Disclosure Writing

Module 11 Topic 7

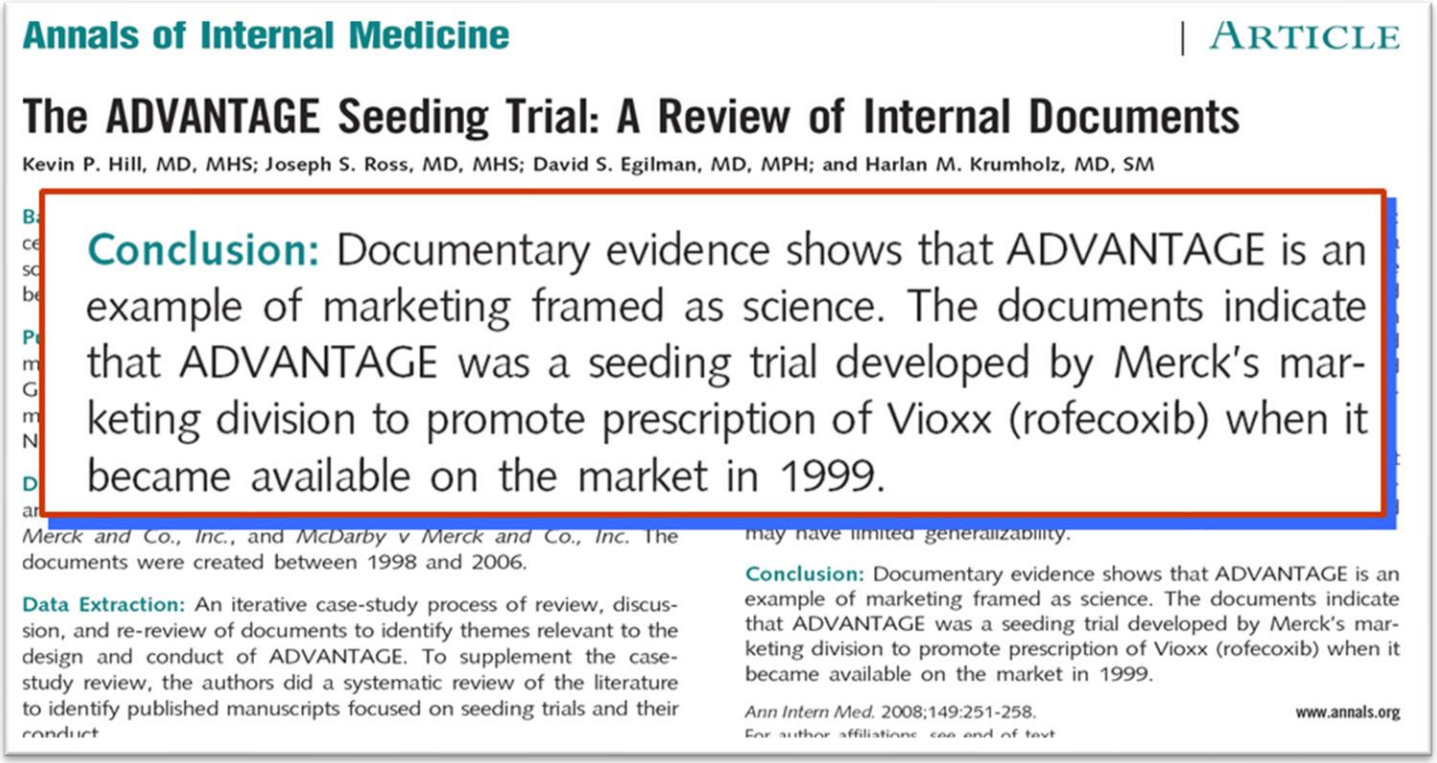
- Why Clinical Trial Disclosure
- Brief history of Clinical Trial Disclosure
- Overview of current global Clinical Trial Disclosure requirements
  - Clincaltrials.gov
  - EudraCT
- Latest and Upcoming Key Regulatory Reforms Worldwide
  - EFPIA/PhRMA “Principles for Responsible Clinical Trial Data Sharing”
  - EMA Policy on Publication of Clinical Data

Why Clinical Trial Disclosure?

The intention of clinical trial disclosure is to:

- Inform patients/investigators of research programs
- Inform healthcare professionals about ongoing trials
- Reduce unnecessary duplication of research & accelerate knowledge creation
- Improve trial participation
- Publish in peer-reviewed journals
- Transparency and build mutual trust
- Fulfill legal, statutory and ethical obligations

Events: Lack of Transparency in Clinical Research



Annals of Internal Medicine | ARTICLE

The ADVANTAGE Seeding Trial: A Review of Internal Documents

Kevin P. Hill, MD, MHS; Joseph S. Ross, MD, MHS; David S. Egilman, MD, MPH; and Harlan M. Krumholz, MD, SM

Conclusion: Documentary evidence shows that ADVANTAGE is an example of marketing framed as science. The documents indicate that ADVANTAGE was a seeding trial developed by Merck's marketing division to promote prescription of Vioxx (rofecoxib) when it became available on the market in 1999.

Merck and Co., Inc., and *McDarby v Merck and Co., Inc.* The documents were created between 1998 and 2006.

Data Extraction: An iterative case-study process of review, discussion, and re-review of documents to identify themes relevant to the design and conduct of ADVANTAGE. To supplement the case-study review, the authors did a systematic review of the literature to identify published manuscripts focused on seeding trials and their conduct.

may have limited generalizability.

Conclusion: Documentary evidence shows that ADVANTAGE is an example of marketing framed as science. The documents indicate that ADVANTAGE was a seeding trial developed by Merck's marketing division to promote prescription of Vioxx (rofecoxib) when it became available on the market in 1999.

Ann Intern Med. 2008;149:251-258. www.annals.org

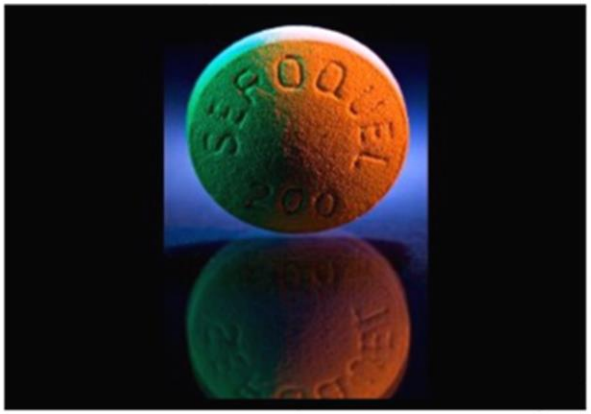
For author affiliations, see end of text.

Events: Lack of Transparency in Clinical Research (contd)

AstraZeneca Seroquel Studies 'Buried,' Papers Show (Update3)

Email | Print | A A A

By Jef Feeley and Margaret Cronin Fisk



Feb. 27 (Bloomberg) -- **AstraZeneca Plc** "buried" unfavorable studies on its antipsychotic drug Seroquel, according to an internal e-mail unsealed as part of litigation over the medicine.

The drugmaker failed to publicize results of at least three clinical trials of Seroquel and engaged in "cherry picking" of data from one of those studies for use in a presentation, an AstraZeneca official said in a December 1999 e-mail unsealed yesterday under an agreement between the company and lawyers for patients. The London-based company faces about 9,000 **lawsuits** claiming it failed to properly warn users that Seroquel can cause diabetes and other health problems.

"The larger issue is how we face the outside world when they begin to criticize us for suppressing data," John Tumas, an AstraZeneca publications manager, told colleagues in the e-mail.

Where to disclose?

- National Registries - Clinical Trials.gov, EU Clinical Trial Registry, Pan African Clinical Trials Registry (PACTR), Clinical Trial Registry (India) to name a few.
- WHO International Clinical Trials Registry Platform
- Company Registries
- Peer reviewed Journals
- SHARE initiative (Clinicalstudydatarequest.com)

International Databases and National Registries

International registries

Country/Region	Regulatory Body	Clinical Trial Disclosure Database
US	National Institute of Health (NIH)	Clinicaltrials.gov,
	Food and Drug Administration (FDA)	http://www.clinicaltrials.gov
European Economic Area (EEA)	European Medical Agency (EMA) European Clinical Trial Database (EudraCT)	EudraCT, https://www.clinicaltrialsregister.eu

International Databases and National Registries

National Registries

Country/ Region	Regulatory Body	Clinical Trial Disclosure Database
India	Drugs Controller General of India (DCGI)	Clinical Trial Register of India http://www.ctri.in/
Germany	Federal Ministry of Education and Research (BMBF) University Medical Centre Freiburg: German Clinical Trials Register (DRKS)	University Medical Centre Freiburg: German Clinical Trials Register (DRKS) http://www.germanctr.de
China	Center for Drug Evaluation (CDE) Chinese Clinical Trial Register (ChiCTR)	Chinese Clinical Trial Register (ChiCTR) http://www.cde.org.cn/news.do?method=changePage&pag eName=serviceLcsy&frameStr=126
Japan	Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Database	Clinical Trials Information /JapicCTI http://www.clinicaltrials.jp/user/cte_main.jsp

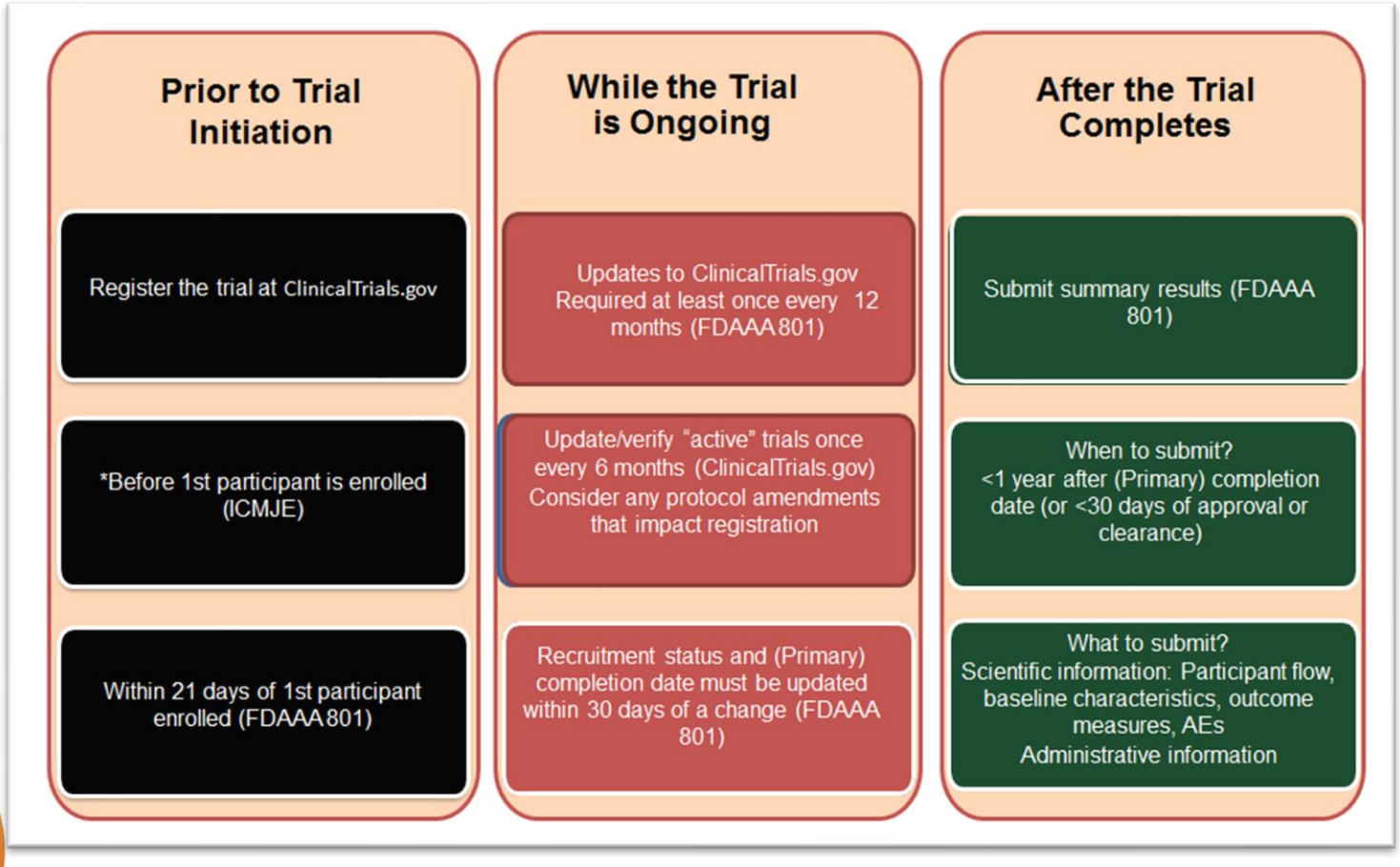
Importance of disclosure on public registry

- For those with medical conditions…
  - Finding a trial in which to participate
  - Finding an expanded access drug
  - Finding a center of research for a given condition/intervention
- For those concerned with human subjects protections…
  - Complete list of ongoing and completed trials of relevance
  - Assurance that information about the trial of interest
    - is in the public domain
    - results will become public

Importance of disclosure on public registry

- For those concerned with research integrity…
  - Relatively complete list of trials
  - Description of protocol
  - Tracking of changes to protocols
  - Identifying all outcome measures
  - Providing results, regardless of journal publication status
- For those seeking study results…
  - Linkages to PubMed
  - Summary Results in database
  - Results for all pre-specified outcome measures
  - Standardized format facilitating comparisons

What Needs to be Disclosed on ClinicalTrials.gov?



*http://www.icmje.org/about-icmje/faqs/clinical-trials-registration/

European Union (EU) Clinical Trial Register

- Provides access to information on interventional clinical trials
- The information available dates from 1st May 2004, when national medicine regulatory authorities began populating EudraCT, the application that is used by national medicines regulatory authorities to enter clinical trial data
- The website, launched on 22nd March 2011, enables users to search for information that has been included in the EudraCT database

European Union (EU) Clinical Trial Register

- The EU Clinical Trials Register currently displays 30159 clinical trials with a EudraCT protocol
- EudraCT- A database that includes information on clinical trials taking place in the European Union and clinical studies conducted worldwide in accordance with a paediatric investigation plan

Ref: http://www.ema.europa.eu/ema/
https://eudract.ema.europa.eu/

EudraCT V10: In Scope and Out of scope Activities

Out of Scope Activities

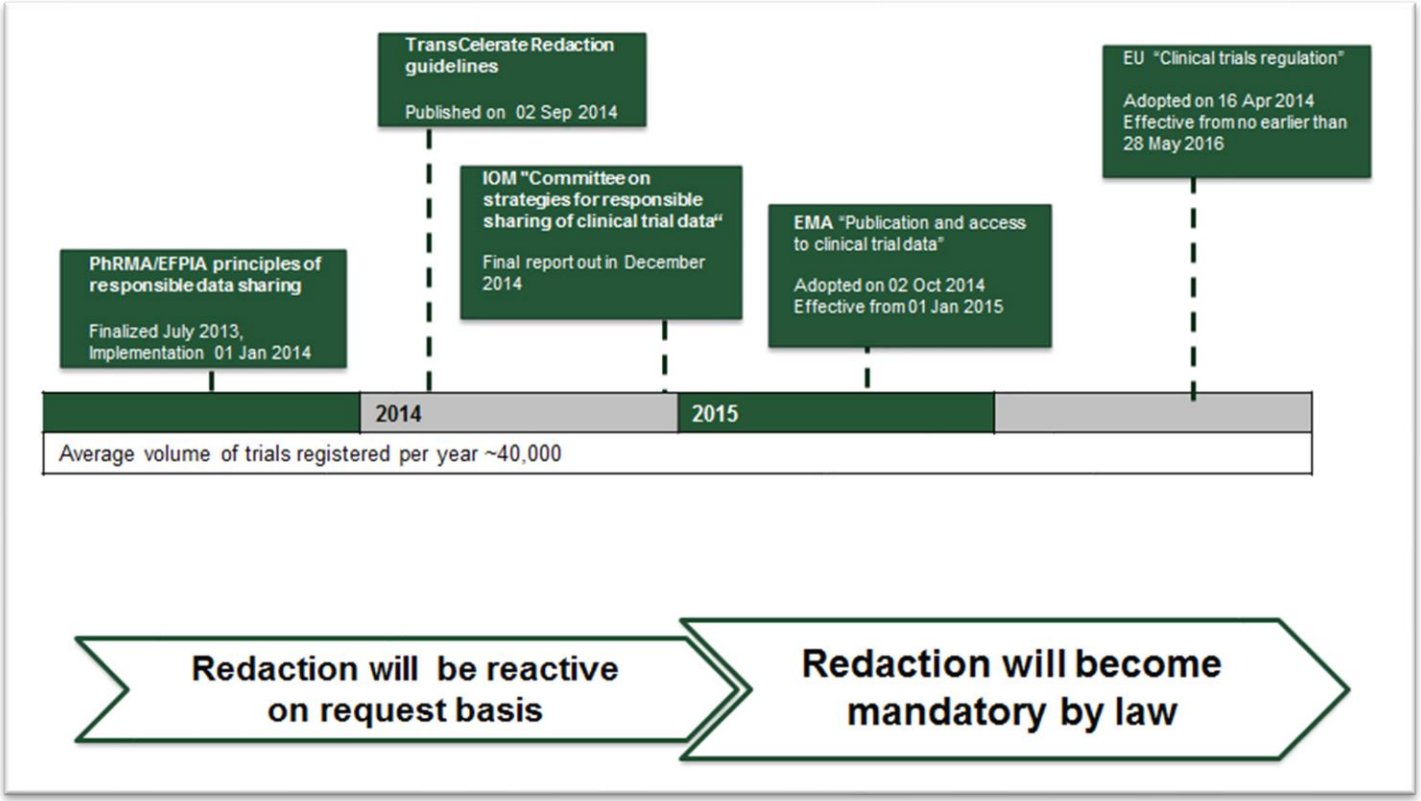
- Non-interventional studies (NIS)
- Investigator sponsored trials (ISTs)
- Trials completed before 01 May 2004
- Non-pediatric trials outside EU/ EEA

EudraCT V10: In Scope and Out of scope Activities

In Scope Activities

- Interventional trials
  - Approved as well as unapproved products
- Phase 1 to 4
- Trials completed on or after 01 May 2004

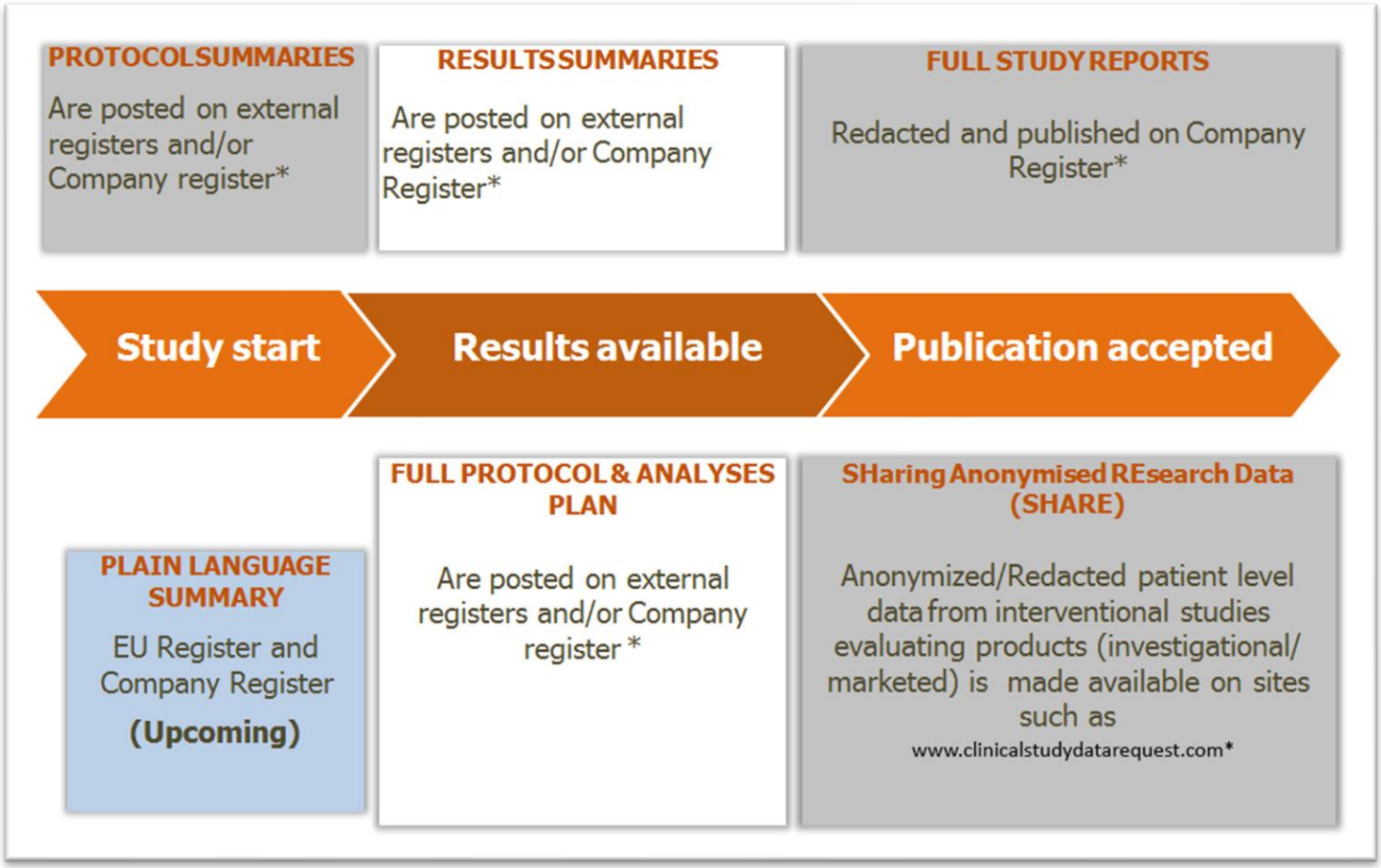
Based on upcoming regulation, Redaction is key to disclosure, between 2013 – 2016



Clinical Trial Data and Transparency

- Introduction of new legislation & regulations and the evolution of clinical trial disclosure and data transparency in the pharmaceutical industry
- Guidelines regarding clinical trial disclosure exists in >40 countries globally
- Augmented regulatory requirements in regions like US, EU and EEA in last 5 years

Scope of Disclosure & Transparency



Major Disclosure documents

- Protocol Summary
- Result Summary
- Plain Language Summary

Protocol Summary

- Summarises the protocol briefly in a defined format
- Needs to be prepared after finalization of the protocol but before starting the actual trial.
- Needs to be concise but should cover all important and mandatory elements of the protocol
- Intended for understanding of layman and patients/volunteers who want to know more about the clinical trials.
- Should clearly outline the benefits and the risks associated with the trial.

Result summary

- Summarises the outcome of the clinical trial in a structured tabular form with neutral and non interpretative way of presentation.
- The results section consists of the following:
  - scientific information, consisting of discrete modules that represent information in a series of data tables with supporting notes
  - administrative information, consisting of semi-structured fields

Basic Results Modules

Basic Results Module	Summary Description	Overview of Minimum Required Information
Participant flow	Description of the No. of research participants starting and completing the study, including exclusions and dropouts, for each arm or comparison group (frequently reported as a CONSORT diagram in a journal article)	No. of participants who entered study; and No. of participants who completed study
Baseline characteristics	Demographic and baseline data for the study population and each arm or comparison group	Overall No. of participants analysed; age; gender; for all other measures reported: name (and description); unit of measurement; and summary data, total and by arm
Outcome measures and statistical analyses	Table of outcome measure values for each arm/comparison group, including appropriate statistical analyses	For all pre-specified primary and secondary outcome measures: name and description; unit of measurement; time frame; analysis population; and summary data, total and by arm
Adverse events (optional prior to September 2009)	Number and frequency of all serious adverse events and other adverse events exceeding a specified frequency threshold in each arm/group, grouped by organ system	For all adverse events reported: adverse event term; organ system; type of assessment (spontaneous vs systematic); and No. of participants affected, No. of participants at risk, and total No. affected, by arm

Plain Language Summary

- ‘A plain English summary is a brief summary that has been written for members of the public. It should be written clearly and simply, without jargon and with an explanation of any technical terms .
- Help disseminate research to patients, participants, other scientists, health professionals and policy makers. Plain English is something that the intended audience can read, understand and act upon the first time they read it

- Ensure that no promotional content is included
- Research across Europe suggests that text for the public should be aimed at a literacy proficiency level of 2 -3
- Communications written for the public should use simple everyday language to ensure ease of reading and understanding
- Avoid long and complex sentences that include many clauses as these are difficult to understand
- Use simple vocabulary familiar to non-medical people

- Numeracy
  - Study results summaries are likely to include a variety of numerical data that should be easily understandable by the target audience
- Visuals
  - Well-chosen and clearly designed visual aids can help enhance understanding of text
  - Patient friendly summaries of clinical trial results which combine clear infographics with explanatory text can be a good way of presenting complex information

- Using Microsoft Word, writers can test the readability of writing in English by using the Flesch Reading Ease Test or the Flesch-Kincaid Grade Level Test based on counting syllables and sentence length
- The Flesch Reading Ease Test assesses readability on a scale from 1 to 100
  - The higher the Flesch Reading Ease test score, the easier the text is to read
  - Anything that scores 70 and above is easy to read
  - An ideal reading grade level is 6th grade which is close to the literacy level of the general population
  - Even if the writer cannot achieve this, strive to get as close to this as possible

The Art and Science of Being a Disclosure Expert

*Tables, Figures & Listings

Key messages

- Disclosure is essential for human subjects protection, research integrity, evidence based medicine and legal obligation
- Disclosure a significant step towards more transparent clinical research world
- In order to match up with upcoming regulatory requirements world wide, companies need to invest more time and resources to ensure proper and timely public disclosures
- ‘Good Disclosure Practices’ are as important as ‘Good Clinical Practice’