

## **DIRECTOR v BAYER**

### **Clinical trial disclosure**

**A study published online in the British Medical Journal (12 September 2018) was entitled 'Compliance with requirement to report results on the EU Clinical Trials Register: cohort study and web resource' (Goldacre *et al* 2018).**

**The study objectives included assessing compliance rates with the European Commission's requirement that all trials on the EU Clinical Trials Register (EUCTR) posted results to the registry within 12 months of completion (final compliance date 21 December 2016). The study objectives also included identifying features associated with non-compliance, ranking sponsors by compliance and building a tool for live ongoing audit of compliance. The published paper listed the trial sponsors with the highest proportion of trials reported and the trial sponsors with the highest proportion of trials unreported. The results were that of 7,274 trials where results were due, 49.5% (95% confidence interval 48.4% to 50.7%) reported results.**

**Goldacre *et al* stated that the European Commission (EC) Guideline required the results of all trials to be reported in structured form on to the register itself. It was possible that some trials that did not report results to EUCTR reported results elsewhere eg in a conference presentation, an academic journal article, as part of a meta-analysis after data were requested by systematic reviewers, or in the grey literature. Such publications did not meet the reporting requirements of the EC Guideline and were therefore outside the scope of the study.**

**Goldacre *et al* listed sponsors with more than 50 trials on the EUCTR and did not mention products or specific clinical trials. Goldacre *et al* gave details of disclosure of clinical trial results for each sponsor.**

**The Director decided that the Goldacre *et al* article was such that she had received information from which it appeared that Bayer might have breached the Code and decided in accordance with Paragraph 5.1 of the Constitution and Procedure to take the matter up as a complaint.**

**As Bayer had previously been ruled in breach of the 2008 Code in relation to its failure to disclose the results of studies on Xofigo within the permitted timeframe an alleged breach of undertaking was raised.**

**The detailed response from Bayer is given below.**

**General detailed comments from the Panel are given below.**

**The Panel noted the data in Goldacre *et al* in that the results for one of Bayer's due trials had not been reported on EUCTR; the disclosure percentage was 98.6%.**

**The Panel noted Bayer's submission that the trial in question (2012-004857-10) was authorised to proceed on 19 September 2013 but was cancelled before any patients were enrolled. The Panel noted Bayer's submission that the EudraCT database did not provide functionality for sponsors to inform readers of EUCTR that recruitment for withdrawn trials never started, and so 'completed' was the only designation available to assign to this trial, which had led to the inappropriate inclusion of this trial in the BMJ article as a 'due trial'.**

**The Panel noted Bayer's submission that following receipt of this complaint the completion date had been deleted and the statement 'Trial was withdrawn before start of recruitment, therefore no trial results available' added in a data field below the study title in EudraCT.**

**The Panel noted that there were no results to publish and therefore ruled no breach of the Code including no breach of Clause 2.**

**Given the above there could be no breach regarding the undertaking given by Bayer in Case AUTH/2908/11/16 and therefore no breach of the Code was ruled in the present case including no breach of Clause 2.**

A study published online in the British Medical Journal (12 September 2018) was entitled 'Compliance with requirement to report results on the EU Clinical Trials Register: cohort study and web resource' (Goldacre *et al* 2018).

The study objectives included assessing compliance rates with the European Commission's requirement that all trials on the EU Clinical Trials Register (EUCTR) posted results to the registry within 12 months of completion (final compliance date 21 December 2016). The study objectives also included identifying features associated with non-compliance, ranking sponsors by compliance and building a tool for live ongoing audit of compliance. The published paper listed the trial sponsors with the highest proportion of trials reported and the trial sponsors with the highest proportion of trials unreported. The results were that of 7,274 trials where results were due, 49.5% (95% confidence interval 48.4% to 50.7%) reported results. Results from trials with a commercial sponsor were substantially more likely to be posted than those from a non-commercial sponsor (68.1% v 11.0%, adjusted odds ratio 23.2, 95% confidence interval 19.2 to 28.2) as were trial results from a sponsor who conducted a large number of trials (77.9% v 18.4%, adjusted odds ratio 18.4, 15.3 to 22.1). More recent trials were more likely to report results (per year odds ratio 1.05, 95% confidence interval 1.03 to 1.07). Extensive evidence was found of errors, omissions, and contradictory entries in EUCTR data that prevented ascertainment of compliance for some trials.

The Director decided that the Goldacre *et al* article was such that she had received information from which it appeared that Bayer might have breached the Code and decided in accordance with Paragraph 5.1 of the Constitution and Procedure to take the matter up as a complaint.

## **COMPLAINT**

The study concluded that compliance with the European Commission requirement for all trials to post results on to the EUCTR within 12 months of completion had been poor, with half of all trials non-compliant. EU registry data commonly contained inconsistencies that might prevent

even regulators assessing compliance. Accessible and timely information on the compliance status of each individual trial and sponsor might help to improve reporting rates.

Goldacre *et al* noted that any trial of any medicinal product conducted since 2004 in an EU country had already been required to register on the EUCTR, which was administered by the European Medicines Agency (EMA). Following the 2012 European Commission (EC) guideline 2012/c302/03, sponsors must ensure that they disclosed their results of all trials registered on EUCTR since 2004 to the EMA within 12 months of trial completion; Phase I trials were exempt unless they were denoted as being part of a paediatric investigation plan. These trial reports were posted publicly on to the EUCTR within 15 working days of receipt by the EMA and were required to include salient features such as results for all pre-specified trial outcomes and statistical analyses, details of 'serious' and 'non-serious' adverse events, participants' baseline characteristics, and protocol deviations, as well as discussion of design limitations and caveats. Following various delays in the EMA's implementation of the software platform for results posting, the final date for sponsors' compliance was 21 December 2016.

Goldacre *et al* assessed compliance with the EU requirement to post results on to EUCTR for all trials on the registry, explored factors associated with non-compliance, identified the individual trial sponsors that were best at complying, and created a live online service, driven by regular updates of the EUCTR data, to give ongoing and regularly updated performance statistics for compliance.

The publication listed a number of variables.

Goldacre *et al* stated that the EUCTR data underlying this study were updated regularly. An interactive online website presenting the overall reporting rate for all due trials, the reporting rates for each sponsor, ranks for these reporting rates, and details of each sponsor's individual reported and unreported trials was developed. The data underlying this site was updated regularly following each new download of the EUCTR database: the results and ranks for each individual sponsor were therefore always current and changed as performance changed. All software underlying this service was shared as open source and available for open code review or for adaptation and re-use.

Goldacre *et al* stated that the European Commission (EC) Guideline required the results of all trials to be reported in structured form on to the register itself. Ascertainment of the outcome – a results report on EUCTR – was therefore accurate and complete. It was possible that some trials that did not report results to EUCTR reported results elsewhere eg in a conference presentation, an academic journal article, as part of a meta-analysis after data were requested by systematic reviewers, or in the grey literature. Such publications did not meet the reporting requirements of the EC Guideline and were therefore outside the scope of the study. A manual search of academic journals and grey literature for a random sample of 100 trials unreported on EUCTR was conducted as requested as part of the peer review of the publication. Five were reported in the grey literature and 46 in a journal publication.

Goldacre *et al* listed sponsors with more than 50 trials on the EUCTR and did not mention products or specific clinical trials. The study publication listed the sponsors with the highest proportion of trials reported and those with the lowest proportion of trials reported.

Goldacre *et al* gave details of disclosure of clinical trial results for each sponsor. The data for Bayer were as follows:

### Sponsors with highest proportion of trials reported

Sponsor	Total trials on EUCTR	Due trials	Due trials with results	% reported
Bayer	274	72	71	98.6

When writing to Bayer the Authority asked it to bear in mind the requirements of Clauses 2, 9.1, 1.11 and 13.1 of the Code. The Authority noted that previous editions of the Code might be relevant and provided details.

As Bayer had previously been ruled in breach of Clauses 9.1 and 21.3 of the 2008 Code in relation to its failure to disclose the results of studies on Xofigo within the permitted timeframe Bayer was also asked to bear in mind Clauses 2, 9.1 and 29 in this regard.

### RESPONSE

Bayer noted that the BMJ article reported that the company had 274 trials on the EU Clinical Trial Register (EUCTR) that met the search criteria; 72 of these trials were reported as 'due trials', of which 71 trials were reported to have results published on the database. This implied that one Bayer sponsored trial on the register was a due trial that had failed to report its results. Bayer stated that the trial in question was trial EudraCT Number: 2012-004857-10 which fell within the scope of the ABPI Code but noted that as it was cancelled before any patients were enrolled there were no results to publish. The national competent authority (Germany) was informed that the study had been discontinued in December 2016 (relevant documents were provided).

Bayer explained that the EudraCT database did not provide functionality for sponsors to inform that recruitment for withdrawn trials never started and so 'completed' was the only designation available to assign to this trial. This had most likely led to the inappropriate inclusion of this trial in the BMJ article as a 'due trial'. The European Medicines Agency (EMA) acknowledged this limitation and addressed it in its EudraCT Frequently Asked Question document (copy provided).

Bayer noted that the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases required registration of clinical trials or publication or clinical trial results on any one of a number of free, publicly accessible, internet-based registries and listed the US National Library of Medicine registry ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)) as a credible registry to post clinical trial details and results.

Details of the trial in question were also successfully reported on the US National Library of Medicine Registry (ClinicalTrials.gov Identifier: NCT02047019). In this registry, where trial status could be designated as 'withdrawn', the trial status of the trial in question was appropriately reported as 'withdrawn' which more accurately reflected the actual and current status of the trial in question.

Based on the explanation above and the fact that the trial never started and no results were generated, Bayer did not consider that it had failed to disclose clinical trial results as reported in the BMJ article and thus the company denied breaches of Clauses 1.11, 13.1, 9.1 and 2.

### **Alleged breach of undertaking**

With regard to the alleged breach of undertaking given in Case AUTH/2908/11/16, Bayer submitted that it had and would continue to take appropriate steps to avoid similar breaches in the future. The company's current standard operating procedure (SOP) on publication and clinical trial transparency provided evidence of its current global approach to registering clinical trials and reporting clinical trial results.

Bayer stated that its timelines for trial results posting on EUCTR was 12 months after the end of the study for adult trials and 6 months after the last patient last visit (LPLV) for paediatric trials. For the US National Library of Medicine registry ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)) it was 1 year after primary completion date or at market approval.

Bayer noted that it submitted information on its clinical trials to the publicly funded website [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov) (as well as [www.clinicaltrialsregister.eu](http://www.clinicaltrialsregister.eu), if applicable). Therefore, its timelines and level of transparency (submitting trial information to more than one registry) were both in accordance with and more transparent than the Joint Position statement mandated.

Bayer stated that it was committed to maintaining a high industry standard and had not undermined any previously agreed undertakings in relation to disclosures of clinical trial results and thus it denied breaches of Clauses 29, 9.1 or 2. Any misinformation regarding clinical trial status was secondary to data capturing issues on the EUCTR database and an inherent limitation of the retrospective cohort database study where the actual trial status of all the trials in EUCTR was not verified through manual searches.

In a subsequent letter to the Authority, Bayer stated that its clinical trials transparency and regulatory affairs teams had worked to correct the misinformation and had engaged with the principal author of the BMJ article to clarify the true status of clinical trial 2012-004857-10. Bayer had also engaged with the competent regulatory authority (Germany) responsible for the trial to update the trial details on the EUCTR to reflect that it was withdrawn and no results were available to report.

As 'withdrawn' was not a designation available on the EUCTR for withdrawn trials, a creative compromise, in this instance, was to delete the completion date and to add a clarifying statement, 'Trial was withdrawn before start of recruitment, therefore no trial results available' in a data field below the study title. The German authority promptly amended the trial details and this updated trial status was currently available to the public.

Inputting data into an undesignated data field on EUCTR was neither an ideal nor sustainable solution for reporting trials that ended before patients were recruited and it had raised its concerns with the relevant competent authorities. Currently, both the European Federation of Pharmaceutical Industries and Associations (EFPIA) and the European Medicines Agency (EMA) knew of and acknowledged the limitations to the EUCTR system and the EMA was currently considering solutions to address the issue. Bayer stated that it also aimed to assess internal processes that might help avoid such misinformation during end-of-trial notifications in the future.

Subsequent to the amendment to trial 2012-004857-10 on EUCTR, the EU Clinical Trials Tracker for Bayer trials had been updated to better reflect the true status of Bayer's 'due trials'.

Trial 2012-004857-10 had now been appropriately removed from the list leaving all 79 of Bayer's 'due trials' listed on the system as being reported ie Bayer's reporting on 'due trials' was currently 100%. Bayer provided a list of its trials in the EU Clinical Trials Registry that had been completed more than 12 months ago and should have reported results within a year of completion. As trial 2012-004857-10 had its application withdrawn before commencement and had subsequently been removed from the EUCTR list of Bayer's 'due trials', Bayer considered that it had not failed to disclose due clinical trials and hence it denied breaches of Clauses 1.11 and 13.1. Bayer also considered that it had complied with previously agreed undertakings relating to clinical trial disclosure, maintained high industry standards and therefore it was not in breach of Clauses 29, 9.1 or 2.

### **GENERAL COMMENTS FROM THE PANEL**

The Panel noted that Goldacre *et al* was not the subject of external complaint but was taken up under Paragraph 5.1 of the Constitution and Procedure.

The Panel noted that Goldacre *et al* was the basis of the complaint in relation to the allegation that sponsors with less than 100% reported trials were not meeting the requirements of the EC Guideline.

The Panel noted that all the cases would be considered under the Constitution and Procedure in the 2016 Code as this was in operation when Goldacre *et al* was published and the complaint proceedings commenced.

The Panel noted that there had been three previous studies looking at the disclosure of clinical trial data all published in Current Medical Research and Opinion (CMRO). The first study was the subject of an external complaint which gave rise to 27 cases in 2013 and 2014. The second study (Rawal and Deane 2015) was not the subject of external complaint but was taken up under Paragraph 5.1 of the Constitution and Procedure in 2015 and led to 15 cases. The third study (Deane and Sivarajah 2016) was not the subject of external complaint but was also taken up under Paragraph 5.1 in 2016 and led to 17 cases. Most of these cases were not in breach of the Code because they were not within the scope of the Code as there was no UK involvement and therefore only limited details were published on the PMCPA website.

The previous studies surveyed various publicly available information sources for clinical trial registration and disclosure of results searched between specific dates covering medicines (except vaccines) that were approved by the European Medicines Agency (EMA) in a particular year or years. The Panel noted that the previous cases had established a number of principles including deciding which Code applied.

Goldacre *et al* was different to the previous three studies which assessed compliance with the Joint Positions; it only assessed compliance with the EU requirement to post results on to the European Union Clinical Trial Register (EUCTR) for all trials listed on the registry. In that regard, trials involving investigational products that were not licensed for use anywhere in the world might be included. Companies had not made a detailed submission on this point.

The Panel noted that the European Clinical Trials Database (EudraCT) was a database hosted by the EMA in which clinical trial sponsors would upload summary results. These results would then be published on the EUCTR.

The Panel considered that in these circumstances the trial completion date would be the trigger for results disclosure on EUCTR. The Panel noted that the publicly available EudraCT and EUCTR Q&A document stated in response to the question 'if the trial is prematurely ended/early terminated due to lack of subjects or lack of data to analyse, do I have to provide results?', that in the case that no subjects were recruited, it was not appropriate to complete the full dataset. However, there was currently no functionality for sponsors to inform that recruitment never started or that the trial was prematurely ended in the results data model. In this specific case sponsors had to liaise directly with the National Competent Authority confirming that no results would be available for a specific trial due to 'lack of subjects' or that the trial was 'prematurely ended' so a statistical analysis could not be provided. The Panel noted that according to the Commission Guideline 'Guidance on posting and publication of result-related information on clinical trials in relation to the implementation of Article 57(2) and Regulation No 726/2001 and Article 41(2) of Regulation No 1901/2006', if the clinical trial ends prematurely, that date should be considered the end of trial date.

The Panel noted that according to Goldacre *et al* any trial of any medicinal product conducted since 2004 in an EU country had already been required to register on the EUCTR, which was administered by the European Medicines Agency (EMA). Following the 2012 European Commission (EC) guideline 2012/c302/03, sponsors must ensure that they disclosed the results of all trials registered on EUCTR since 2004 to the EMA within 12 months of trial completion; Phase I trials were exempt unless they were denoted as being part of a paediatric investigation plan. These trial reports were posted publicly on to the EUCTR within 15 working days of receipt by the EMA and were required to include salient features. Goldacre *et al* noted that following delays in the EMA's implementation of the software platform for results posting, the final date for sponsors' compliance was 21 December 2016.

The Panel considered that the subject matter of the complaint was failure to publish results on EUCTR. It appeared to the Panel that under EUCTR for non-paediatric trials, at least one investigator site of the clinical trial should be located in Europe or in a contracting state of the European Economic Area (EEA). The Panel noted that it could only consider the matter with regard to the Code. In the Panel's view, only those with a UK nexus would be considered to be within the scope of the Code.

The Panel noted that the Code did not explicitly refer to publication on the EUCTR. Clause 13.1 referred, *inter alia*, to disclosure of clinical trials in accordance with the Joint Positions on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases and the Publication of Clinical Trial Results in the Scientific Literature. According to the 2009 Joint Position, publication of clinical trial results in any free, publicly accessible internet-based clinical trials database should achieve the intended objectives.

The Panel noted the differences between the Joint Positions and the requirement to publish clinical trial results on the EUCTR; it was possible that results might not need to be published under the Joint Positions (for instance because the medicine was not licensed for use or commercially available) but might nonetheless be required to be published on the EUCTR. The Panel considered that companies would be well advised to ensure that all the clinical trial results were disclosed as required by the law, codes and Joint Positions. The Panel noted that Goldacre *et al* had not commented on whether the results disclosed met the requirements of the Joint Positions so this was not considered; in the Panel's view the only matter for consideration was whether or not trial results had been disclosed within the required timeframe as required by the Commission Guideline 2012/C302/03 which came into operation in 2012, and by 21

December 2016 which was referred to by Goldacre *et al* as the final data for sponsor's compliance. The Panel considered, therefore, that in this particular case it would make its rulings under the Code in operation on 21 December 2016, the 2016 Code. The Panel considered that its approach was a fair one.

The Panel noted that the companies had been asked to respond, *inter alia*, to Clause 13.1. Given that Goldacre *et al* did not refer to the Joint Positions and noting the differences between the requirements to disclose under the Joint Positions and under the Commission Guidelines the Panel considered, taking a pragmatic approach, that the matters raised by Goldacre *et al* would be considered under Clause 9.1, rather than Clause 13.1. The companies had been asked to respond to, *inter alia*, Clauses 9.1 and 1.11 at the outset and had been provided with a copy of Goldacre *et al*. The Panel noted that the publicly available EudraCT and EUCTR Q&A document referred to sponsors who were not fulfilling the legal requirements in providing results in EudraCT.

The Panel considered that the first issue to be determined was whether the matter was covered by the ABPI Code. If the clinical trial was conducted on behalf of a UK pharmaceutical company (whether directly or via a third party) then it would be covered by the ABPI Code. If a trial was run by a non-UK company but had UK involvement such as centres, investigators, patients etc it was likely that the Code would apply. The Panel appreciated the global nature of much pharmaceutical company sponsored clinical research and a company located in the UK might not be involved in research that came within the ABPI Code. It was a well-established principle that UK pharmaceutical companies were responsible for the activities of overseas affiliates if those activities came within the scope of the Code such as those related to UK health professionals or carried out in the UK.

The Panel noted that the Authority was not an investigative body as such and its consideration of these cases relied upon the information provided by the parties. The quantitative data published by Goldacre *et al* formed the basis of the complaint. The Panel noted that in that regard the case preparation manager had not used the live data web resource to identify the trials at issue.

## **PANEL RULING**

The Panel noted its general comments above about the subject matter of the complaint as set out in Goldacre *et al*. The Panel had decided that the alleged failure to publish results in accordance with the Commission Guidelines was more appropriately covered by Clause 9.1 and potentially Clause 1.11. The Panel made no ruling in relation to Clause 13.1.

The Panel noted the data in Goldacre *et al* in that the results for one of Bayer's due trials had not been reported on EUCTR; the disclosure percentage was 98.6%.

The Panel noted Bayer's submission that the trial in question (2012-004857-10) involved Nifedipine gastrointestinal therapeutic system (GTIS) and Candesartan Cilexil in combination and was authorised to proceed on 19 September 2013 but was cancelled before any patients were enrolled. The Panel noted Bayer's submission that the EudraCT database did not provide functionality for sponsors to inform readers of EUCTR that recruitment for withdrawn trials never started, and so 'completed' was the only designation available to assign to this trial, which had led to the inappropriate inclusion of this trial in the BMJ article as a 'due trial'.



The Panel noted Bayer's submission that following receipt of this complaint the completion date had been deleted and the statement 'Trial was withdrawn before start of recruitment, therefore no trial results available' added in a data field below the study title in EudraCT.

The Panel noted that there were no results to publish and therefore ruled no breach of Clauses 1.11, 9.1 and 2.

Given the above there could be no breach regarding the undertaking given by Bayer in Case AUTH/2908/11/16 and therefore no breach of Clauses 29, 9.1 and 2 was ruled in the present case.

**Complaint received      12 September 2018**

**Case completed         15 May 2019**