Clinical Trial Transparency

UK perspective

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Outline

- Transparency timeline
  - Campaign groups
  - UK government enquiries
  - EU and global discussions
- ABPI activities:
  - Research on public disclosure of results
  - Clinical Trials Disclosure Toolkit
  - Monitoring disclosure of results
  - Workshops & stakeholder engagement activities
ABPI clinical trial disclosure toolkit

Transparency timeline

- 2005: IFMPA joint position
- 2008: ABPI guidelines 2008 update
- 2009: IFPMA joint position 2009
- 2010: IFPMA position re: pubn in literature 2010
- 2012: Draft CT regulation Jul 2012
- 2012: ABPI & IFPMA Codes updated
- 2012: Launch of STC Inquiry
- 2012: Bad Pharma Sep 2012
Transparency timeline

**January: 2013**
- launch of AllTrials
- submission of written evidence to STC Inquiry

**April: 2013**
- Wellcome Trust Workshop

**March: 2013**
- ABPI Technical workshop

**May: 2013**
- Draft HRA position published
- NAO inquiry
- EU Parliament view on CT Regulation

**June: 2013**
- RIAT launched
- EMA consultation

**July: 2013**
- EFPIA - PhRMA principles

**August: 2013**
- Updated AllTrials position
- Launch of ABPI CT disclosure toolkit

**November: 2013**
- ABPI study published

**2014**
- PAC Report ClinicalStudyData Request.com
- EFPIA - PhRMA principles
- STC Report
- ABPI/PSI Workshop and ABPI Disclosure Monitoring
- Council view on CT regulation
ABPI activities - overview

Research:
• Commissioned a study to measure extent to which any CT result information is made publicly accessible, within 12 months of product approval or trial completion.

Commitments (made February 2013 to STC):
• Clinical Trials Disclosure Toolkit: Launched August 2013
• Monitoring compliance to trials disclosure provisions in the ABPI Code of Practice: through third party service provider

Evidence:
• Written and oral evidence submitted to House of Commons Science and Technology Committee (STC):
  • All Party Parliamentary Group meeting on ‘Sharing results and data in medical research’

Public discussion and statements:
• Public debates – head to head with Ben Goldacre and others
• Multiple Blogs

Workshops and meetings:
• ABPI/PSI workshops (March + December 2013): Discussing how historical clinical trial information could best be shared
The objective of this study was to assess the timely disclosure in the public domain of results of all the company-sponsored clinical trials in patients, related to all the new medicines approved by the European Medicines Agency (EMA) over a recent 3 year period (2009 – 2011).

It has not attempted to monitor compliance against any specific transparency requirements.

The study, published in the peer-review journal Current Medical Research and Opinion (CMRO), highlights a positive trend of increasing levels of disclosure for industry-sponsored clinical trials, but shows that more remains to be done.
Original article
Clinical trial transparency: an assessment of the disclosure of results of company-sponsored trials associated with new medicines approved recently in Europe

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Key words:
Clinical trial – Publication – Results disclosure – Transparency – Trial registration – Trial registers

Abstract
Background:
Previous studies have raised concerns about the transparency and disclosure rates of clinical trial results in the scientific literature. The objective of this study was to assess the timely disclosure in the public domain of results of company-sponsored clinical trials conducted on new medicines approved by the European Medicines Agency (EMA) over a recent 3-year period.

Methods:
The study surveyed various publicly available information sources for both clinical trial registration and disclosure of results (including clinical trial registries, the International Federation of Pharmaceutical Manufacturers and Associations [IFPMA] Clinical Trial Portal, EMA, European Public Assessment Reports and Publications), accessed from 27 December 2012 to 31 January 2013. The study covered all 53 new medicines except vaccines and fixed-dose combinations approved for marketing by 34 pharmaceutical companies by the EMA in 2009, 2010 and 2011. It included all completed company-sponsored clinical trials conducted in patients and recorded on a clinical trial registry and held in an IFPMA.

Outcome measure and results:
The main outcome measure was the proportion of trials for which results had been disclosed on a registry or in the scientific literature either within 12 months of the later of either the first regulatory approval or trial completion, or by 31 January 2013 (whichever is earlier). Of the completed clinical trials associated with all 53 new medicines approved by the EMA between 2009 and 2011, 77% had results disclosed within 12 months. By 31 January 2013, this had increased to 89%. Rates of results disclosure within 12 months were 71%, 81% and 86% for new medicines approved in 2009, 2010 and 2011 respectively. Disclosure increased to 86%, 93% and 91% respectively by 31 January 2013.

Conclusion:
Disclosure increased to 86%, 93% and 91% respectively by 31 January 2013.
ABPI/PSI Workshops

March 2013:
Clinical trial reporting: Definitions and guiding principles:
http://www.abpi.org.uk/our-work/library/industry/Pages/clinical-trial-reporting.aspx

• December 2013:
• Clinical Trial Transparency: Technical standards for data sharing for old, current and future clinical trials:
Monitoring disclosure of results

• In Feb 2013, ABPI announced it will put in place measures to monitor compliance to the CT transparency provisions in the ABPI Code of Practice.

• An independent, third party service provider has been appointed to undertake this work.

• Will look at products approved in 2012 and 2013 and check compliance, follow-up publications will be produced.

• The ABPI will take on the responsibility for reporting to the PMCPA non-compliance with trial registration and posting of summary results.

Code of Practice provisions

These measures support the current requirement in the ABPI Code of Practice which stipulates that current and future trials must be registered within 21 days of enrolling the first patient, and results must be published within one year of marketing authorisation or one year from completion for marketed products.

As per 2009 IFPMA Joint Position
Clinical Trial Disclosure Toolkit

In February 2013 ABPI committed to providing a disclosure toolkit to help companies meet their requirement for trial transparency in the ABPI Code. It provides practice guidelines, disclosure checklists and a template SOP. These materials will be updated regularly. It contains 11 documents:

1. Points to consider when managing disclosure
2. Template SOP on clinical trial registry, results posting and publications
3. Process flow maps
4. Self-training and Q&A materials: Template SOP
5. Form R100 – this template form provides a framework for assigning named individuals to the SOP tasks.
6. Process checklist: Trial registration
7. Task checklist: Trial registration
8. Process checklist: Results disclosure
9. Task checklist: Results disclosure
10. Self-training and Q&A materials: Checklists
11. Links to regulatory/government publications on transparency/disclosure commitments.
Process flow maps:

Clinical trial registration and results disclosure process
The information provided in this toolkit for companies is provided in good faith, and every reasonable effort is made to ensure that it is accurate. The toolkit is not intended and should not be construed as regulatory or legal advice. The ABPI cannot in any circumstances accept responsibility for any errors or omissions and users should satisfy themselves as to their legal obligations.
Process flow maps:

Clinical trial registration process
# Standard notification for process flow maps

<table>
<thead>
<tr>
<th>Icon</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Arrows direction" /></td>
<td>Arrows indicating direction to next process</td>
</tr>
<tr>
<td><img src="image2" alt="Arrows direction" /></td>
<td>Arrows indicating direction to next process step</td>
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<tr>
<td><img src="image3" alt="Process" /></td>
<td>Process</td>
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<tr>
<td><img src="image4" alt="Process step" /></td>
<td>Process step</td>
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<td><img src="image5" alt="Process decision" /></td>
<td>Process step indicating a decision</td>
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<tr>
<td><img src="image6" alt="Process end" /></td>
<td>Process step signaling an end of a process</td>
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<tr>
<td><img src="image7" alt="Input" /></td>
<td>Input: Process triggering next process step</td>
</tr>
<tr>
<td><img src="image8" alt="Output" /></td>
<td>Output: Process followed after previous process step</td>
</tr>
</tbody>
</table>

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*Note: Images of icons are placeholders and should be replaced with actual images.*
Process assumptions

• The company has a disclosure process in place.

• The steps on the following pages are based on the assumption that the company’s process is followed.

• The company policy/SOP or other company guidelines define:
  – which trials or type of trials are in scope of the company’s disclosure policy
  – which registries/disclosure databases are to be managed
  – what timelines apply for disclosure of new clinical trials and results of these trials
  – the data flow for initiating and maintaining the disclosure process
  – roles and responsibilities for disclosure tasks.

• If the company maintains a dedicated website to disclose results of clinical trials, the company has documentation for the systems in use and a risk assessment with regard to compliance with Computerised Systems’ Validation (CSV) requirements.

• For results of clinical trials the workflow covers posting of an ICH E3 summary as well as of registry-defined structured outputs.
Registation of a clinical trial (Part 1)

(Process described is a possible flow and should not be viewed as a mandatory process)

1. Registration of a clinical trial
   - Share draft protocol (close to final version) with Disclosure Team
     - Prepare registry posting & verify draft protocol meets business rules of applicable registries and identify technical and editorial issues in draft protocol*

2. Maintaining registry postings
   - Review draft registry posting for consistency with protocol & address requests for change*
     - Update draft registry posting

3. Disclosure of clinical trial results
   - Business rules/requirements met?
     - Yes
       - Update registry posting & verify final protocol meets business rules of applicable registries
     - No
       - Provide final protocol to Disclosure Team

- Business rules/requirements met?
  - Yes
    - Update registry posting & verify final protocol meets business rules of applicable registries
  - No
    - Provide final protocol to Disclosure Team

- Responsibility and task assigned as per company SOP
Registration of a clinical trial (Part 2)

(Process described is a possible flow and should not be viewed as a mandatory process)

1. **Registration of a clinical trial**
   - **Clinical Team**
     - Identify non-compliance & request change(s) to protocol
     - File protocol with IECs/IRBs & HAs
     - Update protocol
     - **Protocol meets requirements?**
       - Yes: Update registry posting & verify final protocol meets business rules of applicable registries
       - No: Identify non-compliance & request change(s) to protocol

2. **Maintaining registry postings**
   - **Disclosure Team**
     - Submit postings to applicable registries
     - Receive requests for amendments from registries
     - Update posting
     - **Impact on protocol?**
       - Yes: Inform stakeholders
       - No: Finalise postings
## Registration of a clinical trial

### Responsible Party

#### Clinical Team
- Informs the Disclosure Team of the close-to-final protocol
- Reviews the draft registry posting prepared by the Disclosure Team
- Finalises the protocol and communicates this to the Disclosure Team
- Updates the protocol, if applicable
- Files the protocol with IECs/IRBs and Health Authorities as per applicable regulations

#### Disclosure Team
- Prepares the registry posting and identifies protocol issues in terms of applicable registry business rules and identifies technical and editorial inconsistencies in the protocol
- Updates draft registry posting based on input received from Clinical Team
- Verifies feedback registry received is consistent with applicable registries business rules
- Updates registry posting and verifies final protocol meets business rules of applicable registries
- Submits postings to applicable registries
- Identifies non-compliance with registry business rules and requests changes to protocol
- Follows up on feedback received from registries
- Updates postings
- Informs company stakeholders of completed postings as per applicable SOP
Maintaining registry postings

(Applicable updates to registries such as www.clinicaltrials.gov, etc)
Managing protocol amendments & registry postings (Part 1)

(Process described is a possible flow and should not be viewed as a mandatory process)

1. Registration of a clinical trial
2. Maintaining registry postings
3. Disclosure of clinical trial results

- Initiate protocol amendment
- Review draft update of registry posting for consistency with amended protocol & address requests for change*
- Prepare update to registry posting & verify protocol amendment meets business rules of applicable registries and identify technical and editorial issues in the amendment
- Verify final amendment text meets business rules of applicable registries
- Final amendment meets business rules of registries
- File amendment with IECs/IRBs & HAs

Responsibility and task assigned as per company SOP
Managing protocol amendments & registry postings (Part 2)

(Process described is a possible flow and should not be viewed as a mandatory process)
Maintaining registry postings

### Responsible Party

<table>
<thead>
<tr>
<th>Party</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Team</td>
<td>- Updates CTMS according to progress report from clinical sites&lt;br&gt;- Amend protocol, if applicable on feedback from Disclosure Team</td>
</tr>
<tr>
<td>Disclosure Team</td>
<td>- Updates registries with new information from clinical sites through CTMS&lt;br&gt;- Follow-up on feedback received from registries&lt;br&gt;- Assess impact of amendment on information disclosed on applicable registries&lt;br&gt;- Update registry entry, if applicable&lt;br&gt;- Communicate to Clinical Team change to registry following a protocol amendment</td>
</tr>
<tr>
<td>Clinical Site</td>
<td>- Communicates progress on the study, eg number of patients enrolled and others&lt;br&gt;- Communicates LPLV via updates to CTMS (either through the monitor or by directly updating the CTMS)</td>
</tr>
</tbody>
</table>
Process flow maps:

Results disclosure process
Disclosure of clinical trial results (structured/tabular outputs)

(Managing disclosure of results on registries requiring structured/tabular outputs, e.g. www.clinicaltrials.gov)

1. Registration of a clinical trial
2. Maintaining registry postings
3. Disclosure of clinical trial results

**Data Management / Biometrics**
- Prepare output as per business rules of registries
- Update outputs and resubmit to Disclosure Team
- Review and approve outputs for medical & scientific integrity
- Review and approve output for compliance with business rules of registries
- Post on registries

**Clinical Team**
- By month 4 following LPLV: submit publication & results disclosure plans including timelines
- Request changes to output
- Track timelines & verify whether plan is aligned with company policy & legal / registry requirements
- Review output for compliance with business rules of registries

**Disclosure Team**
- Within 4 months of LPLV date request publication & results posting plans from Clinical Team
- Compliant with business rules
- Request changes to output
Disclosure of clinical trial results as ICH E3 summaries

(Managing disclosure of results on registries)
Disclosure of clinical trial results

<table>
<thead>
<tr>
<th>Responsible party</th>
<th>Procedure</th>
</tr>
</thead>
</table>
| Clinical Team          | - Submit publication and results disclosure plans including timelines to Disclosure Team  
                          | - If applicable, send ICH E3 summary of clinical study report to Disclosure Team  
                          | - Update ICH E3 summary on feedback from Disclosure Team  
                          | - Review and approve output from Data Management for medical and scientific integrity  |
| Disclosure Team        | - Request publication and results posting plans from Clinical Team  
                          | - Track timelines and verify whether plan is aligned with company policy & legal/registries’ requirements  
                          | - Remind Clinical Team of timelines  
                          | - Review and approve output from data management for compliance with registry business rules  
                          | - Post output on applicable registry  
                          | - If applicable, review ICH E3 summary for compliance with business rules of applicable registry and  
                          | - If applicable, approve ICH E3 summary and post on applicable registry  |
| Data Management/Biometrics | - Prepare output as per business rules of applicable registries             |