CASE AUTH/3084/9/18 ***NO BREACH OF THE CODE***

DIRECTOR v BOEHRINGER INGELHEIM

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 Boehringer Ingelheim 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.

The detailed response from Boehringer Ingelheim 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 of seven of Boehringer Ingelheim's due trials had not been reported on EUCTR; the disclosure percentage was 92.2%.

The Panel noted Boehringer Ingelheim's submission that four of the seven trials (1298.3, 248.641, 1230.25 and 1188.31) were never started and therefore there were no results to

report. The Panel therefore ruled no breaches of the Code including no breach of Clause 2 in relation to those four trials.

The Panel noted Boehringer Ingelheim's submission that a further two trials (1218.5, 1138.10) had no UK involvement, no UK centres, investigators or patients. The Panel considered that as there was no UK involvement, the matter did not come within the scope of the UK Code. No breach of the Code was ruled.

The Panel noted Boehringer Ingelheim's submission that the final trial (1100.1484) was a multinational trial of a licensed HIV medication. Boehringer Ingelheim UK was responsible for the conduct of the trial in the UK involving UK trial sites, investigators and patients. The Panel noted Boehringer Ingelheim's submission that the disclosure of this trial was not required by the UK Code because the product was licensed before 1 November 2008 and the trial completed before 31 October 2008. However, the Panel noted that the complaint concerned the publication of trial results on the EUCTR.

The Panel noted that the results did not appear to be published on EUCTR within the required timeframe. The Panel therefore ruled a breach of the Code.

The Panel noted from the evidence before it that there did not appear to have been any formal finding by any judicial authority or appropriate body charged with determining matters in relation to the Commission Guidelines that the company had not complied with the relevant laws and regulations. The Panel therefore ruled no breach of the Code in that regard. The Panel was unsure whether or not the results were now disclosed on EUCTR or elsewhere. On balance, the Panel did not consider that in the circumstances a breach of Clause 2 was warranted and ruled accordingly.

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Following its completion of the consideration of all four appeals in the clinical trial cases on 18 September 2019 (Cases AUTH/3079/9/18, Pfizer, AUTH/3087/9/18 (GlaxoSmithKline), AUTH/3118/11/18 (Tesaro) and AUTH/3102/9/18 (Lilly), the Appeal Board noted that the respondent companies in Case AUTH/3084/9/18 (Boehringer Ingelheim), Case AUTH/3091/9/18 (UCB), Case AUTH/3097/9/18 (Teva), and Case AUTH/3099/9/18 (Allergan), accepted the Panel's rulings of breaches of the Code and had not appealed. The papers and the reports were before the Appeal Board as completed cases.

The Appeal Board agreed that Boehringer Ingelheim, UCB, Teva and Allergan should be contacted and informed of the outcome of the appeals in Cases AUTH/3079/9/18, AUTH/3087/9/18, AUTH/3118/11/18 and AUTH/3102/9/18. The PMCPA Constitution and Procedure did not cover this unusual situation where more than one company was involved in a similar set of circumstances and the Appeal Board had taken a different view to the Panel. Boehringer Ingelheim, UCB, Teva and Allergan were offered the opportunity to appeal out of time and the appeal process would operate in the usual way. The Appeal Board noted that each case's circumstances might differ, and the result of any appeal could not be guaranteed. UCB and Allergan declined the opportunity to appeal. Boehringer Ingelheim and Teva accepted the opportunity to appeal.

The Appeal Board noted that a series of cases had been taken up by the PMCPA as a result of the data published in Goldacre *et al.* Four cases (noted above) were the subject

of an appeal by the respondent companies. Each were determined on their own merits but there were a number of common themes. The Appeal Board now considered two subsequent appeals from Boehringer Ingelheim and Teva.

The Appeal Board noted that Article 57(2) of Regulation (EC) No 726/2004 and Article 41(2) of Regulation (EC) No 1901/2006 required that clinical trial data be published on EUCTR. European Commission (EC) guideline 2012/c302/03 gave guidance as to when the clinical trial results data should be published. According to the guideline posting of results of clinical trials which ended one year or more prior to finalisation of the programming of the relevant database, should be done within 24 months of finalisation of that programming. According to the 'What's New' section of the EudraCT public website (post-dated 13 January 2016), the deadline for submission of these results was 21 December 2016. This date was referred to in Goldacre *el al*. In this regard, it appeared to the Appeal Board that whilst the regulation mandated disclosure of results on EUCTR, the EC guideline and other material advised companies how to comply with the regulation including in relation to the timing of such disclosures. The Appeal Board considered that it was within the spirit of the Code and good practice to comply with the EC guideline in question.

The Appeal Board noted Boehringer Ingelheim had published trial results for 83 of 90 trials. The Appeal Board noted the data in Goldacre *et al* in that the results of 7 of Boehringer Ingelheim's due trials had results due and yet they had not been reported on EUCTR; the disclosure percentage was 92.2%. Boehringer Ingelheim submitted that one of the trials at issue was conducted in UK and was, therefore, subject to the Code. The Appeal Board noted its comment above about trials with no UK nexus. The trial (trial 1100.1454), with a UK nexus was at issue in the appeal.

The Appeal Board considered that there would be a difference between action to deliberately hide clinical trial data or systematic failure resulting in non or late disclosure and late disclosure of results as part of a retrospective exercise contrary to non-mandatory timelines due to mitigating factors. The Appeal Board, nonetheless, noted its view above about good practice and disclosure in accordance with the EC guideline.

The Appeal Board noted that Boehringer Ingelheim's submission that it had discovered it was not the sponsor of the trial 1100.1454. The sponsor was International Antiviral Therapy Evaluation Center (IATEC), an academic clinical research organisation based in the Netherlands. Boehringer Ingelheim had been monitoring the study but it had been listed as the sponsor in error. The Appeal Board further noted Boehringer Ingelheim's submission that trial 1100.1454 was a retrospective observational trial, with no trial medication administered and consequently did not require to be published on EUCTR.

The Appeal Board noted, however, that Boehringer Ingelheim had published the results from trial 1100.1454, on 17 February 2018 on EUCTR which was before it was notified of the complaint. The Appeal Board noted that the trial was also published in scientific literature. The Appeal Board noted from Boehringer Ingelheim's submission that at the time of the complaint its disclosure percentage on the EUCTR database was 100%.

Whilst the Appeal Board was concerned about the apparent failure to disclose the summary results of trial 1100.1454 on EUCTR within the timelines advised by the EC guideline and other relevant advice, it noted Boehringer Ingelheim's submission that it

was not the sponsor of the trial nor was the trial one that needed to be disclosed on EUCTR. Noting both the exceptional circumstances of this case, and that Boehringer Ingelheim was not the sponsor of the trial, the Appeal Board did not consider that the late posting of the result of one trial on the EUCTR as part of a retrospective exercise warranted a breach of the Code as far as Boehringer Ingelheim was concerned. The Appeal Board ruled no breach of the Code. The appeal was successful.

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 Boehringer Ingelheim 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 Boehringer Ingelheim were as follows:

Sponsors with highest proportion of trials reported

Sponsor	Total trials on EUCTR	Due trials	Due trials with results	% reported
Boehringer Ingelheim	340	90	83	92.2

When writing to Boehringer Ingelheim 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.

RESPONSE

Boehringer Ingelheim submitted that it had a dedicated group, based in Germany, which oversaw clinical trial transparency. Boehringer Ingelheim submitted that it disclosed the results of all trials (all phases) initiated on or after 1 January 1998.

Boehringer Ingelheim submitted that it was aware of the discrepancy of seven trials (83 trials with results published vs 90 with results due) as presented in the BMJ article. All seven trials were legacy trials which completed between 2004 and the cut-off date of 21 July 2013, where results could be posted in a summary (synopsis) pdf format on the EMA platform.

Boehringer Ingelheim detailed the seven trials in a table format but summarised the findings below:

- Four trials (Boehringer Ingelheim trial numbers: 1298.3, 248.641, 1230.25 and 1188.31) were never started, therefore, had no trial results and should not have triggered disclosure. The error arose because a competent authority in one of the proposed countries ticked the wrong box 'completed' and since the EMA platform did not allow deletion of records, these trials were inappropriately flagged for disclosure. The issue was resolved earlier this year when Boehringer Ingelheim submitted a statement clarifying that the trials were cancelled before starting and so no results were possible.
- The remaining three legacy trials (Boehringer Ingelheim numbers: 1218.5, 1138.10 and 1100.1484) all completed over a decade ago (the last of these 3 trials finished in August 2007).

Trial 1218.5

This was a phase 2 trial of a medicine that was unlicensed and not commercially available at the time of the trial (global initiation 19 May 2006, last patient out 22 August 2007). There were no UK sites, investigators or patients and there was no Boehringer Ingelheim UK funding or any other connection to Boehringer Ingelheim UK.

Therefore, according to the PMCPA decision tree, the UK Code did not apply.

Trial 1138.10

This was a trial with a product that was not registered in the UK as it was counted as a food/dietary supplement. The trial started on 6 March 2006 and the last patient was out 18 October 2006. The trial had no UK sites, investigators or patients. There was no Boehringer Ingelheim UK funding or any other connection to Boehringer Ingelheim UK.

Boehringer Ingelheim stated that as a food/dietary supplement and with no UK involvement this product/trial did not fall under the scope of the UK Code.

Trial 1100.1484

This was a multinational Phase IV trial of a licensed HIV medication. Boehringer Ingelheim UK was responsible for the conduct of the trial in the UK involving UK trial sites, investigators and

patients. The first trial site globally was initiated on 8 September 2004 and the trial had last patient out on 27 April 2007.

Boehringer Ingelheim's submitted that according to the PMCPA decision tree, disclosure of this trial was not required by the UK Code since it involved a product licensed before 1 November 2008 and the trial completed before 31 October 2008.

Boehringer Ingelheim submitted that the PMCPA's decision tree confirmed that none of the completed trials, which the BMJ article alleged were late with disclosure, were subject to disclosure under the UK Code. Boehringer Ingelheim thus denied breaches of Clauses 2, 1.11, 9.1 and 13.1.

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 of seven of Boehringer Ingelheim's due trials had not been reported on EUCTR; the disclosure percentage was 92.2%.

The Panel noted Boehringer Ingelheim's submission that four of the seven trials (1298.3, 248.641, 1230.25 and 1188.31) were never started and therefore there were no results to report. The Panel therefore ruled no breach of Clauses 1.11, 9.1 and 2 in relation to those four trials.

The Panel noted Boehringer Ingelheim's submission that a further two trials (1218.5, 1138.10) had no UK involvement, no UK centres, investigators or patients. The Panel considered that as

there was no UK involvement, the matter did not come within the scope of the UK Code. No breach of the Code was ruled.

The Panel noted Boehringer Ingelheim's submission that the final trial (1100.1484) was a multinational trial of a licensed HIV medication. Boehringer Ingelheim UK was responsible for the conduct of the trial in the UK involving UK trial sites, investigators and patients. The Panel noted Boehringer Ingelheim's submission that the disclosure of this trial was not required by the UK Code because the product was licensed before 1 November 2008 and the trial completed before 31 October 2008. However, the Panel noted that the complaint concerned the publication of trial results on the EUCTR.

The Panel noted that the results did not appear to be published on EUCTR within the required timeframe. The Panel therefore ruled a breach of Clause 9.1.

The Panel noted from the evidence before it that there did not appear to have been any formal finding by any judicial authority or appropriate body charged with determining matters in relation to the Commission Guidelines that the company had not complied with the relevant laws and regulations. The Panel therefore ruled no breach of Clause 1.11 in relation to this trial. The Panel was unsure whether or not the results were now disclosed on EUCTR or elsewhere. On balance, the Panel did not consider that in the circumstances a breach of Clause 2 was warranted and ruled accordingly.

[Post advisory note - Boehringer Ingelheim's submitted in its initial response that a check on the 'EU trials tracker' and the 'FDAAA Trials Tracker' (which monitored compliance with US FDA Amendment Act [FDAAA] ClinicalTrials.gov trial results data) would show that Boehringer Ingelheim was standing at 100% compliance. This text had been omitted from the above in error.]

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Following its completion of the consideration of all four appeals in the clinical trial cases on 18 September 2019 (Cases AUTH/3079/9/18, Pfizer, AUTH/3087/9/18 (GlaxoSmithKline), AUTH/3118/11/18 (Tesaro) and AUTH/3102/9/18 (Lilly), the Appeal Board noted that the respondent companies in Case AUTH/3084/9/18 (Boehringer Ingelheim), Case AUTH/3091/9/18 (UCB), Case AUTH/3097/9/18 (Teva), and Case AUTH/3099/9/18 (Allergan), accepted the Panel's rulings of breaches of the Code and had not appealed. The papers and the reports were before the Appeal Board as completed cases.

The Appeal Board agreed that Boehringer Ingelheim, UCB, Teva and Allergan should be contacted and informed of the outcome of the appeals in Cases AUTH/3079/9/18, AUTH/3087/9/18, AUTH/3118/11/18 and AUTH/3102/9/18. The PMCPA Constitution and Procedure did not cover this unusual situation where more than one company was involved in a similar set of circumstances and the Appeal Board had taken a different view to the Panel. Boehringer Ingelheim, UCB, Teva and Allergan were offered the opportunity to appeal out of time and the appeal process would operate in the usual way. The Appeal Board noted that each case's circumstances might differ, and the result of any appeal could not be guaranteed. UCB and Allergan declined the opportunity to appeal. Boehringer Ingelheim and Teva accepted the opportunity to appeal.

APPEAL BY BOEHRINGER INGELHEIM

Boehringer Ingelheim appealed the Panel's ruling of a breach of Clause 9.1 in relation to a trial identified to be within scope of the Goldacre *et al* article published on-line in the British Medical Journal on 12 September 2018.

Summary of Boehringer Ingelheim's response to the PMCPA complaint

Boehringer Ingelheim submitted that it took compliance with all global and national regulations and requirements very seriously. For clinical trial disclosure Boehringer Ingelheim had a dedicated group in Germany who oversaw clinical trial transparency, ensuring requirements for trial disclosure were met. Boehringer Ingelheim had a publicly available corporate website where its clinical transparency policy, trial results, lay summaries and access to trial data and documents were posted. By clicking on the Boehringer Ingelheim product involved in trial(s) the reader was also directed to the ClinicalTrials.gov and EUCTR.

Boehringer Ingelheim submitted that its transparency policy went beyond the requirement for disclosure of trials since 2004 by disclosing results of all trials initiated on or after 1 January 1998.

Boehringer Ingelheim submitted that it had already identified the 7 trials that appeared not to have results according to Table 4 of the BMJ article, explaining that:

- All 7 trials were legacy studies, which completed between 2004 and the cut-off date 21 July 2013 where results could be posted in a summary (synopsis) pdf format on EUCTR, the EMA platform.

- However, on receipt of the complaint, the identity of these 7 trials was personally checked via e-mail by Boehringer Ingelheim's German Disclosure Group with Nicholas DeVito, one of the BMJ authors to confirm the 7 trials on 2 October 2018.

Boehringer Ingelheim summarised these 7 trials as follows:

- Four studies were never started and therefore had no trial results and <u>should not</u> have triggered disclosure.

  The error arose because a competent authority in one of the proposed countries ticked the wrong box 'completed' and since the EMA platform did not allow deletion of records, these studies were inappropriately flagged for disclosure. The issue was resolved by July 2018 (before the publication of the Goldacre article following an internal check of Boehringer Ingelheim's disclosure status) by Boehringer Ingelheim submitting a statement confirming the trial was cancelled before starting and so no results were possible.

  - The remaining 3 studies did complete. In response Boehringer Ingelheim had confirmed that:

    - 2 trials did not involve the UK at all.
    - 1 trial (called the "2NN Long Term Follow Up" and given a Boehringer Ingelheim trial number of 1100.1454, with EudraCT number 2004-

000623-16) did have UK trial sites and completed (trial report) on 1 October 2007.

Boehringer Ingelheim submitted that on further investigation of this trial (1100.1454) in its clinical trial master database, the last UK subject completed on 15 December 2005 with last patients completing outside of the UK on 30 April 2007. In addition, Boehringer Ingelheim had already discovered the omission of these 3 trial results and it had submitted the results synopses appearing on EUCTR on 17 February 2018, some seven months before the publication of the BMJ article.

Boehringer Ingelheim submitted that in its defence it had decided to follow the PMCPA's own guidance available from previous trial disclosure cases, in particular the PMCPA developed decision tree (published in PMCPA's ruling for Case AUTH/2763/5/15 which appeared in the August 2015 Code of Practice Review). So for the 7 trials the PMCPA referred to in Table 4 of the BMJ article, and following the PMCPA's decision tree, Boehringer Ingelheim had responded as follows:

- 4 trials never started, so no results could be disclosed.
- 2 trials, had no UK involvement, so outside of the UK Code.
- 1 trial (1100.1454, the 2NN Long Term Follow Up trial), had UK involvement, but <u>was not</u> required to disclose trial results under the Code according to the PMCPA's decision tree, as nevirapine (the drug which patients had been treated with) was first licensed on 5 February 1998 and the trial finished before 31 October 2008. For ease of reference Boehringer Ingelheim provided a marked up version of the decision tree for this trial.

Summary of the findings of the PMCPA

Boehringer Ingelheim noted from the Panel ruling that:

- In relation to disclosure of trials '…only those with a UK nexus would be considered within the scope of the Code'

- The Code did not explicitly refer to publication on the EUCTR. Clause 13.1 referred 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'.

  Furthermore that 'According to the 2009 Joint Position, publication of clinical trials results in any free, publicly access internet-based clinical trials database should achieve the intended objective'.

- The Panel had applied the 2016 Code. Boehringer Ingelheim noted that no reference was made to the PMCPA published decision tree which Boehringer Ingelheim had followed.

- That Clause 9.1 and not Clause 13.1 would be considered for this complaint in relation to 'matters raised by Goldacre *et al*'.

Boehringer Ingelheim noted that the Panel had ruled as follows:

- No ruling was made in relation to Clause 13.1.

- In relation to the 4 trials that never started, the Panel ruled no breach of Clauses 1.11, 9.1 and 2.

- In relation to the 2 trials that did complete but had no UK involvement whatsoever, the Panel confirmed the matter did not come within the scope of the Code, so no breach was ruled.

In relation to the one remaining trial (1100.1454, the 2NN Long Term Follow Up trial), which had UK trial sites, the Panel ruled:

- A breach of Clause 9.1 as the 'complaint concerned the publication of trial results on the EUCTR.' and the "results did not appear to be published on EUCTR within the required timeframe".

- No breach of Clause 1.11 as '...there did not appear to have been any formal finding …. that the company has not complied with the relevant laws or regulations'.

- A breach of Clause 2 was considered '…on balance…' not warranted.

In summary Boehringer Ingelheim noted that the Panel ruled a single breach of Clause 9.1 in relation to one trial.

Additional information from Boehringer Ingelheim.

Boehringer Ingelheim submitted that it took pride in its excellent disclosure record, as could be readily seen on the EU trials tracker, built by the institution which employed the authors of the BMJ article. Boehringer Ingelheim was one of the (few) organisation (pharma or academia) that consistently had 100% reported. The FDAAA Trials Tracker based on the ClinicalTrials.gov website also showed Boehringer Ingelheim consistently at 100% compliance. Furthermore, its transparency policy went above and beyond the disclosure requirements for clinical trials, since it additionally disclosed all Boehringer Ingelheim sponsored trial results from 1 January 1998 on its publicly accessible clinical trials disclosure website, so six more additional years of trial results than provided by the EUCTR website.

Boehringer Ingelheim submitted that it based its defence of this complaint on the basis of the PMCPA developed and published decision tree clearly stating that disclosure of the trial 1100.1454 was not required under the Code. Boehringer Ingelheim did this in full knowledge that it stood at 100% compliance on EUCTR at the time of its response, as acknowledged with a '*bravo*' by one of the BMJ authors in e-mail correspondence to its disclosure team in Germany on 2 October 2018.

Boehringer Ingelheim had submitted that it had now taken the opportunity to look into the background of trial 1100.1454, the 2NN Long Term Follow Up trial. As a result of this investigation, of upmost relevance, Boehringer Ingelheim had discovered that **Boehringer Ingelheim was not the Sponsor of trial 1100.1454**, this was International Antiviral Therapy Evaluation Center (IATEC), an academic clinical research organisation based in the Netherlands.

Evidence for this was as follows:

- Section 2 of the Monitoring Manual found in Boehringer Ingelheim's trial master file clearly stated IATEC was the Sponsor and Boehringer Ingelheim UK's involvement as a Collaborator involved monitoring of the trial of behalf of the Sponsor IATEC.

Boehringer Ingelheim submitted that the protocol, written by IATEC for the 2NN Long Term Follow Up did not state who the sponsor was, but that it was 'A Multicenter study of the International Antiviral Therapy Evaluation Center'. The protocol was not in Boehringer Ingelheim's format which was mandatory to use for a Boehringer Ingelheim trial.

- The clinical trial protocol for the original 2NN trial clearly stated IATEC was the sponsor of this original trial, to which 1100.1454 was the 3 year retrospective Long Term Follow Up for patients still on treatment.

- Boehringer Ingelheim's clinical trial master database clearly reported it as an investigator initiated trial and therefore not a Boehringer Ingelheim sponsored trial.

- The entry on Clinical Trials.gov listed the sponsor as IATEC (who registered the trial), with Boehringer Ingelheim as a collaborator.

- An e-mail from May 2004 showed IATEC, not Boehringer Ingelheim, requested a EudraCT number. However, as a retrospective observational trial in fact the trial did not need to be registered on EUCTR.

Boehringer Ingelheim submitted that as a retrospective observational trial, with no trial medication administered, no competent authority approval was required, but as a precaution, Boehringer Ingelheim Limited (UK Affiliate) sent the clinical trial protocol to the MHRA as it was monitoring the trial and additional sampling was required. Unfortunately, in sending the trial protocol to the MHRA, it appeared that the 2NN Long Term Follow Up trial was incorrectly stated as a Boehringer Ingelheim sponsored trial in the UK. Therefore, it was wrongly associated with Boehringer Ingelheim on EUCTR as a consequence.

Boehringer Ingelheim submitted that in light of this further investigation and new information discovered, it now confirmed:

- Boehringer Ingelheim was the not the legal Sponsor of this trial.

- So, it followed that it was not the responsibility of Boehringer Ingelheim to disclose results.

- Furthermore, as the trial was a retrospective observational trial, with the benefit of hindsight the trial should not have been registered on EUCTR (the EU PAS Register was the appropriate place to register such observational trials). For such a trial, no results were required under EMA disclosure requirements.

Boehringer Ingelheim submitted that it was known, but not included in its original response that:

- In late 2017, following an internal check of its systems and EUCTR Boehringer Ingelheim submitted had already discovered the omission of trial results for 1100.1454 (and the 6 other studies which were the discrepancy that Goldacre *et al* reported in their September 2018 article based on a January 2018 download from EUCTR).

- With respect to trial 1100.1454, even though Boehringer Ingelheim was not the sponsor, as the trial was attributed to Boehringer Ingelheim, its dedicated Disclosure Team in Germany posted a copy of the IATEC authored trial results on EUCTR. The trial results synopsis became visible on EUCTR on 17 February 2018, one month after Goldacre *et al* did its download. This explained why at the time of the BMJ article, Boehringer Ingelheim were showing 100% in the EU Trials Tracker as confirmed by Nicholas DeVito in his e-mail to Boehringer Ingelheim's Disclosure Team on 2 October 2018.

- IATEC had presented the results of this trial 2NN LTFU at the 4th International Aids Conference in July 2007 ensuring that results were publicly disclosed at the time.

Notwithstanding the above, Boehringer Ingelheim submitted it based its appeal on the PMCPA decision tree. Applying this, trial 1100.1454 was not subject to disclosure. Therefore, following PMCPA guidance and even if it was assumed BI 1100.1454 was a Boehringer Ingelheim sponsored trial (which Boehringer Ingelheim now knew it was not) then the Code according to the PMCPA did not apply for this trial and Boehringer Ingelheim should not be found in breach.

Conclusion

Boehringer Ingelheim submitted that in light of the invitation to appeal, it had looked into the circumstances of the specific trial. Boehringer Ingelheim did not do this at the time of its original response as it based its defence on the PMCPA decision tree and importantly it already knew that the discrepancy with the 7 trials highlighted in the Goldacre study *et al* had already been identified and rectified long before the publication in the BMJ.

Boehringer Ingelheim had now discovered that it was not the sponsor of trial 1100.1454, the one trial for which Boehringer Ingelheim was held in breach of Clause 9.1. As Boehringer Ingelheim was not the sponsor of this trial, Boehringer Ingelheim could not be held responsible for trial disclosure and therefore it asked that the Appeal Board overturn the decision based on this new information. Boehringer Ingelheim apologised that it did not provide this important information at the time of its original response in October 2018, but as mentioned above, it kept its response simple based on prior PMCPA published guidance (namely the decision tree) which clearly indicated that trial disclosure was not required for this trial.

Boehringer Ingelheim submitted that it had provided further background to demonstrate that it paid the upmost diligence to trial transparency and its requirements under all regulations, laws and codes and maintained high standards at all times.

APPEAL BOARD RULING

The Appeal Board noted that a series of cases had been taken up by the PMCPA as a result of the data published in Goldacre *et al.* Four cases (noted above) were the subject of an appeal by the respondent companies. Each were determined on their own merits but there were a

number of common themes. The Appeal Board now considered two subsequent appeals from Boehringer Ingelheim and Teva.

The Appeal Board noted that Goldacre *et al* formed the basis of the complaint. Goldacre *et al* did not refer to disclosure of clinical trial results and the Joint Position which was covered by Clause 13.1 of the Code. The article assessed companies' compliance with EC guideline 2012/c302/03. The Appeal Board noted that disclosure of clinical trial results on EUCTR was not mentioned in Clause 13 and its supplementary information, or indeed elsewhere in the Code. The Appeal Board noted that the Code was not exhaustive and in such circumstances the Appeal Board did not consider it unreasonable to consider the subject matter of the complaint in relation to Clause 9.1. In this regard the Appeal Board noted the long-established broad application of Clause 9.1 to promotional and non-promotional materials and activities including matters within the scope of the Code but not expressly referred to. The Appeal Board did not consider that a ruling of a separate clause was required as a condition precedent to ruling under Clause 9.1; in the Appeal Board's view, Clause 9.1 could be ruled upon in isolation.

The Appeal Board noted that Article 57(2) of Regulation (EC) No 726/2004 and Article 41(2) of Regulation (EC) No 1901/2006 required that clinical trial data be published on EUCTR. European Commission (EC) guideline 2012/c302/03 gave guidance as to when the clinical trial results data should be published. According to the guideline posting of results of clinical trials which ended one year or more prior to finalisation of the programming of the relevant database, should be done within 24 months of finalisation of that programming. According to the 'What's New' section of the EudraCT public website (post-dated 13 January 2016), the deadline for submission of these results was 21 December 2016. This date was referred to in Goldacre *el al*. In this regard, it appeared to the Appeal Board that whilst the regulation mandated disclosure of results on EUCTR, the EC guideline and other material advised companies how to comply with the regulation including in relation to the timing of such disclosures. The Appeal Board considered that it was within the spirit of the Code and good practice to comply with the EC guideline in question.

The Appeal Board noted that, where companies had merged or the rights to a particular product had been bought or sold, there appeared to be difference of opinion as to which company would be responsible for posting the retrospective results. There were also said to be difficulties in correcting information once posted.

The Appeal Board also noted that, according to Goldacre *et al*, Phase I trials that were not part of a paediatric plan did not need to be disclosed.

The Appeal Board noted that Goldacre *et al* assessed all relevant trials on the EUCTR database including those with no UK nexus which were not covered by the Code. There might therefore be a difference between a company's overall disclosure rate and the disclosure rate of those clinical trials with a UK nexus. The results of trials on the registry which did not have a UK nexus and were not disclosed still needed to be disclosed on the registry and the failure to do so would potentially be covered by another code of practice in the relevant jurisdiction.

The Appeal Board noted Boehringer Ingelheim had published trial results for 83 of 90 trials. The Appeal Board noted the data in Goldacre *et al* in that the results of 7 of Boehringer Ingelheim's due trials had results due and yet they had not been reported on EUCTR; the disclosure percentage was 92.2%. Boehringer Ingelheim submitted that one of the trials at issue was conducted in UK and was, therefore, subject to the Code. The Appeal Board noted its comment

above about trials with no UK nexus. The trial (trial 1100.1454), with a UK nexus was at issue in the appeal.

The Appeal Board noted that the Panel had ruled a breach of Clause 9.1 for Boehringer Ingelheim's failure to disclose within the time indicated by the guidance in relation to one trial (trial 1100.1454) and this was subject to the appeal.

The Appeal Board considered that there would be a difference between action to deliberately hide clinical trial data or systematic failure resulting in non or late disclosure and late disclosure of results as part of a retrospective exercise contrary to non-mandatory timelines due to mitigating factors. The Appeal Board, nonetheless, noted its view above about good practice and disclosure in accordance with the EC guideline.

The Appeal Board noted that Boehringer Ingelheim's submission that it had discovered it was not the sponsor of the trial 1100.1454. The sponsor was International Antiviral Therapy Evaluation Center (IATEC), an academic clinical research organisation based in the Netherlands. Boehringer Ingelheim had been monitoring the study but it had been listed as the sponsor in error. The Appeal Board further noted Boehringer Ingelheim's submission that trial 1100.1454 was a retrospective observational trial, with no trial medication administered and consequently did not require to be published on EUCTR.

The Appeal Board noted, however, that Boehringer Ingelheim had published the results from trial 1100.1454, on 17 February 2018 on EUCTR which was before it was notified of the complaint. The Appeal Board noted that the trial was also published in scientific literature. The Appeal Board noted from Boehringer Ingelheim's submission that at the time of the complaint its disclosure percentage on the EUCTR database was 100%.

Whilst the Appeal Board was concerned about the apparent failure to disclose the summary results of trial 1100.1454 on EUCTR within the timelines advised by the EC guideline and other relevant advice, it noted Boehringer Ingelheim's submission that it was not the sponsor of the trial nor was the trial one that needed to be disclosed on EUCTR. Noting both the exceptional circumstances of this case, and that Boehringer Ingelheim was not the sponsor of the trial, the Appeal Board did not consider that the late posting of the result of one trial on the EUCTR as part of a retrospective exercise warranted a breach of Clause 9.1 as far as Boehringer Ingelheim was concerned. The Appeal Board ruled no breach of Clause 9.1. The appeal was successful.

Complaint received **12 September 2018**

Case completed **22 January 2020**