CASE AUTH/3090/9/18 ***NO BREACH OF THE CODE***

DIRECTOR v NOVARTIS

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 Novartis 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 Novartis had previously been ruled in breach of the 2008 Code in relation to its failure to disclose the results of studies on Ilaris (canakinumab) within the permitted timeframe an alleged breach of undertaking was raised.

The detailed response from Novartis 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 fifty-eight Novartis' due trials had not been reported; the disclosure percentage was 87.7%.

The Panel noted Novartis' submission that in its review of the data for Novartis trials on 23 October 2018, 1304 studies were listed, of which 497 were 'due trials' with 473 listed as 'due trials with results'; this implied that 24 were due trials without results.

The Panel noted Novartis' submission that all 24 trials were sponsored by non-UK organisations and only 4 had UK sites. The Panel considered that 20 trials did not have any UK involvement and therefore in relation to these 20 trials, the matter did not come within the scope of the UK Code and no breach of the Code was ruled.

The Panel noted Novartis' submission that of the 4 trials with UK sites, two were cancelled with no patients (2013-002201-66 and 2012-003348-63). The Panel noted that trial 2013-002201-66 was started on 1 November 2013 but it was unclear of the date it prematurely ended. Trial 2012-003348-63 started on 9 February 2013 and ended prematurely on 25 July 2013. There were no results to be disclosed for either trial and the Panel therefore ruled no breaches of the Code including no breach of Clause 2 in relation to trials 2012-003348-63 and 2013-002201-66.

The Panel noted Novartis' submission that trial 2012-003010-14 was a sub-study (with UK involvement) of a global trial 2010-022970-14 which was not yet complete; it therefore did not have results to post. The Panel noted that as the trial was ongoing there was no requirement for the results to be posted yet, therefore the Panel made no ruling with regard to this trial.

The Panel noted Novartis' submission that the final trial (2004-001473-25) was an expanded access program and should not have been submitted to the EUCTR for trial disclosure. The trial started on 27 January 2005 and completed on 24 February 2014. There was no evidence before the Panel about whether the results of expanded access programs were required to be disclosed. The basis of the complaint was Goldacre *et al* which was silent on this point. The Panel therefore ruled no breaches of the Code including no breach of Clause 2 in relation to this trial.

The Panel noted Novartis' submission that based on ongoing and regular reviews by the Novartis Global Disclosure team it identified 58 due trials without results.

The Panel noted Novartis' submission, that two trials (2011-003603-37 and 2011-003573-28) were vaccine studies. Influenza vaccines were sold to Seqirus in 2015 and became their responsibility after that date.

The Panel noted Goldacre *et al* which stated that 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. 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.

The Panel noted that it appeared from the information provided that the circumstances were such that on 21 December 2016 Novartis was not responsible for the disclosure of the trial results at issue. The Panel considered that in the particular circumstances of this

case as far as Novartis was concerned the matter did not come within the scope of the Code.

The Panel noted Novartis' submission that thirteen trials, of which only two had UK sites, were cancelled with no patients. There were no results to be disclosed. The Panel therefore ruled no breaches of the Code including no breach of Clause 2 in relation to the two trials with UK involvement.

The Panel noted that the remaining 11 trials did not have any UK involvement and therefore in relation to these 11 trials, the matter did not come within the scope of the UK Code and no breach of the Code was ruled.

The Panel noted Novartis' submission that three trials (2012-005507-40, 2010-023032-17 and 2008-003883-20) which were expanded access programs and two trials (2004-000829-30 and 20110003065-15) which were observational studies did not have any UK involvement. The Panel considered therefore that these trials did not come within the scope of the UK Code and no breach of the Code was ruled.

The Panel noted Novartis' submission that a further two trials (2012-002859-42 and 2005-003002-28) both completed but did not include any UK involvement. The Panel considered that as there was no UK involvement these two trials did not come within the scope of the UK Code and no breach of the Code was ruled.

The Panel noted Novartis' submission that trial 2014-001085-10 was conducted in Germany and sponsored by Novartis UK and so was within the scope of the Code. The Panel noted Novartis' submission, however, the last patient last visit date for this study was captured incorrectly as May 2017 instead of September 2017 so the EUCTR system may have been showing 'no results' when the authors searched the data. This study has had results posted on the EUCTR and now appeared as a due trial with results. The Panel noted that Goldacre *et al* stated 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. In the Panel's view this trial did not fall within the scope of the complaint and the Panel made no ruling in this regard.

The Panel noted Novartis' submission that trial 2011-000365-12, April 2011, was completed and included UK sites; it was a phase 1 study of a product in development, with all development programs discontinued in 2017. The Panel noted that it was not clear what date the trial ended. The Panel noted Novartis' submission that results were posted within the required timelines to the EMA portal, but the EUCTR might not have been updated when the BMJ publication authors reviewed the data. The Panel noted Novartis' submission that it had submitted a ticket to the EMA to release the result and the study now appeared as a due trial with results and it should not be counted as late as a result of Novartis' actions. The Panel further noted that according to Goldacre *et al* Phase I trials were exempt unless they were denoted as being part of a paediatric investigation plan. The Panel noted that there was no evidence that trial 2011-000365-12 was part of a paediatric investigation plan and from the information before it, it appeared that there was an error at EMA which resulted in the results not being published within the required timeline. The Panel therefore ruled no breaches of the Code including no breach of Clause 2.

The Panel noted Novartis' submission that thirty-two trials (of which 10 included UK sites) were completed studies that required disclosure of trial results but Novartis was discussing how this should occur with the EMA and EUCTR. The Panel noted Novartis' submission that the results of all 32 trials results had been appropriately posted publicly on CT.gov and Novartis Clinical Trial Results website.

The Panel noted that the results of these 10 trials had not been posted on EUCTR within the required timelines due to a dispute between Novartis and EMA with regard to errors caused by the EUCTR system when disclosing results. It was unclear from the evidence before the Panel where the fault lay in relation to the delay in publication. In the exceptional circumstances of this case noting that Novartis was in communications with EMA to resolve these issues since 2015 and Goldacre *et al* was silent on this point the Panel ruled no breaches of the Code including no breach of Clause 2.

The Panel noted that the further 22 trials had no UK involvement. The Panel considered that these trials did not come within the scope of the UK Code and no breach of the Code was ruled.

Given the rulings above, the Panel considered that there was no breach regarding the undertaking given by Novartis in Case AUTH/2662/11/13 and no breaches of the Code including no breach of Clause 2 was ruled.

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 Novartis 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 Novartis were as follows:

Sponsors with highest proportion of trials reported

Sponsor	Total trials on EUCTR	Due trials	Due trials with results	% reported
Novartis	1,260	473	415	87.7

When writing to Novartis 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 Novartis 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 Ilaris (canakinumab) within the permitted timeframe it was also asked to bear in mind Clauses 2, 9.1 and 29 in this regard.

RESPONSE

Novartis submitted that in the BMJ publication 415 out of 473 'due trials' were identified as 'due trials with results'; this suggested that the results of 58 trials had not been appropriately disclosed. Novartis contacted the authors to ask for the data on which their review and publication were based. In response the lead author stated that they could not provide the 'snapshot' of the EU Clinical Trials Register (EUCTR) data that the publication was based on and that the company should review the EU Trial Tracker for its information needs.

Novartis submitted that due to ongoing efforts related to data quality and disclosure, and other factors that might affect data presented on the EUCTR, a recent review of the EU Trials Tracker site presented results for Novartis trials different to those reported in the BMJ. As a result, Novartis was not able to interrogate the EU trials Tracker data to understand specific issues raised in the BMJ but had relied on reviews completed by the Global Disclosure team. Furthermore, there were aspects of the EUCTR system that had created issues and concerns related to how trials were disclosed, and this had impacted Novartis' disclosure through this portal.

Novartis stated that in its review of the data for Novartis trials on 23 October 2018, 1304 studies were listed, of which 497 were 'due trials' with 473 listed as 'due trials with results'; this implied that 24 were due trials without results.

Of these 24 trials all were sponsored by non-UK organisations and only 4 included UK sites.

Of these 4 trials, Novartis did not consider that any required disclosure as required by the Code or by the EUCTR:

- 2 were cancelled with no patients and, therefore, no results to be disclosed, but appeared as due trials without results. The EUCTR had no ability to reflect that results were not due for trials cancelled with no patients. The European Medicines Agency (EMA) was made aware of this in 2016. These trials should not be listed as due trials without results

- 1 trial (2012-003010-14) was a sub-study (with UK involvement) of a global trial (2010-022970-14). The global trial has an expected last patient last visit date of March 2020 and the sub-study should not have had different details listed for it. As the global trial was not yet complete it did not have results to post and should not be considered as a due trial without results
- 1 was an expanded access programme and should not have been submitted to the EUCTR for trial disclosure.

In summary, for all studies that were highlighted as potential 'due trials without results' as of 23 October 2018, 4 fell within scope of the Code but none were required as per the Code, Joint Positions or EC requirements.

With regard to the due trials without results, as reported in the BMJ article, Novartis provided the following information, based on ongoing and regular reviews by the Novartis Global Disclosure Team:

- 2 trials (2011-003603-37 and 2011-003573-28) were vaccine studies:
    - Influenza vaccines were sold to Seqiris in 2015 and became their responsibility after that date.
    - Neither study had a sponsor based in the UK or included UK sites and were, therefore, outside the scope of the Code.
    - Both studies now had results included on EUCTR, but EU Trials Tracker continued to list them as due trials without results.
- 13 trials were cancelled with no patients and, therefore, no results to be disclosed, but appeared as due trials without results. Of these studies 2 included UK sites. The EUCTR had no ability to reflect that results were not due for trials cancelled with no patients. EMA was made aware of this situation in 2016. These trials should not be listed as due trials without results.
- 3 trials were expanded access programmes (2012-005507-40 and 2008-003883-20 (no UK involvement) and 2004-001473-25 (UK involvement)). Two did not include UK involvement so were outside the scope of the Code. None required EUCTR disclosure but were listed in EUCTR in error. As these projects were expanded access programmes and not 'clinical trials' they were out of scope for disclosure on the EUCTR.
- 2 trials were observational trials (2004-000829-30, 2011-003065-15), did not include UK involvement and did not require EUCTR disclosure but were listed in the EUCTR in error. As these studies did not include UK involvement they were out of scope of the Code, furthermore they were not 'clinical trials' as requiring disclosure on the EUCTR.
- 1 trial (2010-023032-17), was an expanded treatment protocol and did not include UK involvement, so was outside the scope of the Code. This trial was listed under 2 separate clinical trial applications (CTAs) in error, with only one having the results posted against its listing. Duplicate results had now been posted against the other CTA listing.
- 1 trial was completed (2012-002859-42) but had no UK involvement, so was outside the scope of the Code. This study was eligible for disclosure and results were posted with the EUCTR system on time, but the system had failed to post those results appropriately.

- 1 trial was completed (2005-003002-28) but had no UK involvement, so was outside the scope of the Code. This trial was appropriately disclosed on the Novartis trials disclosure site and should have appeared on the EUCTR but Novartis could not find a posting receipt from the EMA. Novartis had re-released the results and raised this with the EMA and the study now appeared as a due trial with results.
- 1 completed trial (2014-001085-10) was conducted in Germany and sponsored by Novartis UK and so was within the scope of the Code. However, the last patient last visit date for this study was captured incorrectly (May 2017 instead of Sept 2017) so the EUCTR system may have been showing 'no results' when the authors searched the data. The UK Authority had the responsibility to correct the date. This study has had results posted on the EUCTR and now appeared as a due trial with results.
- 1 trial (2011-000365-12, April 2011) was completed and included UK sites. This was a phase 1 study of a product in development, with all development programmes discontinued in 2017. Results were posted within the required timelines to the EMA portal, but the EUCTR might not have been updated when the BMJ publication authors reviewed the data. Novartis had submitted a ticket to the EMA to release the result and the study now appeared as a due trial with results. This should not be counted as late as a result of Novartis' actions.
- 1 trial (2012-003010-14) was a sub-trial (with UK involvement) of a global trial (2010-022970-14). The global study had an expected last patient last visit date of March 2020 and the sub-study should not have had different details listed for it. As the global study was not yet complete it did not have results to post and should not be considered as a due trial without results.
- 32 trials (of which 10 included UK sites) were completed trials that required disclosure of trial results but Novartis was discussing how this should occur with the EMA and EUCTR. Novartis did not believe these trials should be listed as due trials without results because:
    - Novartis was fully aligned with the need for disclosure consistent with the requirements presented in the relevant Joint Positions and had posted results for these 32 trials appropriately (as per Code and Joint Position requirements)
    - Novartis believed that any results made public should align with the clinical study report and be identical to the results posted publicly on CT.gov and Novartis Clinical Trial Results website, where all Novartis trials are appropriately disclosed, including these 32
    - The EMA was apprised by Novartis in July 2015 that the EUCTR system caused errors in the data posted and made it clear that results would not be released by Novartis, due to the risk of flawed disclosure, until either:
    1 The EMA placed a disclaimer on its website, or
    2 The EMA provided a solution for the EUCTR application issue
    - In April 2017 the EMA informed Novartis that it would not fix the system as it was working on the new EU portal
    - Novartis agreed to release the results to the EUCTR, despite the risk that the results could be modified by the system, on the condition that a statement describing the potential discrepancy, and signposting to where an original results posting could be found, was added to each flawed record prior to release on the EUCTR
    - Novartis notified the EMA that it was releasing the results and the EMA acknowledged the letter during the summer of 2018

- 32 completed trial results were released in June/July 2018 with a note that the results had flaws (9999/cross over) caused by the EUCTR and to go to www.novartisclinicaltrials.com for the correct results.

In summary, in relation to the 58 studies highlighted as potential 'due trials without results', Novartis was unable to review the actual study database that was used to provide the listing presented in the BMJ. Based on reviews done by the Novartis Global Disclosure Team, the company was able to identify studies that were likely to have contributed to the 58 highlighted. Of these, many did not fall within the scope of the Code or did not require disclosure of study results by Novartis (due to, for example, being cancelled, currently ongoing, were outside the requirements of trial disclosure or had transitioned to other organisations) or had been actioned appropriately by Novartis but issues with other organisations' systems had resulted in delayed disclosure. An additional 32 studies were under discussion with the EMA on how best to disclose them. They had not had their results posted to the EMA for disclosure on the EUCTR, due to the way that the EUCTR system handled the information, but Novartis intended to have them posted onto the EUCTR in a way that was consistent with other public postings of the data. This had subsequently been resolved, with results and appropriate signposts appearing on the EUCTR.

Based on the above, Novartis did not consider that there had been breaches of the Code and, therefore, there had been no breach of undertaking.

Furthermore, Novartis considered that it had acted wholeheartedly with the spirit of trial disclosure and conformed to the requirements of the Joint Positions and the Code. Even though trial disclosure on the EUCTR was not explicitly required as part of the Joint Position, Novartis had engaged with this portal with the aim of providing aligned and consistent trial disclosure.

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 fifty-eight Novartis' due trials had not been reported; the disclosure percentage was 87.7%.

The Panel noted Novartis' submission that in its review of the data for Novartis trials on 23 October 2018, 1304 studies were listed, of which 497 were 'due trials' with 473 listed as 'due trials with results'; this implied that 24 were due trials without results.

The Panel noted Novartis' submission that all 24 trials were sponsored by non-UK organisations and only 4 had UK sites. The Panel considered that 20 trials did not have any UK involvement and therefore in relation to these 20 trials, the matter did not come within the scope of the UK Code and no breach of the Code was ruled.

The Panel noted Novartis' submission that of the 4 trials with UK sites, two were cancelled with no patients (2013-002201-66 and 2012-003348-63). The Panel noted that trial 2013-002201-66 was started on 1 November 2013 but it was unclear of the date it prematurely ended. Trial 2012-003348-63 started on 9 February 2013 and ended prematurely on 25 July 2013. There were no results to be disclosed for either trial and the Panel therefore ruled no breach of Clauses 1.11, 9.1 and 2 in relation to trials 2012-003348-63 and 2013-002201-66.

The Panel noted Novartis' submission that trial 2012-003010-14 was a sub-study (with UK involvement) of a global trial 2010-022970-14 which was not yet complete; it therefore did not have results to post. The Panel noted that as the trial was ongoing there was no requirement for the results to be posted yet, therefore the Panel made no ruling with regard to this trial.

The Panel noted Novartis' submission that the final trial (2004-001473-25) was an expanded access program and should not have been submitted to the EUCTR for trial disclosure. The trial started on 27 January 2005 and completed on 24 February 2014. There was no evidence before the Panel about whether the results of expanded access programs were required to be disclosed. The basis of the complaint was Goldacre *et al* which was silent on this point. The Panel therefore ruled no breach of Clauses 9.1, 1.11 and 2 in relation to this trial.

The Panel noted Novartis' submission that based on ongoing and regular reviews by the Novartis Global Disclosure team it identified 58 due trials without results.

The Panel noted Novartis' submission, that two trials (2011-003603-37 and 2011-003573-28) were vaccine studies. Influenza vaccines were sold to Seqirus in 2015 and became their responsibility after that date.

The Panel noted Goldacre *et al* which stated that 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. 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.

The Panel noted that it appeared from the information provided that the circumstances were such that on 21 December 2016 Novartis was not responsible for the disclosure of the trial results at issue. The Panel considered that in the particular circumstances of this case as far as Novartis was concerned the matter did not come within the scope of the Code and it therefore ruled no breach in relation to these two trials. Both trials were taken up with Seqirus (Case 3117/11/18).

The Panel noted Novartis' submission that thirteen trials, of which only two had UK sites, were cancelled with no patients. There were no results to be disclosed. The Panel therefore ruled no breach of Clauses 1.11, 9.1 and 2 in relation to the two trials with UK involvement.

The Panel noted that the remaining 11 trials did not have any UK involvement and therefore in relation to these 11 trials, the matter did not come within the scope of the UK Code and no breach of the Code was ruled.

The Panel noted Novartis' submission that three trials (2012-005507-40, 2010-023032-17 and 2008-003883-20) which were expanded access programs and two trials (2004-000829-30 and 20110003065-15) which were observational studies did not have any UK involvement. The Panel considered therefore that these trials did not come within the scope of the UK Code and no breach of the Code was ruled.

The Panel noted Novartis' submission that a further two trials (2012-002859-42 and 2005-003002-28) both completed but did not include any UK involvement. The Panel considered that as there was no UK involvement these two trials did not come within the scope of the UK Code and no breach of the Code was ruled.

The Panel noted Novartis' submission that trial 2014-001085-10 was conducted in Germany and sponsored by Novartis UK and so was within the scope of the Code. The Panel noted Novartis' submission, however, the last patient last visit date for this study was captured incorrectly as May 2017 instead of September 2017 so the EUCTR system may have been showing 'no results' when the authors searched the data. This study has had results posted on the EUCTR and now appeared as a due trial with results. The Panel noted that Goldacre *et al* stated 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. In the Panel's view this trial did not fall within the scope of the complaint and the Panel made no ruling in this regard.

The Panel noted Novartis' submission that trial 2011-000365-12, April 2011, was completed and included UK sites; it was a phase 1 study of a product in development, with all development programs discontinued in 2017. The Panel noted that it was not clear what date the trial ended. The Panel noted Novartis' submission that results were posted within the required timelines to the EMA portal, but the EUCTR might not have been updated when the BMJ publication authors reviewed the data. The Panel noted Novartis' submission that it had submitted a ticket to the EMA to release the result and the study now appeared as a due trial with results and it should not be counted as late as a result of Novartis' actions. The Panel further noted that according to Goldacre *et al*, Phase I trials were exempt unless they were denoted as being part of a paediatric investigation plan. The Panel noted that there was no evidence that trial 2011-000365-12 was part of a paediatric investigation plan and from the information before it, it appeared that there was an error at EMA which resulted in the results not being published within the required timeline. The Panel therefore ruled no breach of Clauses 1.11, 9.1 and 2.

The Panel noted Novartis' submission that thirty-two trials (of which 10 included UK sites) were completed studies that required disclosure of trial results but Novartis was discussing how this should occur with the EMA and EUCTR. The Panel noted Novartis' submission that the results of all 32 trials results had been appropriately posted publicly on CT.gov and Novartis Clinical Trial Results website. The Panel noted Novartis' submission that the EMA was apprised by Novartis in July 2015 that the EUCTR system caused errors in the data posted and made it clear that results would not be released by Novartis, due to the risk of flawed disclosure, until either the EMA placed a disclaimer on its website, or the EMA provided a solution for the EUCTR application issue; the 32 completed trial results were released in June/July 2018 with a note that the results had flaws (9999/cross over) caused by the EUCTR and to go to www.novartisclinicaltrials.com for the correct results.

The Panel noted Novartis' submission that the results of the 10 trials with UK involvement had been posted in line with the requirements of the relevant Joint Positions. The Panel noted that the results of these 10 trials had not been posted on EUCTR within the required timelines due to a dispute between Novartis and EMA with regard to errors caused by the EUCTR system when disclosing results. It was unclear from the evidence before the Panel where the fault lay in relation to the delay in publication. In the exceptional circumstances of this case noting that Novartis was in communications with EMA to resolve these issues since 2015 and Goldacre *et al* was silent on this point the Panel ruled no breach of Clauses 9.1, 1.11 and 2.

The Panel noted that the further 22 trials had no UK involvement. The Panel considered that these trials did not come within the scope of the UK Code and no breach of the Code was ruled.

Given the rulings above, the Panel considered that there was no breach regarding the undertaking given by Novartis in Case AUTH/2662/11/13 and no breach of Clauses 29, 9.1 and 2 was ruled.

Complaint received **12 September 2018**

Case completed **15 May 2019**