Η διαφάνεια στις κλινικές μελέτες και η επίδραση της στο μέλλον της έρευνας και υγείας

Δημοσιοποίηση των δεδομένων των κλινικών μελετών
Ένα βήμα προς την αριστεία

Βαρβάρα Μπαρούτσου

Αθήνα 19-3-2016

Δήλωση σύγκρουσης συμφερόντων

Conflict of interest

- Παθολόγος
- Chief Scientific Officer Novartis
- Συντονίστρια Επιτροπής Ιατρικών Διευθυντών
- Αντιπρόεδρος ΕΛΕΦΙ
- Οι απόψεις είναι προσωπικές και δεν εκφράζουν υποχρεωτικά τους αναφερομένους φορείς
- Να μην αναπαράγεται χωρίς την συμφωνία του ομιλητή και των φορέων

Η διαφάνεια στις κλινικές μελέτες

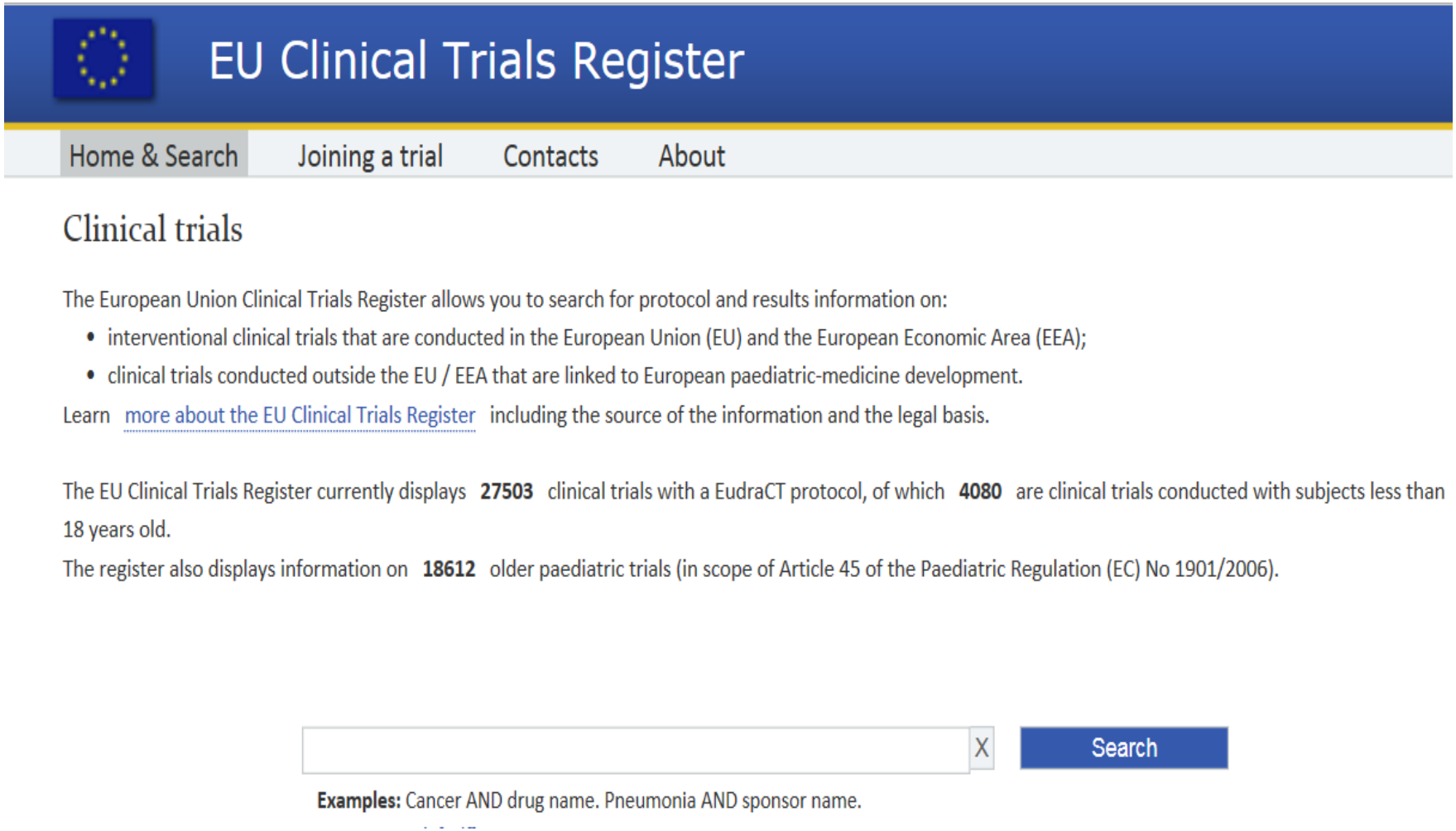
Ένα βήμα προς την αριστεία

Διαφάνεια : οι συνθήκες και οι διαδικασίες που επιτρέπουν να γίνεται φανερός ο τρόπος διαχείρισης

Αριστεία : η δυναμική διαδικασία που αποσκοπεί στην συστηματική επιδίωξη υψηλής επιστημονικής ποιότητας κατά την ανάπτυξη νέων θεωριών ή και ερευνητικών μεθοδολογιών με στόχο την επίτευξη του βέλτιστου αποτελέσματος

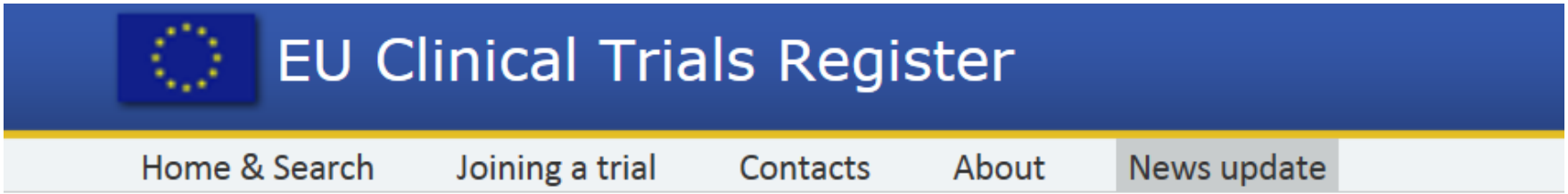
Διαφάνεια στις κλινικές μελέτες στην Ευρώπη

EU Clinical Trials Register



Περιλήψεις αποτελεσμάτων κλινικών μελετών

Ανάρτηση



News update

The system has been made available on 13 January 2016. The summary results will be gradually made available for public access from that date, once the information has been reviewed and verified. Full access for sponsors has also been restored from that date.

In the context of clinical trial sponsors' or PIP addressees' inability to meet regulatory reporting timeframes while the system was offline: The new deadline for submission for all summary results affected by the period that the system was offline will be 13 July 2016, allowing a period of six months from the date of re-opening of the system. Affected results are those whose submission deadline fell due during the period that the system was offline, as well as those whose submission deadline falls within a period of two months from the re-opening date.

In addition, for trials categorised as to be posted ≤ 24 months after finalisation of the programming (see document "Trial results: modalities and timing of posting"), the deadline for submission of summary results will be 21 December 2016, being five months from the current deadline in July 2016.

Πρόσβαση στις κλινικές μελέτες στις ΗΠΑ

Ιστότοποι και εφαρμογές

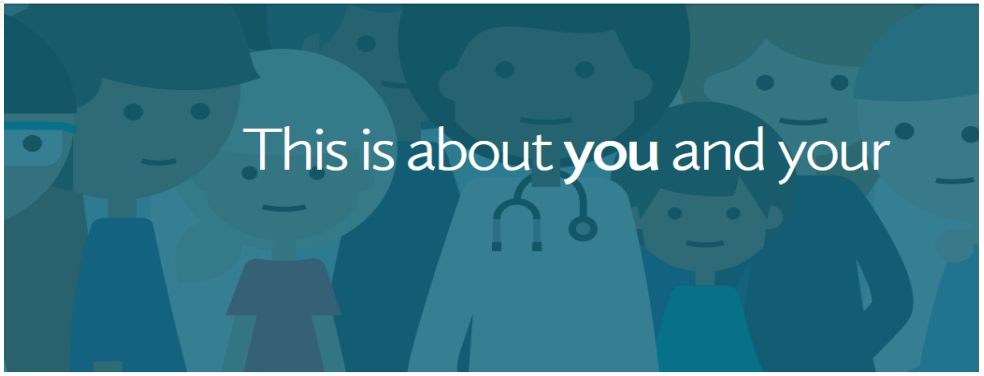
TrialReach

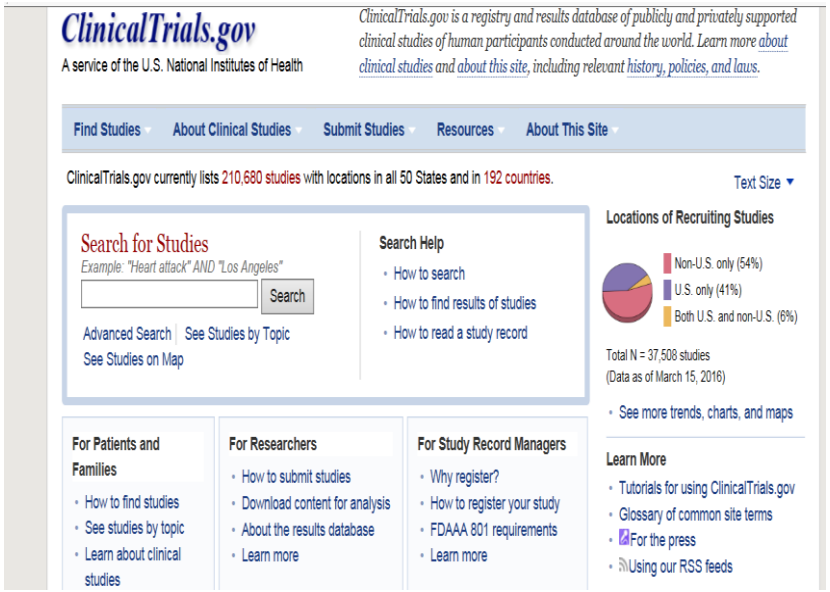
Online search tool aims to help patients find clinical trials

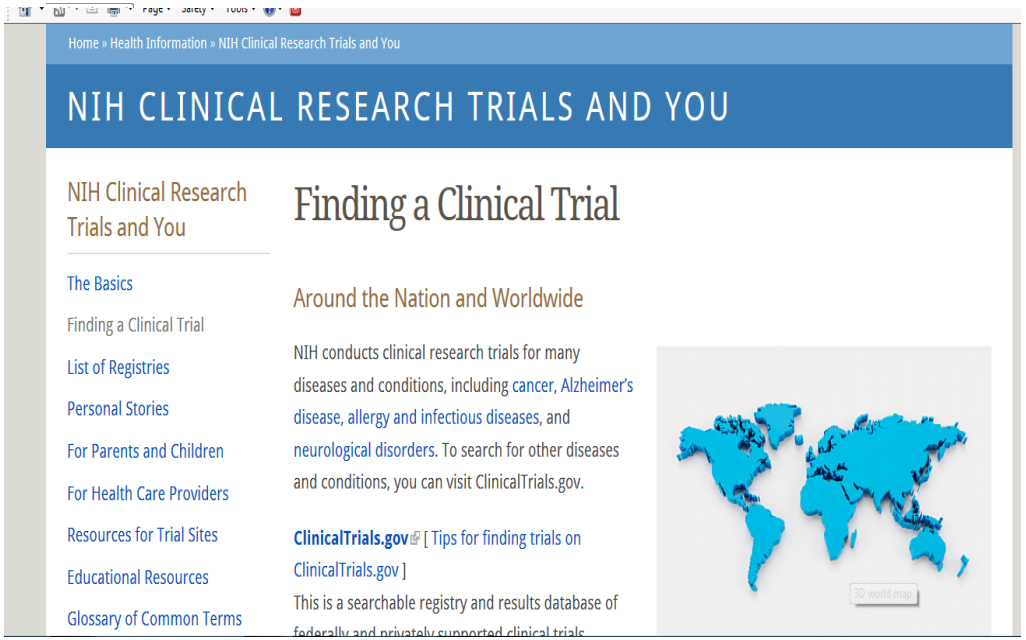
(Ref: Bloomberg)

March 11th, 2016

By: Joe Barber







BMJ

BMJ 2013;346:f105 doi: 10.1136/bmj.f105 (Published 9 January 2013)

EDITORIALS

All trials must be registered and the results published

Academics and non-commercial funders are just as guilty as industry

Iain Chalmers *coordinator*[1], Paul Glasziou *professor*[2], Fiona Godlee *editor in chief*[3]

[1]James Lind Initiative, Oxford OX2 7LG, UK ; [2]Centre for Research in Evidence-Based Practice, Faculty of Health Sciences, Bond University, Gold Coast, QLD, Australia; [3]BMJ, London, UK

Biased under-reporting of research has been documented for well over two decades and the evidence for it is now overwhelming.[1-4] Under-reporting is research misconduct and has serious consequences.[5,6] It leads to overestimates of the

This matters because participants in clinical trials assume that they are contributing to the advancement of medical knowledge; non-publication of study results negates this reasonable assumption and betrays those who have volunteered

Reanalysing the data

The potential of open data is realised only when those data are subject to independent scrutiny, and in a recent review, Ebrahim and colleagues identified just 37 published reanalyses of clinical trials. Only five were conducted by investigators not associated with the original report. David Healy and colleagues, in an editorial, describe the potential of this approach, and *The BMJ* supports this through the RIAT initiative. Proposed in April 2013, by Peter Doshi and colleagues, the RIAT (Restoring invisible and abandoned trials) initiative calls on authors of abandoned trials, or those trials with hidden data, to publish or re-publish their research in an open manner.

In 2014 *BMJ Open* published the first RIAT paper, Tom Treasure and colleagues investigated an abandoned randomised controlled trial that remained unpublished for 20 years, and their reanalysis casts doubt on the survival benefit of further surgery after curative resection of colorectal cancer.

Restoring Confidence in the Pharmaceutical Industry

Howard Bauchner, MD
Phil B. Fontanarosa, MD, MBA

LACK OF TRUST IN THE PHARMACEUTICAL INDUSTRY threatens the future of biomedical research. Although more than half of funded clinical trials in the United States are supported by industry[1] and many scientists, clinicians, and others in industry are committed to advancing biomedical science and improving the health of patients, there is a need to restore confidence in pharmaceutical companies and the research they sponsor. As editors of a journal that publishes articles supported by industry, we are familiar with many of the complicated issues related to industry-supported and industry-analyzed studies. We have had discussions with leaders of the pharmaceutical industry about concerns they have regarding the

applications (NDAs) with information published in journal articles found that many clinical trials included in the NDAs were not published 5 years after drug approval had been granted.[4] The study also found important discrepancies between the primary outcomes, statistical analyses, and conclusions reported in NDAs compared with that information reported in journal articles. The information found in published trials was often more favorable than the data reported in the NDAs.[4] Moreover, some companies have incurred substantial fines for unethical and illegal marketing practices of approved products. In addition, a recent study suggested that clinicians devalue the credibility of industry-funded trials, as compared with the same trials characterized as having National Institutes of Health funding or having no source of support listed, and were less likely to prescribe a drug evaluated in a clinical trial that was supported by industry, even if the study was of high quality.[5]

Κλινικά δεδομένα

Φορείς που δήλωσαν στήριξη στην διαφάνεια

Click to show one page at a time

Information for clinical researchers on transparency of clinical research reporting

abpi Bringing medicines to life

ACADEMY OF MEDICAL ROYAL COLLEGES

BMA

BMJ

BPS BRITISH PHARMACOLOGICAL SOCIETY Today's science, tomorrow's medicines

Institute of Healthcare Management

THE LANCET

PMCPA Prescription Medicines Code of Practice Authority

RCGP Royal College of General Practitioners

Royal College of Nursing

Royal College of Physicians

RCPE Royal College of Physicians of Edinburgh

RC PSYCH ROYAL COLLEGE OF PSYCHIATRISTS

ROYAL PHARMACEUTICAL SOCIETY

This document has been produced by leading UK healthcare organisations including the medical Royal Colleges and senior

Χρήσιμες πηγές

i. The EudraCT clinical trials database can be accessed at https://eudract.ema.europa.eu and the EU Clinical Trials Register at https://www.clinicaltrialsregister.eu/

ii. The WHO ICTRP portal for evaluated clinical trial registries can be accessed at http://www.who.int/ictrp

iii. UK Medicines and Healthcare products Regulatory Agency can be accessed at http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/index.htm

iv. The ABPI *Best Practice Model for the Disclosure of Results and Transparent Information on Clinical Trials* can be obtained from: http://www.abpi.org.uk/our-work/library/guidelines

v. The General Medical Council Guidance on gc clinical practice can be accessed at http://www.gmc-uk.org/guidance/good_med_practice.asp

vi. Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Stateme updated guidelines for reporting parallel grou randomised trials. BMJ 2010;340:c332.

vii. ICMJE Uniform Requirements for Manuscript can be obtained from: http://www.icmje.org/urm_main.html

viii. The Faculty of Pharmaceutical Medicine Guic Principles for Pharmaceutical Physicians includes a section on Clinical Trial Transparer and it can be found here: www.fpm.org.uk

The need for trial transparency

52. Clinical trials generate large amounts of information, much of which is used by regulators when evaluating a drug for licensing. The term clinical trial transparency generally refers to the extent to which this data is made more widely available, to other scientists, clinicians and members of the public.[178] Witnesses to our inquiry broadly supported the notion of greater trial transparency and pointed out that this would be likely to bring about a number of benefits, including:

- **Improved patient outcomes:** several witnesses drew a connection between greater transparency and improved clinical decision-making—the AllTrials campaign[179] claimed that failures to register and publish trials led directly to "bad treatment decisions" and "missed opportunities for good medicine".[180] Dr Ben Goldacre, co-founder of the AllTrials campaign and a practising clinician and author, explained that "healthcare professionals and patients need the results of clinical trials to make informed choices about which treatment is best" and added that it was "not satisfactory to say that the results of trials should be reported only to regulators".[181] The Academy of Medical Sciences (AMS) agreed that if only a subset of clinical trials "with extreme, or favourable, results" reached the public domain, "a biased conclusion" could be drawn about a treatment's effectiveness, potentially leading to the wrong medical decisions being made.[182]
- **Enhanced scientific knowledge**: according to the AMS, "greater access to appropriately controlled data for valid scientific inquiry offers significant scientific benefits and helps ensure scientific validity" by opening research up to greater scrutiny.[183] Tracey Brown, Managing Director of Sense about Science, agreed that this ability to "self-correct" is essential to science, explaining that:

  We do not have the modern scientific approach that we have today because everybody has secretly gone off and done things in the cupboard; we have it because people have tested each other's ideas, pulled them apart and asked if something could have been done better. That is a very important part of scientific medical advance.[184]

The four levels of clinical trial transparency

59. The costs and benefits of making clinical trials more transparent are closely linked to the types of information being discussed, which can range from high-level facts about the aims and planned methods of a trial, to the thousands of lines of raw data generated over its course. The AMS explained that "clarity about which aspect of transparency" was being discussed was important, "as each presents different issues" which could significantly affect the arguments for and against making a particular level of trial data more transparent.[210] We agree and have therefore differentiated between four levels of trial transparency in drawing our conclusions. These are:

- trial registration (level 1): a record that the trial has been conducted, from a clinical trial register detailing basic trial information;
- summary-level trial results (level 2): a brief summary of the trial's results, together with key conclusions, most commonly in an academic journal or trial register;
- clinical study report (level 3): a detailed report, usually prepared for regulatory purposes, of the method, conduct and outcome of a trial, often running to several hundred pages in length; and
- individual patient-level data (level 4): the raw patient data generated over the course of a trial, from which aggregate results and other conclusions are drawn.

Clinical Trials - Science and Technology Committee Contents

- **Increased public trust in research**: it was a common view that greater transparency of trial data would engender greater public trust in medical research. Dr Margaret McCartney, a General Practitioner and medical writer, told us that lack of transparency in the past meant that she could currently "have no faith that patients taking part in clinical trials are not doing themselves harm".[186] INVOLVE, the national advisory group for public involvement in research, agreed that there needed to be "far greater openness and transparency in the publishing and accessibility of research findings" if the public were to "trust and have confidence" in clinical trials.[187]
- **Fulfilment of basic ethical standards**: several witnesses felt that it was unethical not to make the results of clinical trials public. A group from the Cochrane Collaboration, an independent research organisation, stated that for "experiments conducted on human beings" the full reporting of results "should be a right, not a gift".[188] Dr Goldacre agreed, telling us that by failing to make trial data transparent researchers were "breaching the ethical pacts" forged with patients when they agreed to take part in a clinical trial.[189] A letter from 53 trial participants to the European Medicines Agency (EMA), provided to us by Sense about Science, stated that failure to publish the results of clinical trials was "a betrayal of our trust in clinical trial regulation, and the trust of the families of those patients who volunteer for trials having had a terminal diagnosis".[190]

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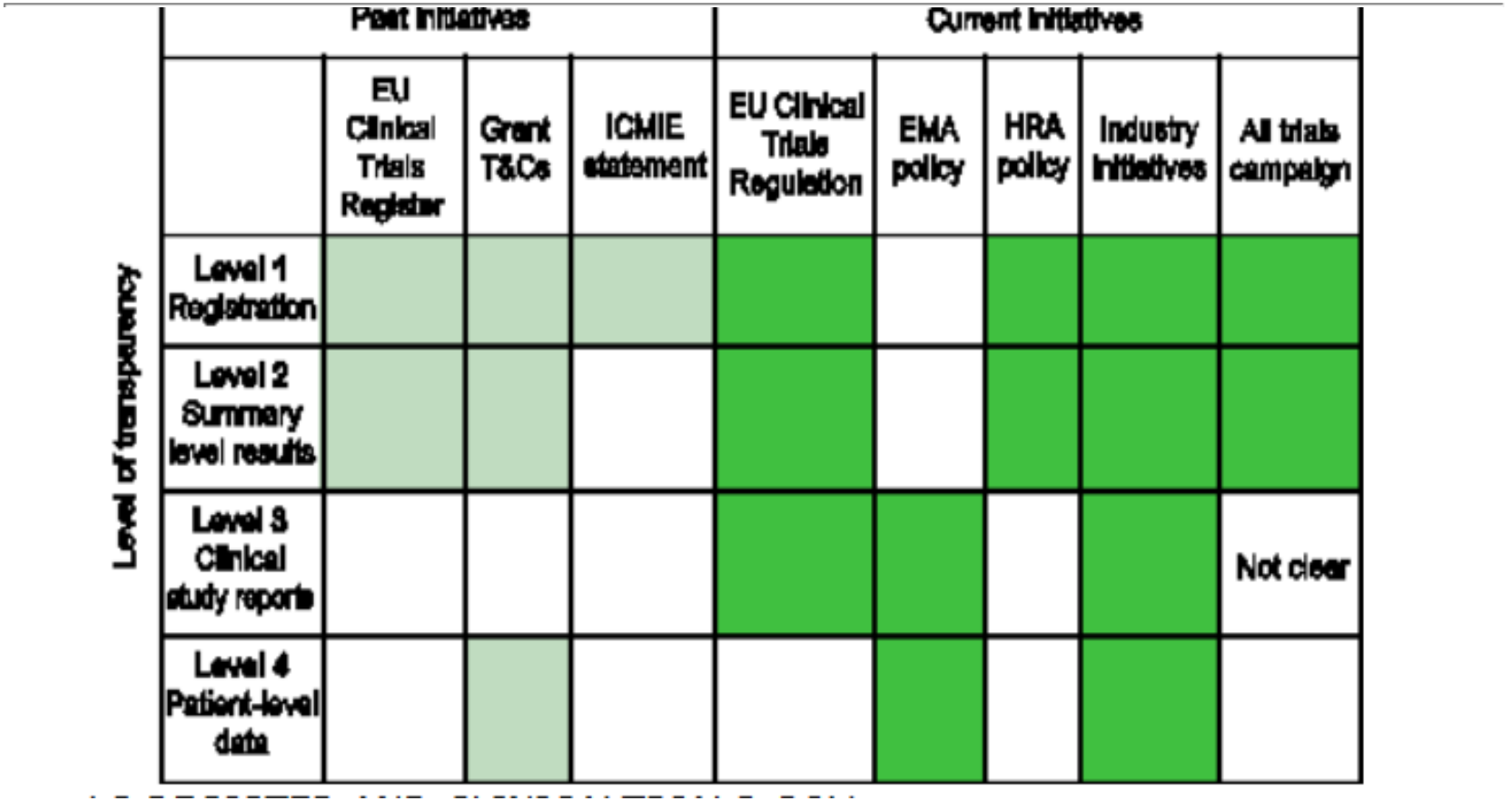
Clinical Trials - Science and Technology Committee Contents



INDUSTRY-LED INITIATIVES

In recent years, select members of the pharmaceutical industry, led by GSK, have taken steps to increase the transparency of the clinical trials that they sponsor.

In 2004, GSK became the first company to launch its own dedicated trials register and was quickly followed by other companies including Roche, AstraZeneca and Novartis.

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Select Committees > Science and Technology > Science and Technology

Clinical Trials - Science and Technology Committee Contents

53. While support for the notion of greater trial transparency was strong, witnesses acknowledged that there were challenges, including the need to:

- protect the privacy of patients participating in clinical trials and ensure that data disclosure did not go beyond the confines of patient consent;
- protect any intellectual property contained within clinical trial data and respect commercial sensitivities, and
- mitigate the risk that clinical trial data would be re-analysed in an inexpert or irresponsible way, potentially leading to regulatory decisions being undermined and misleading conclusions reaching the public domain.

UK

NHS

REC

HRC

EFPIA-PhRMA joint position
Principles for Responsible Clinical Trials Data Sharing (July 2013)

Biopharmaceutical companies are committed to enhancing public health through responsible sharing of clinical trial data in a manner that is consistent with the following Principles:

- **Safeguarding the privacy of patients**
- **Respecting the integrity of national regulatory systems**
- **Maintaining incentives for investment in biomedical research**

EFPIA/PhRMA commitments

- Enhancing Data Sharing with Researchers
- Enhancing Public Access to Clinical Study Information
- Sharing Results with Patients Who Participate in Clinical Trials
- Certifying Procedures for Sharing Clinical Trial Information
- Reaffirming Commitments to Publish Clinical Trial Results: disclosing Results regardless of positive or negative outcomes

efpia

7

Δημοσιοποίηση κλινικών δεδομένων

23 νέα φάρμακα που εγκρίθηκαν το 2012

CMRO

Current Medical Research & Opinion Vol. 31, No. 7, 2015, 1431–1435

0300-7995
doi:10.1185/03007995.2015.1047749

Article ST-0103.R1/1047749

Brief report

Clinical trial transparency update: an assessment of the disclosure of results of company-sponsored trials associated with new medicines approved in Europe in 2012

Phase	Total trials	Unevaluable at 12 months*	Results disclosed within 12 months#	Unevaluable at 31 July 14*		Results disclosed by 31 July 14	
I/II	235	22	187/213	88%	22	191/213	90%
III	143	24	114/119	96%	24	115/119	97%
IV	9	4	4/5	80%	4	4/5	80%
other	5	2	2/3	67%	2	2/3	67%
Total	392	52	307/340	90%	52	312/340	92%

*Unevaluable if a key date was missing or unclear, or 12 months had not elapsed since trial completion.
#Twelve months measured from the later of either the date of first regulatory approval (Europe or US) or trial completion date.

The EU journey

Bio/Pharma Industry under increased scrutiny; calls for greater clinical trial transparency and release of clinical reports

2003
EMA starts publication of EPARs

2012
July - EU PV Regulation

2013
EFPIA/PhRMA Responsible Data Sharing Principles

2014
June – New EU Clinical Trial Regulation

2014
October – New EMA Policy 070 supporting the CTR

2016
May – New EU database

efpia

5

Annals of Internal Medicine

EDITORIAL

Sharing Clinical Trial Data: A Proposal From the International Committee of Medical Journal Editors

The International Committee of Medical Journal Editors (ICMJE) believes that there is an ethical obligation to responsibly share data generated by interventional clinical trials because participants have put themselves at risk. In a growing consensus, many funders around the world–foundations, government agencies, and industry–now mandate data sharing. Here we outline ICMJE's proposed requirements to help meet this obligation. We encourage feedback on the proposed requirements. Anyone can provide feedback at www.icmje.org by 18 April 2016.

The ICMJE defines a clinical trial as any research project that prospectively assigns people or a group of people to an intervention, with or without concurrent comparison or control groups, to study the cause-and-effect relationship between a health-related intervention and a health outcome. Further details may be found in the *Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals* at www.icmje.org.

As a condition of consideration for publication of a clinical trial report in our member journals, the ICMJE proposes to require authors to share with others the deidentified individual-patient data (IPD) underlying

added an element to its registration platform to collect data-sharing plans. We encourage other trial registries to similarly incorporate mechanisms for the registration of data-sharing plans. Trialists who want to publish in ICMJE member journals (or nonmember journals that choose to follow these recommendations) should choose a registry that includes a data-sharing plan element as a specified registry item or allows for its entry as a free-text statement in a miscellaneous registry field. As a condition of consideration for publication in our member journals, authors will be required to include a description of the data-sharing plan in the submitted manuscript. Authors may choose to share the deidentified IPD underlying the results presented in the article under less restrictive, but not more restrictive, conditions than were indicated in the registered data-sharing plan.

ICMJE already requires the prospective registration of all clinical trials prior to enrollment of the first participant. This requirement aims, in part, to prevent selective publication and selective reporting of research outcomes, and to prevent unnecessary duplication of research effort. Including a commitment to a data-sharing plan is a logical addition to trial registra-

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIALS

Data Sharing

Dan L. Longo, M.D., and Jeffrey M. Drazen, M.D.

The aerial view of the concept of data sharing is beautiful. What could be better than having high-quality information carefully reexamined for the possibility that new nuggets of useful data are lying there, previously unseen? The potential for leveraging existing results for even more benefit pays appropriate increased tribute to the patients who put themselves at risk to generate the data. The moral imperative to honor their collective sacrifice is the trump card that

This issue of the *Journal* offers a product of data sharing that is exactly the opposite. The new investigators arrived on the scene with their own ideas and worked symbiotically, rather than parasitically, with the investigators holding the data, moving the field forward in a way that neither group could have done on its own. In this case, Dalerba and colleagues[1] had a hypothesis that colon cancers arising from more primitive colon epithelial precursors might be more

Official Journal of the European Union

L 158

English edition

Legislation

Volume 57

27 May 2014

Contents

(39) The sponsor should submit a summary of the results of the clinical trial together with a summary that is understandable to a layperson, and the clinical study report, where applicable, within the defined timelines. Where it is not possible to submit the summary of the results within the defined timelines for scientific reasons, for example when the clinical trial is still ongoing in third countries and data from that part of the trial are not available, which makes a statistical analysis not relevant, the sponsor should justify this in the protocol and specify when the results are going to be submitted.

ANNEX V

CONTENT OF THE SUMMARY OF THE RESULTS OF THE CLINICAL TRIAL FOR LAYPERSONS

The summary of the results of the clinical trial for laypersons shall contain information on the following elements:

1. Clinical trial identification (including title of the trial, protocol number, EU trial number and other identifiers);
2. Name and contact details of the sponsor;
3. General information about the clinical trial (including where and when the trial was conducted, the main objectives of the trial and an explanation of the reasons for conducting it);
4. Population of subjects (including information on the number of subjects included in the trial in the Member State concerned, in the Union and in third countries; age group breakdown and gender breakdown; inclusion and exclusion criteria);
5. Investigational medicinal products used;
6. Description of adverse reactions and their frequency;
7. Overall results of the clinical trial;
8. Comments on the outcome of the clinical trial;
9. Indication if follow up clinical trials are foreseen;
10. Indication where additional information could be found.

EFPIA Guiding Principle paper

This Reflection Paper aims at providing high level principles to help sponsors drafting the summary of a clinical trial in lay language, in order to comply with the EU Clinical Trial Regulation.

What is the purpose of the laypersons' summary of clinical trial results?

- To address patient, families and the public's interest in transparent dissemination of trial results;
- To inform and educate research participants about the trial in which they participated;
- To honor the voluntary contribution of research participants and recognize patients as partners in research
- To meet the requirements of relevant laws and regulations;
- To fulfill the EFPIA-PhRMA 'Principles for Responsible Clinical Trial Data Sharing'.

In the meanwhile…
On going discussions and Challenges faced

- Agreement within Sponsors and Patients' organisations about the utility
- Patients' organisations advocate for the development of templates
- Most of Sponsors found that the right template is Annex V of the EU CT regulation
- Agreement on limiting to Phase 2-4 studies (Phase 1 being of limited interest and raising patent and legal issues)
- Some studies may have less interest for the patients (e.g. epidemiological, observational registries, disease natural History)
- NHS tasked by EMA to deliver a Guidance on information for participants at the end of a study – draft expected Nov. 2015
- Need to educate Layperson on the meaning of a "single" study result

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SCIENCE MEDICINES HEALTH
Text size: A A A
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The European Medicines Agency (EMA) bases its scientific opinions on the results of clinical trials carried out and submitted by pharmaceutical companies. Under EMA's policy on the publication of clinical data, the Agency proactively publishes the clinical reports submitted under the centralised marketing authorisation procedure for human medicines. The policy entered into force on 1 January 2015 and is currently being implemented.
By proactively publishing clinical data, EMA intends to help:
avoiding duplication of clinical trials, foster innovation and encourage development of new
Related content
Transparency
Clinical trials in human medicines
Clinical Trial Regulation
Related documents
European Medicines Agency policy on publication of clinical

Οδηγία για την δημοσιοποίηση των δεδομένων ΚΜ

1-1-2015 Μάρτιος 2016 – Clinical trials Results for MAA on or after

- Implementation of Policy 070
- Patient level data
- 4 chapters
  - Scope & definitios
  - Procedural aspects
  - Recommendations for the anonymization of patient data
  - Redaction of commercial confidential information CCI
  - First data to be available on EU Clinical trials registry – Sept 2016
  - EMA Webinar 2Q 2016 for Pharma Companies

BY KENDALL POWELL

148 | NATURE | VOL 530 | 11 FEBRUARY 2016

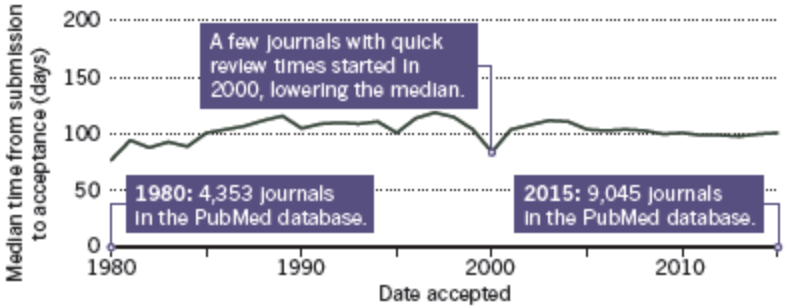
NEWS FEATURE

PAPER WAIT

Some scientists complain that publishing papers takes too long, but data show a complex picture.

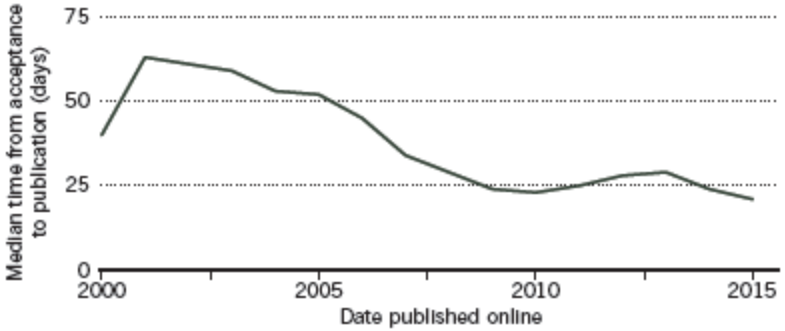
REVIEW TIME

An analysis of all papers in PubMed up to 2015 with listed submission and acceptance dates suggests that the median time from submission to acceptance has hovered at around 100 days, although it has gone up at some journals.



PRODUCTION TIME

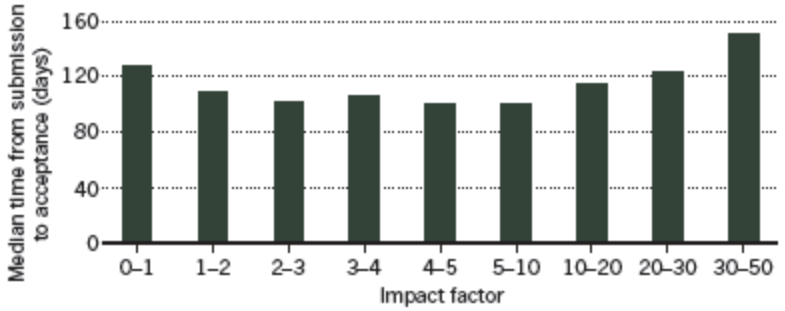
The same analysis of Pubmed papers suggests that the time between acceptance and publication has dropped, probably because technology has improved.



SOURCES: REVIEW TIME: DANIEL HIMMELSTEIN; WAIT TIMES: STEPHEN ROYLE; PRODUCTION TIME: DANIEL HIMMELSTEIN; DATA: REF. 5

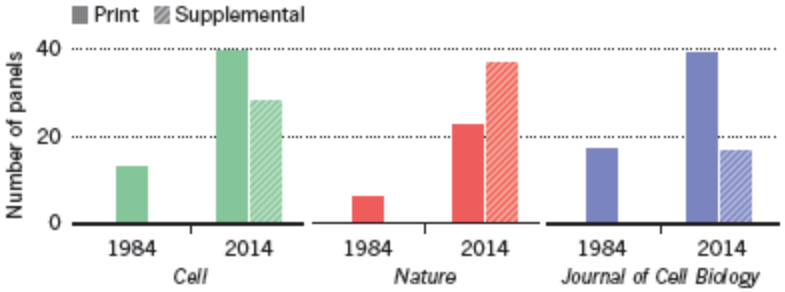
WAIT TIMES BY IMPACT FACTOR

An analysis of PubMed papers published in 2013 suggests that journals with the lowest and highest impact factors have the longest review times.



DATA PER PAPER

An analysis of biology papers published in 3 journals showed that the number of panels in experimental figures jumped between 1984 and 2014, a hint that the amount of data per paper is increasing.



Σας ευχαριστώ πολύ

Συζήτηση

Τ. Βιδάλης, Κ.Κουτσογιάννη, Ε Φούζα, Sini Eskola