4.3 ; - 0.6]
gonarthrose (n = 112)	10.1 ± 0.3	9.6 ± 0.3	6.1 ± 0.4	7.9 ± 0.4	-1.8 ± 0.6	0.003	[- 3.0 ; - 0.6]
tous les patients	9.7 ± 0.3	9.4 ± 0.3	6.8 ± 0.4	8.9 ± 0.4	- 2.1 ± 0.5	< 0.001	[- 3.2 ; - 1.0]
Douleur sur EVA† (mm) :							
coxarthrose	55.8 ± 2.6	56.7 ± 3.2	37.5 ± 3.7	51.3 ± 4.5	-13.8 ± 5.8	0.02	[- 25.3 ; - 2.3]
gonarthrose	56.5 ± 1.9	55.4 ± 1.9	33.0 ± 2.7	40.1 ± 2.6	-7.1 ± 3.8	0.07	[- 14.6 ; + 0.5]
tous les patients	56.1 ± 1.6	56.1 ± 1.8	35.3 ± 2.3	45.7 ± 2.6	-10.4 ± 3.5	0.003	[- 17.3 ; - 3.6]

A moins d'une autre indication, les valeurs sont exprimées en moyennes et déviation standard de la moyenne. † Analyse statistique par analyse de covariance ajustée pour le facteur localisation de l'arthrose. ‡ Analyse statistique par le test de Mantel-Haenszel ajusté pour le facteur localisation de l'arthrose.

Souvent plus difficile (surtout pour des critères continus)

Critère de jugement principal:

Mean Change From Baseline in Subject-Reported Total Sleep Time (TST) over 12 Weeks



Results: Subjects treated with 2 mg eszopiclone slept longer at night on average and at every individual time point compared to baseline than placebo subjects, as measured by TST over the 12-week double-blind period ($P < 0.0001$). Mean sTST over the double-blind period for eszopiclone-treated subjects was 360.08 min compared to 297.86 min at baseline, a mean change of 63.24 min. Over the double-blind period, eszopiclone-treated subjects also experienced a significantly greater improvement in sSL compared to placebo, with a mean decrease of 24.62 min versus a mean decrease of 19.92 min, respectively ($P = 0.0014$). Eszopiclone subjects also experienced a significantly greater decrease in WASO (mean decrease of 36.4 min) compared to placebo subjects (decrease of 14.8 min) ($P < 0.0001$). Post-discontinuation, sleep parameters were statistically improved versus baseline for eszopiclone (P-values ≤ 0.01), indicating no rebound. The most common AEs ($\geq 5\%$) were headache (eszopiclone 13.9%, placebo 12.4%), unpleasant taste (12.4%, 1.5%), and nasopharyngitis (5.7%, 6.2%).

Enregistrement des essais: un moyen de lutter contre l' underreporting of trial results

Comment

Clinical trial registration: a statement from the International Committee of Medical Journal Editors

Altruism and trust lie at the heart of research on human subjects. Altruistic individuals volunteer for research because they trust that their participation will contribute to improved health for others and that researchers will minimise risks to participants. In return for the altruism and trust that make clinical research possible, the research enterprise has an obligation to conduct research ethically and to report it honestly. Honest reporting begins with revealing the existence of all clinical studies, even those

The ICMJE member journals will require, as a condition of consideration for publication, registration in a public trials registry. Trials must register at or before the onset of patient enrolment. This policy applies to any clinical trial starting enrolment after July 1, 2005. For trials that began enrolment before this date, the ICMJE member journals will require registration by Sept 13, 2005, before considering the trial for publication. We speak only for ourselves, but we encourage editors of other biomedical journals to adopt similar policies.

Published online
September 9, 2004
http://image.thelancet.com/extras/04cmt265web.pdf

ClinicalTrials.gov

ClinicalTrials.gov

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

ClinicalTrials.gov is a registry and results database of publicly and privately supported clinical studies of human participants conducted around the world. Learn more about clinical studies and about this site, including relevant history, policies, and laws.

Find Studies | About Clinical Studies | Submit Studies | Resources | About This Site

ClinicalTrials.gov currently lists 163,936 studies with locations in all 50 states and in 185 countries.

Text Size

Search for Studies

Example: "Heart attack" AND "Los Angeles"

Search

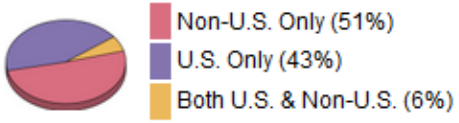
Advanced Search | See Studies by Topic

See Studies on a Map

Search Help

- How to search
- How to find results of studies
- How to read a study record

Locations of Recruiting Studies



Total N = 32,550 studies
Data as of March 27, 2014

- See more trends, charts, and maps

For Patients & Families

- How to find studies
- See studies by topic
- Learn about clinical studies
- Learn more...

For Researchers

- How to submit studies
- Download content for analysis
- About the results database
- Learn more...

For Study Record Managers

- Why register?
- How to register study records
- FDAAA 801 Requirements
- Learn more...

Learn More

- ClinicalTrials.gov Online Training
- Glossary of common site terms

For the Press

Using our RSS Feeds

HOME | RSS FEEDS | SITE MAP | TERMS AND CONDITIONS | DISCLAIMER | CONTACT NLM HELP DESK

Plateforme de l'OMS

World Health Organization

International Clinical Trials Registry Platform
Search Portal

Home | Advanced Search | List By | Search Tips | UTN | ICTRP website | Contact us

Example: liver cancer OR breast cancer NOT genetic [Search] Search tips

Welcome

- The Clinical Trials Search Portal provides access to a central database containing the trial registration data sets provided by the registries listed on the right. It also provides links to the full original records.
- To facilitate the unique identification of trials, the Search Portal bridges (groups together) multiple records about the same trial. More information
- Please note: This Search Portal is not a clinical trials registry. How to register a trial
- For mobile users, please use this link http://apps.who.int/trialsearch/ictrpmob.aspx. It can be opened from any smartphone
- It is now possible to export the results of the search into XML. More information
- Crawling the ICTRP database now requires a username/password. To request access to the crawling pages please send an email to ictrpinfo@who.int

Data Providers

Data sets from data providers are updated every Tuesday evening according to the following schedule
Every week:

- Australian New Zealand Clinical Trials Registry, last data file imported on **24 March 2014**
- ClinicalTrials.gov, last data file imported on **24 March 2014**
- EU Clinical Trials Register (EU-CTR), last data file imported on **24 March 2014**
- ISRCTN, last data file imported on **24 March 2014**

Every 4 weeks:

- Brazilian Clinical Trials Registry (ReBec), last data file imported on **10 March 2014**
- Chinese Clinical Trial Registry, last data file imported on **10 March 2014**
- Clinical Trials Registry - India, last data file imported on **11 March 2014**
- Clinical Research Information Service - Republic of Korea, last data file imported on **10 March 2014**
- Cuban Public Registry of Clinical Trials, last data file imported on **10 March 2014**
- German Clinical Trials Register, last data file imported on **10 March 2014**

FDA Amendment Act

- Amendement à la loi fédérale américaine en 2007:
  - Résultats des essais doivent être postés dans ClinicalTrials.gov au plus tard un an après le recueil du critère de jugement principal pour le dernier patient inclus
- Essais concernés:
  - Au moins un site aux Etats-Unis
  - Médicaments, biothérapies, dispositifs médicaux approuvés par la FDA
- Mais tous les essais peuvent poster leurs résultats!!

Adaptation de ClinicalTrials.gov pour poster les résultats

Phase III Randomized Study of Lucinactant in Full Term Newborn Infants With Meconium Aspiration Syndrome

This study has been terminated.

(Slow enrollment and administrative reasons)

Sponsor:
Discovery Laboratories, Inc.

Information provided by (Responsible Party):
Discovery Laboratories, Inc.

ClinicalTrials.gov Identifier:
NCT00004500

First received: October 18, 1999
Last updated: May 1, 2012
Last verified: May 2012
History of Changes

Full Text View | Tabular View | **Study Results** | Disclaimer | How to Read a Study Record

Results First Received: April 2, 2012

Study Type:	Interventional
Study Design:	Allocation: Randomized; Endpoint Classification: Safety/Efficacy Study; Intervention Model: Parallel Assignment; Primary Purpose: Treatment
Condition:	Meconium Aspiration
Interventions:	Drug: Lucinactant Other: Standard Care

« Template » pour remplir les résultats

The study results will be displayed in a tabular format that includes the following information:

- Participant flow
- Baseline characteristics
- Outcome measures and statistical analyses
- Adverse events
- Administrative information

Note that when the results of a study are not displayed on ClinicalTrials.gov, the results tab is labeled "No Study Results Posted". See About the Results Database from the About This Site menu.

Recommandations pour rapporter le flow chart

Recruitment Information

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

Arm/Group

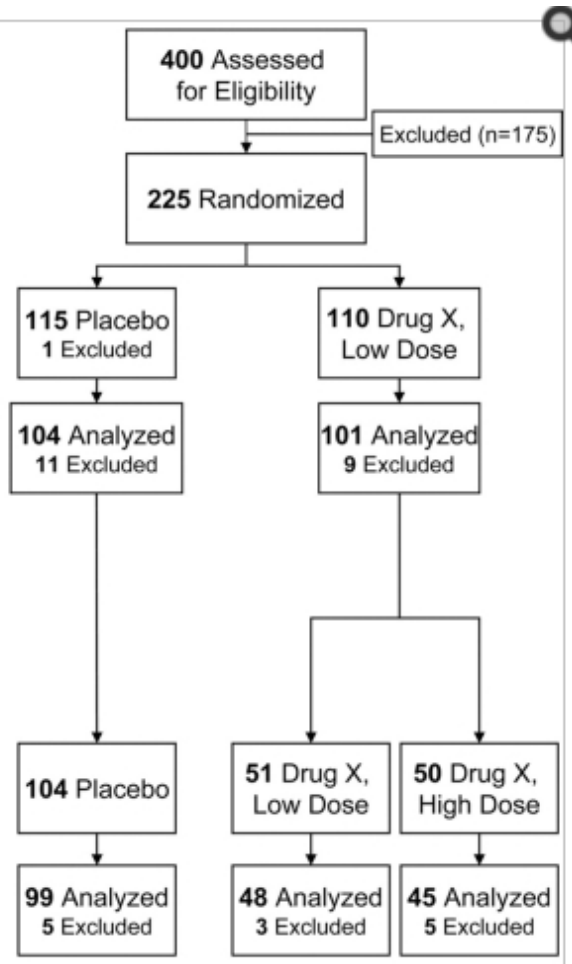
Participant Flow: Treatment Initial Randomization (Period 1)

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)

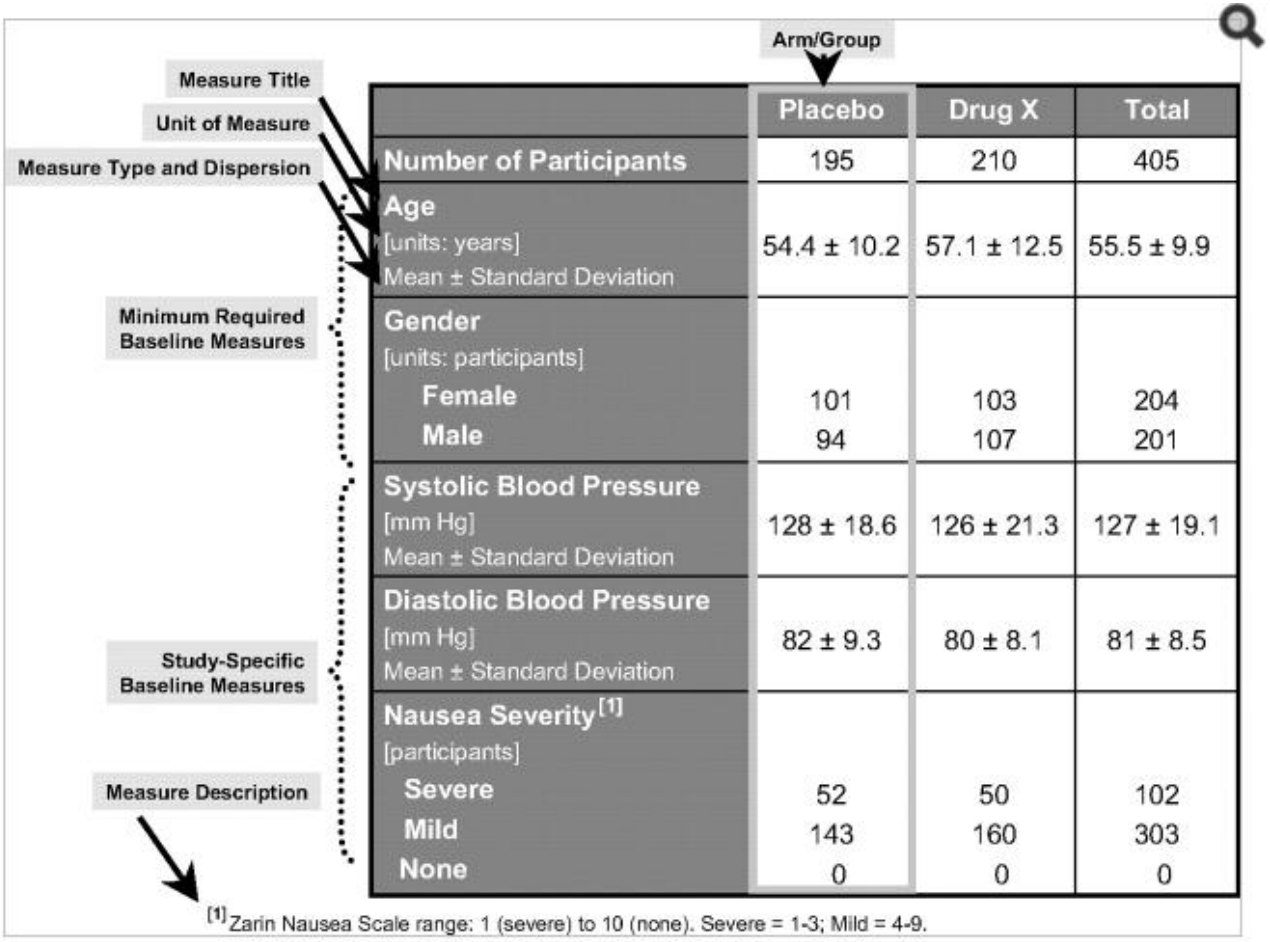
	Placebo	Drug X, Low Dose	Drug X, High Dose
STARTED	104	51	50
COMPLETED	99	48	45
NOT COMPLETED	5	3	5
Lost to Follow-up	2	2	5
Neutropenia	3	1	0

"Customized" Reason for Non-completion



Zarin et al., Chest, 2009

Recommandations pour rapporter les caractéristiques à baseline



	Placebo	Drug X	Total
Number of Participants	195	210	405
Age [units: years] Mean ± Standard Deviation	54.4 ± 10.2	57.1 ± 12.5	55.5 ± 9.9
Gender [units: participants]			
Female	101	103	204
Male	94	107	201
Systolic Blood Pressure [mm Hg] Mean ± Standard Deviation	128 ± 18.6	126 ± 21.3	127 ± 19.1
Diastolic Blood Pressure [mm Hg] Mean ± Standard Deviation	82 ± 9.3	80 ± 8.1	81 ± 8.5
Nausea Severity[1] [participants]			
Severe	52	50	102
Mild	143	160	303
None	0	0	0

[1] Zarin Nausea Scale range: 1 (severe) to 10 (none). Severe = 1-3; Mild = 4-9.

Recommandations pour rapporter les résultats du CJP

Primary Outcome Measure: Systolic Blood Pressure

Measure Type	Primary
Measure Name	Systolic Blood Pressure
Measure Description	Average of two measures in seated position
Time Frame	6 months
Safety Issue	No

Reporting Groups

	Description
Drug X	Drug X, 20 mg, administered twice daily
Drug Y	Drug Y, 10 mg, administered twice daily

Arm/Group Description

Measured Values

Arm/Group

	Drug X	Drug Y
Number of Participants	233	215
Systolic Blood Pressure [units: mm Hg] Mean ± Standard Deviation	147 ± 16.3	124 ± 17.5

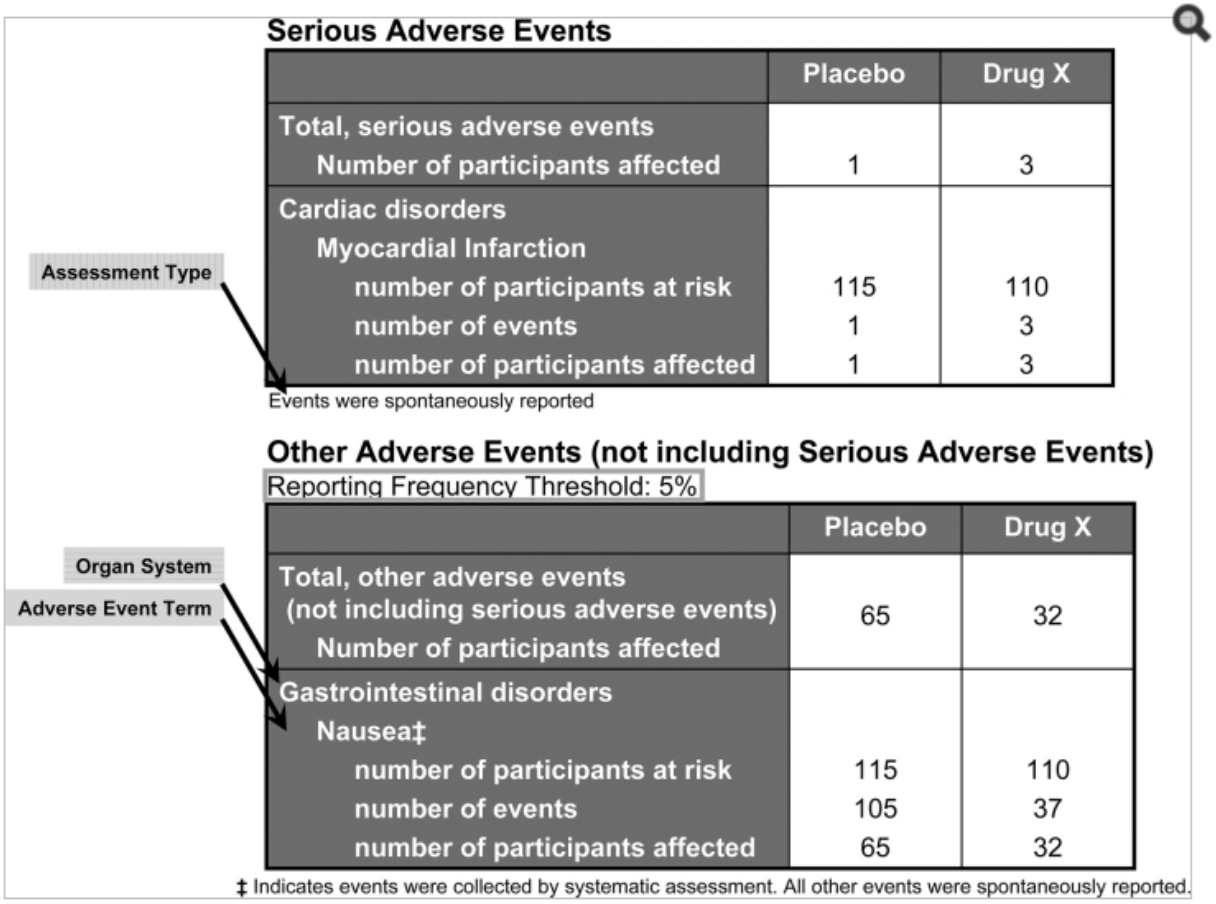
Measure Title

Unit of Measure

Measure Type and Dispersion

Zarin et al., Chest, 2009

Recommandation pour rapporter les évènements indésirables



Serious Adverse Events

	Placebo	Drug X
Total, serious adverse events		
Number of participants affected	1	3
Cardiac disorders		
Myocardial Infarction		
number of participants at risk	115	110
number of events	1	3
number of participants affected	1	3

Assessment Type

Events were spontaneously reported

Other Adverse Events (not including Serious Adverse Events)

Reporting Frequency Threshold: 5%

	Placebo	Drug X
Total, other adverse events (not including serious adverse events) Number of participants affected	65	32
Gastrointestinal disorders		
Nausea‡		
number of participants at risk	115	110
number of events	105	37
number of participants affected	65	32

Organ System

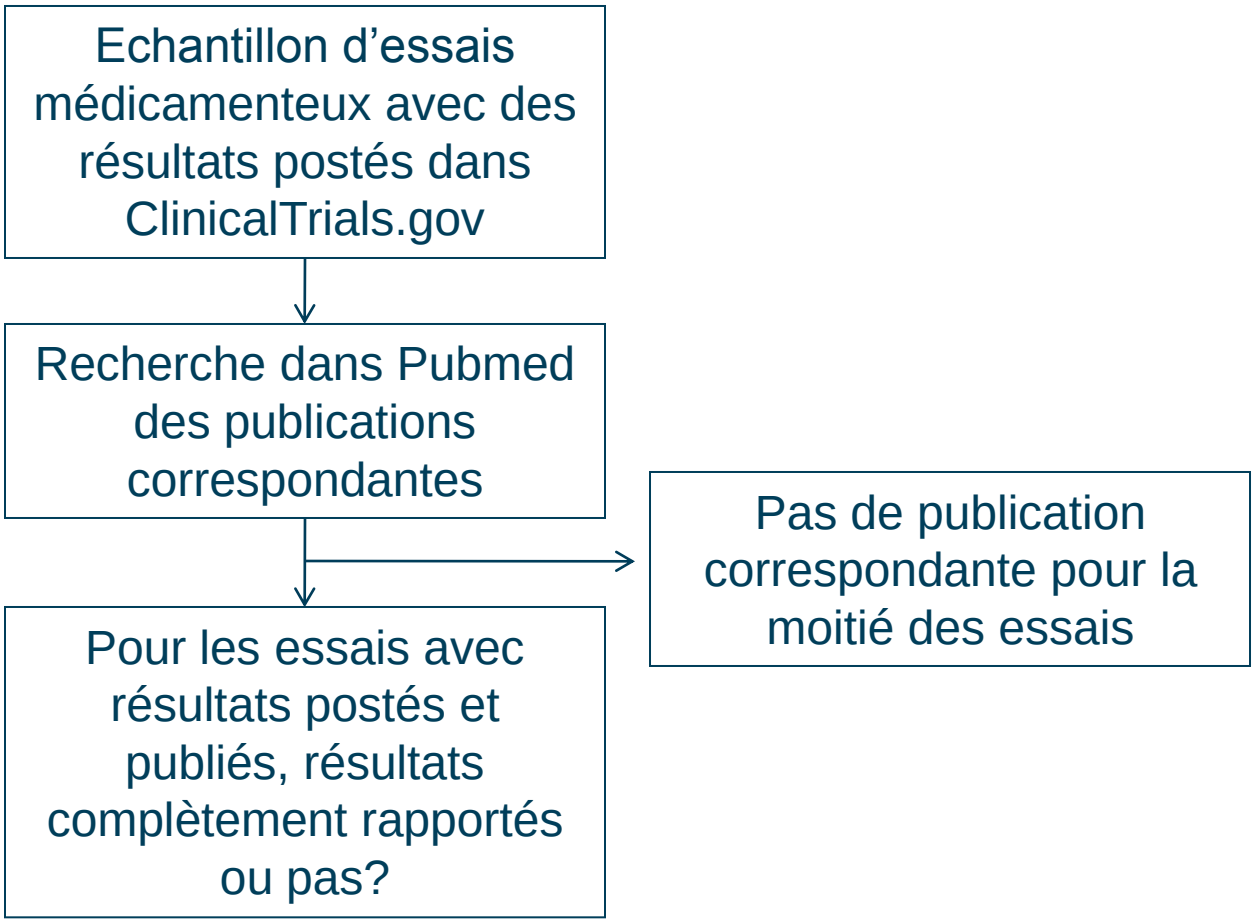
Adverse Event Term

‡ Indicates events were collected by systematic assessment. All other events were spontaneously reported.

Travail

- Hypothèse: les résultats sont mieux rapportés dans ClinicalTrials.gov que dans les publications
- Objectif: comparer la manière dont sont rapportés les résultats dans ClinicalTrials.gov et dans les publications

Méthodes


Echantillon d'essais médicamenteux avec des résultats postés dans ClinicalTrials.gov
Recherche dans Pubmed des publications correspondantes
Pas de publication correspondante pour la moitié des essais
Pour les essais avec résultats postés et publiés, résultats complètement rapportés ou pas?

Est-ce que les résultats étaient complètement rapportés ou pas?

- Point de vue méta-analytique
- Extraction des résultats indépendamment dans ClinicalTrials.gov et dans la publication
- Par 2 personnes en aveugle des définitions

Flow of participants

Number of patients randomized per arm and
Number of patients lost to follow-up per arm and
Number of patients analyzed per arm

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 (difference in means or standardized mean difference) 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

Des résultats plus complets dans ClinicalTrials.gov que dans la publication

Domain	Definition of Completeness	Number (Percent) of Trials with Complete Reporting at ClinicalTrials.gov (n = 202)	Number (Percent) of Trials with Complete Reporting in Published Article (n = 202)	p-Value
Flow of participants	Reporting of: - Number of patients randomized per arm and - Number of patients lost to follow-up per arm and - Number of patients analyzed per arm	129 (64)	96 (48)	<0.001
Efficacy results	Reporting of: - For binary data: number of events and analyzed patients per arm - For continuous data: mean or median per arm and SD or SE or 95% CI or Q1–Q3 per arm, or effect size (difference in means or standardized mean difference) with 95% CI - For time-to-event data: hazard ratio and 95% CI	159 (79)	140 (69)	0.02
Adverse events	Reporting of: - Number of adverse events per arm, without restriction to statistically significant differences between arms, for all randomized patients or for those who received at least one treatment dose	147 (73)	91 (45)	<0.001
Serious adverse events	Reporting of: - Number of serious adverse events per arm	199 (99)	127 (63)	<0.001

Discussion

- Intérêt du « template »
  - Indique aux chercheurs ce qu'ils doivent rapporter
  - Permet un « reporting » standardisé
- Vérification par l'équipe de ClinicalTrials.gov
- Les journaux pourraient s'en inspirer…
  - *JAMA*: tableau dans abstract

Recommandations

- Consulter systématiquement ClinicalTrials.gov dans le cadre d'une méta-analyse
  - Identification des essais non publiés
  - Extraction des résultats si les résultats sont postés
  - Comparaison des résultats postés et publiés
    - En cas de désaccord: contacter les auteurs

Limites de cette approche

- Faible compliance à la FDAAA
  - Malgré des pénalités financières
  - Difficile de savoir quels essais sont vraiment concernés par la loi[1]

[1] Prayle, *BMJ*, 2009

Faible compliance à la FDAAA

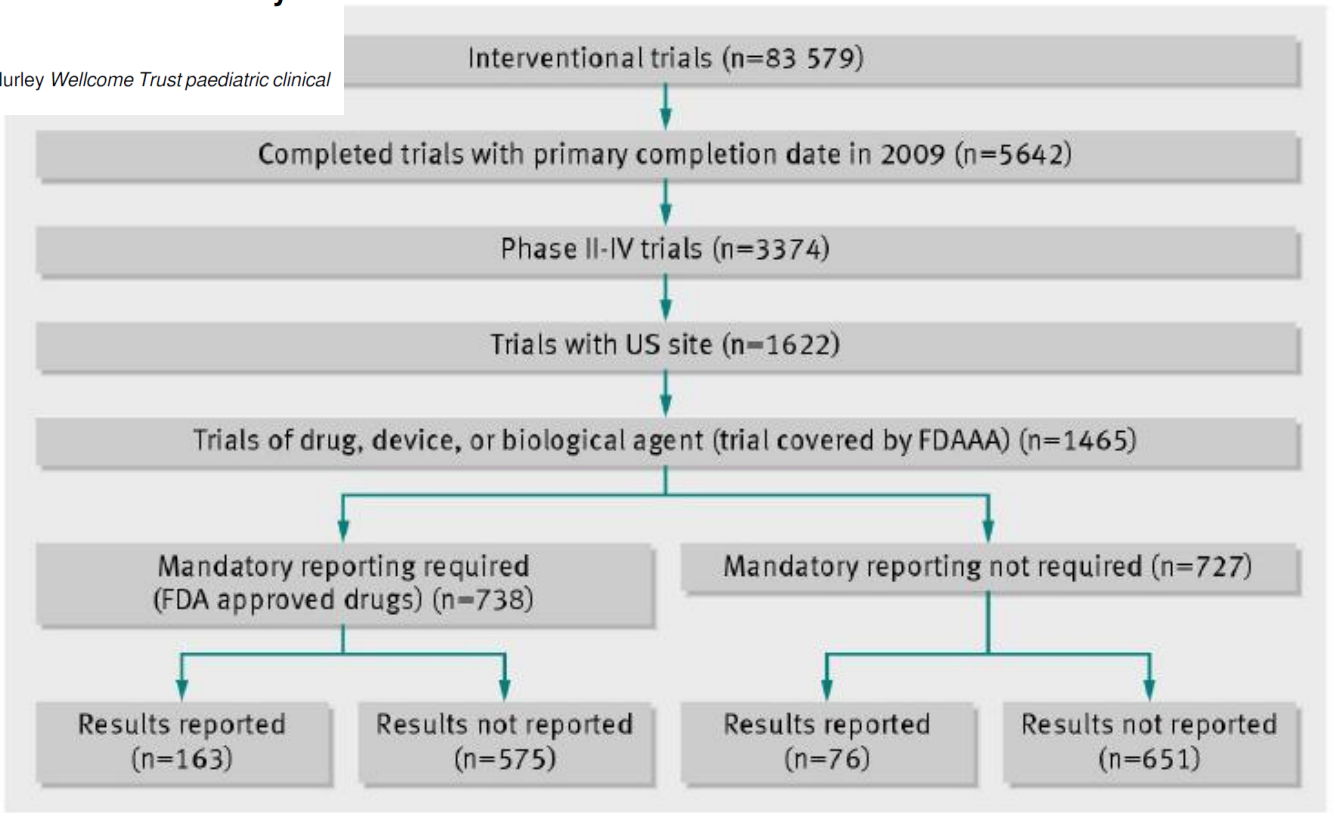
BMJ 2011;344:d7373 doi: 10.1136/bmj.d7373 (Published 3 January 2012)

BMJ

RESEARCH

Compliance with mandatory reporting of clinical trial results on ClinicalTrials.gov: cross sectional study

Andrew P Prayle *NIHR doctoral research fellow*, Matthew N Hurley *Wellcome Trust paediatric clinical research fellow*, Alan R Smyth *professor of child health*



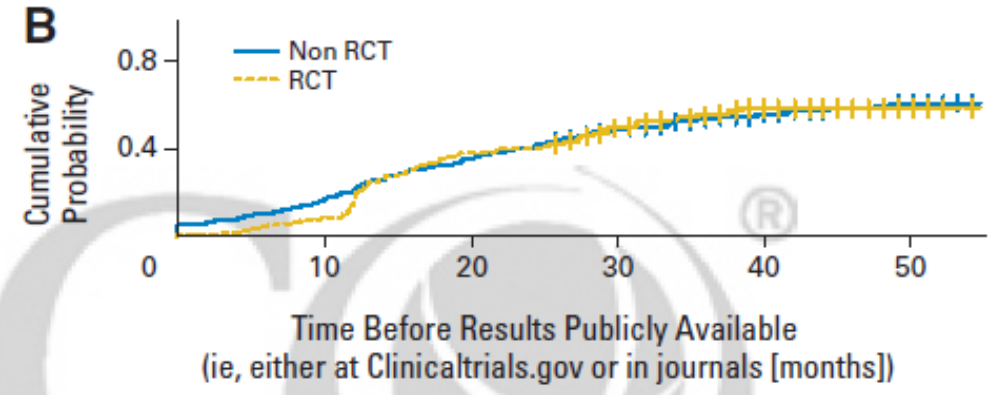
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

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

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

See accompanying editorial doi: 10.1200/JCO.2013.49.7339



646 essais terminés entre 2007 et 2010 (théoriquement sous la FDAAA)

56 % des résultats des essais publiés ou postés 3 ans après la fin de l'essai

Limites de cette approche

- Faible compliance à la FDAAA
  - Malgré les pénalités
  - Difficile de savoir quels essais sont vraiment concernés par la loi

- Cette loi concerne les essais réalisés aux Etats-Unis

All Trials Registered | All Results Reported

It's time all clinical trial results are reported.

Patients, researchers, pharmacists, doctors and regulators everywhere will benefit from publication of clinical trial results. Wherever you are in the world please sign the petition:

Thousands of clinical trials have not reported their results; some have not even been registered.

Information on what was done and what was found in these trials could be lost forever to doctors and researchers, leading to bad treatment decisions, missed opportunities for good medicine, and trials being repeated.

All trials past and present should be registered, and the full methods and the results reported.

We call on governments, regulators and research bodies to implement measures to achieve this.

The petition has also been translated into many different languages. If you would like to sign the petition on behalf of an organisation then please contact us. Data will be held by Sense About Science. Read our privacy policy here.

Sign the petition

First Name **

Last Name **

Email **

Country

Occupation

I signed this because... (add your comment for the wall here)

Sign Now

64129 signatures

Share this with your friends:

facebook twitter

LATEST NEWS:

NEWS

All trials registered and results reported

Résultats disponibles pour les essais européens à partir de 2016!

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 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.

Référence

OPEN ACCESS Freely available online

PLOS | MEDICINE

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]

1 INSERM U738, Paris, France, **2** Université Paris Descartes—Sorbonne Paris Cité, Paris, France, **3** Centre d'Épidémiologie Clinique, Hôpital Hôtel-Dieu, Assistance Publique-Hôpitaux de Paris, Paris, France, **4** French Cochrane Centre, Paris, France, **5** Mailman School of Public Health, Columbia University, New York, New York, United States of America

Citation: Riveros C, Dechartres A, Perrodeau E, Haneef R, Boutron I, et al. (2013) Timing and Completeness of Trial Results Posted at ClinicalTrials.gov and Published in Journals. PLoS Med 10(12): e1001566. doi:10.1371/journal.pmed.1001566