CASE AUTH/2908/11/16

DIRECTOR v BAYER

Clinical trial disclosure (Xofigo)

A study published online in Current Medical Research & Opinion (CMRO) on 25 November 2016 was entitled 'Clinical trial transparency update: an assessment of the disclosure of results of company-sponsored trials associated with new medicines approved in Europe in 2013'. The study authors were B R Deane, a freelance consultant in pharmaceutical marketing and research and Dr J Sivarajah, Head of Medical Affairs, ABPI. Publication support for the study was funded by the ABPI.

The study surveyed various publicly available information sources for clinical trial registration and disclosure of results searched between 1 May and 31 July 2015. It covered 34 new medicines (except vaccines) from 24 companies that were approved by the European Medicines Agency (EMA) in 2013. It included all completed company-sponsored clinical trials conducted in patients and recorded on a clinical trial registry and/or included in a European Public Assessment Report (EPAR). The CMRO publication did not include the specific data for each product. This was available in the supplemental information via a website link. Neither the study nor the supplemental information identified specific clinical trials. The study did not assess the content of disclosure against any specific requirements.

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

The summary output for each medicine set out the sources for all trials found, irrespective of sponsor and an analysis of publication disclosure in the form of a table which gave details for the studies for Xofigo (radium-223 dichloride).

The detailed response from Bayer is given below.

General detailed comments from the Panel are given below.

The Panel noted the CMRO publication in that one evaluable Phase I trial had not been disclosed within the 12 month timeframe. The disclosure percentage at 12 months measured from the later of the first date of regulatory approval or trial completion date was 88%. The disclosure percentage at 31 July 2015 of trials completed by the end of July 2015 was 88

The Panel noted Bayer's submission that the trial in question was conducted in the UK on 6 patients to explore the bio-distribution, pharmacokinetics, and dosimetry of radium 223; it was neither a confirmatory clinical trial nor an exploratory efficacy trial and it completed on 3 December 2008.

The Panel noted Bayer's interpretation of the 2009 Joint Position that trials '…initiated 6 months after the publication date of this Joint Position should be included in a public clinical trial registry'. It was Bayer's understanding that the trial in question qualified as an 'additional trial' under the 2009 Joint Position as it was not required to be disclosed under the 2008 Joint Position. In the Panel's view, Bayer had mixed up requirements regarding clinical trial registries with those of clinical trial results databases. The 2009 Joint Position clearly stated that the posting of clinical trial results should occur in compliance with the timelines and conditions defined in that Joint Position.

The Panel noted that Xofigo was first licensed and commercially available in May 2013 and this, as stated in the Panel's general comments above, was the trigger date for disclosure. The Second 2012 Code and thus the Joint Position 2009 applied which meant that for all licensed and commercially available medicines, all clinical trials from Phase I onward needed to be disclosed regardless of their completion date. Disclosure had to be within 1 year of the product first being licensed and commercially available or within one year of the trial's completion whichever was later.

The Panel noted on the information before it results from the trial should have been posted on a publicly accessible, internet-based clinical trials database by May 2014. As this had not happened the Panel ruled a breach of the Code. The delay in disclosure meant that high standards had not been maintained and a breach of the Code was ruled.

The Panel noted Bayer's submission that there had been four clinical publications drawn from the results of the trial from 2011 to 2015. Details were provided and all four clinical papers had also been linked to disclosure on clinicaltrials.gov and were publicly accessible with full trial results published online in July 2015 and in print in September 2015. In addition Bayer added the results synopsis to the EudraCT database in May 2016. As the data had been disclosed the Panel considered there was no breach of Clause 2 and ruled accordingly.

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The study referred to the two previously reported studies which covered medicines approved in

Europe in 2009, 2010 and 2011 (Rawal and Deane 2014) and in 2012 (Rawal and Deane 2015). The 2016 study surveyed various publicly available information sources for clinical trial registration and disclosure of results searched between 1 May and 31 July 2015. It covered 34 new medicines (except vaccines) from 24 companies that were approved by the European Medicines Agency (EMA) in 2013. It included all completed company-sponsored clinical trials conducted in patients and recorded on a clinical trial registry and/or included in a European Public Assessment Report (EPAR). The CMRO publication did not include the specific data for each product. This was available in the supplemental information via a website link. Neither the study nor the supplemental information identified specific clinical trials. The CMRO study did not assess the content of disclosure against any specific requirements.

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

COMPLAINT

The study assessed the proportion of trials for which results had been disclosed on a registry or in the scientific literature either within 12 months of the later of either first regulatory approval or trial completion, or by 31 July 2015 (end of survey). Of the completed trials associated with 34 new medicines licensed to 24 different companies in 2013, results of 90% (484/539) had been disclosed within 12 months and results of 93% (500/539) had been disclosed by 31 July 2015.

Tresiba

The supplemental information gave details of disclosure of clinical trial results for each product irrespective of sponsor. The data for Xofigo (radium-223 dichloride) were as follows:

Phase	Total	Un-evaluable	Evaluable	Disclosed in 12-month timeframe	Disclosure Percentage	Complete before 31 July 2015	Disclosed at 31 July 2015	Disclosure percentage at 31 July 2015
Phase I & II	8	1	7	6	86%	7	6	86%
Phase III	1	0	1	1	100%	1	1	100%
Phase IV	0	0	0	0		0	0	
Other	0	0	0	0		0	0	
Total	**9**	**1**	**8**	**7**	**88%**	**8**	**7**	**88%**

Footnote (company communication): The one remaining undisclosed phase I trial was originally out of scope of disclosure requirements; results will be posted on EudraCT.

The explanation of terms given in the documentation was as follows:

Total	Total number of company sponsored trials identified which were completed by 31 July 2015
Unevaluable	Trials with completion date within the last 12 months or key dates missing – excluded from the analysis
Evaluable	Trials with all criteria present including dates, and hence the base number of trials which could be evaluated for the assessment
Results disclosed in 12 month timeframe	Evaluable trials which were disclosed within the target 12 months measured from the later of either first regulatory approval date in Europe or the US, or trial completion date
Disclosure percentage	Proportion of evaluable trials which were disclosed within 12 months measured from the later of either first regulatory approval date in Europe or the US, or trial completion date
Completed before 31 July 2015	Number of evaluable trials completed before 31 July 2015
Disclosed at 31 July 2015	Number of evaluable trials with results disclosed by 31 July 2015
Disclosure percentage at 31 July 2015	Proportion of evaluable trials which were disclosed by 31 July 2015

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

RESPONSE

Bayer stated that Radium 223's first licence was granted in the US on 15 May 2013 for the treatment of patients with symptomatic bone metastatic, castrate-resistant prostate cancer; and within Europe on 13 November 2013 for the same indication. The date of first commercialisation was May 2013 in the US and January 2014 in the UK. Therefore the company submitted that the Second 2012 Edition of the Code was relevant.

With regard to the one trial which had not been disclosed Bayer noted the footnote which read 'The one remaining undisclosed Phase I trial was originally out of scope of disclosure requirements; results will be posted on EudraCT'. Details of the trials, UK involvement and disclosure parameters in relation to the publication were provided. The trial in question was Trial #15302 (NCT00667537), a Phase I, open-label, dosimetry, bio-distribution and pharmacokinetic trial of alpharadin in patients with hormone refractory prostate cancer and skeletal metastases. The trial completed on 3 December 2008 and was conducted in the UK on 6 patients to explore the bio-distribution, pharmacokinetics, and dosimetry of radium 223. It was neither a confirmatory clinical trial nor an exploratory efficacy trial.

Bayer considered clinical trial disclosure obligations at a global level; the Global Headquarters based in Germany, provided overarching determinations in such matters. As such, Bayer Plc had no involvement in the analysis and decision-making process regarding the company's overarching determination on whether a clinical trial's results should be disclosed under the relevant Joint Position. Notwithstanding global management of this decision-making process, Bayer Plc acknowledged that as the UK affiliate of a global organisation it was bound to comply with the ABPI Code and the various Joint Positions.

Bayer submitted that the results of Trial #15302 had not been disclosed because globally, the disclosure decision was made with only the Joint Positions without sight of the Decision Tree cited in numerous PMCPA cases from early 2014 onwards.

The company stated that the Joint Position 2008, published one month before Trial #15302 completed, identified which clinical trials were required to be listed and results disclosed. These footnotes could be summarised as stating that disclosure obligations detailed in the Joint Position 2008 were relevant only to confirmatory clinical trials and exploratory efficacy trials, with Phase I clinical trials expressly excluded from the definition of disclosable studies. Bayer submitted that as Trial #15302 was a Phase I clinical trial it fell into this exemption for disclosure purposes; under the Joint Position 2008, Trial #15302 was not required to be disclosed within one year of licensing and commercialisation of Xofigo. However, within 12 months of the publication of the Joint Position 2008 it was updated by the Joint Position 2009 and Bayer looked again to see if its evaluation of non-disclosure of Trial #15302 remained appropriate.

The Joint Position 2009 expanded the disclosure obligations to include Phase I trials, and as such all interventional trials involving human subjects from Phase I and beyond were required to be disclosed. For Trial #15302 this expanded definition of disclosable clinical trial results was considered by Bayer Global to determine if disclosure was now required within one year of licensing.

Bayer referred to the 'Implementation dates' and the section:

> 'Additional trials that fall within the scope of this revised Joint Position and are initiated 6 months after the publication date of this Joint Position should be included in a public clinical trial registry.'

Bayer submitted that Trial #15302 qualified as an 'additional trial' under the Joint Position 2009 as it had not been the subject of disclosure requirements under the Joint Position 2008, but as a Phase I study now fell within the scope of Joint Position 2009. Bayer understood that such Phase I trials were only subject to disclosure requirements if the trial was initiated 6 months after the publication of the Joint Position 2009. Trial #15302 completed on 3 December 2008 and therefore, under Bayer's construction of the above text, it did not fall within the category of 'additional trials' requiring disclosure under the Joint Position 2009. The company submitted that there was no posting obligation for Trial # 15302 under the Joint Position 2009.

Previous Case Guidance

Bayer highlighted the complexity when looking at previous cases, particularly in relation to the correct interpretation on which Joint Position was relevant and whether a Phase I trial which completed prior to 2009, came within scope of disclosure (ie Joint Position 2008 or earlier) even when the date of commercialisation followed thereafter.

The ambiguity surrounding this came from the decision tree used during a number of cases in 2014 all cited in the August 2014 Code of Practice review:

Bayer appreciated that the updated decision tree of June 2015 provided greater clarity around this, however it was not available to Bayer nor, from its understanding, was it in the public domain prior to being provided to the company in December 2016.

Bayer drew attention to a box in the 2014 decision tree which stated:

> 'Was product first licensed and available before 1 November 2008 and/or trial completed on or after 1 November 2008?'

This box contained an and/or which allowed the trial to be considered in variance to the date of commercialisation (this had been removed in the updated decision tree dated June 2015). If the 2014 decision tree was followed in relation to this case then:

Was the product first licensed and available before 1 November 2008 – NO and/OR trial completed on or after 1 November 2008 – Yes. (This created variance from date of licence to the date of trial completion)

The next question on the 2014 decision tree was when did the trial complete, the answer to which in relation to this case would be assigned to the box '1 November 2008 - 30 April 2011' and consideration of the trial in this case under the 2008 Code and the Joint Position 2005.

It was not Bayer's position that this case should be considered under the Joint Position 2005 or the 2008 Code. However Bayer would like to highlight the large degree of ambiguity under which Joint Position Trial #15302 should be considered. Had Bayer Plc sought confirmation regarding its disclosure obligations at the time of licensing and commercialisation of Xofigo and reviewed previous Code cases and particularly the 2014 decision tree, this would have contributed to rather than eliminated the ambiguity surrounding disclosure requirements. The company submitted that this should be taken into consideration by the Panel when reviewing this case.

Disclosure of Trial #15302

Bayer stated it was committed to the principles and obligations placed upon it for disclosure of clinical trial results as set out in both the Joint Position and the Code. Bayer did not consider that Trial #15302 was subject to disclosure, however it was still committed to disclosing the results and there had been 4 clinical publications drawn from the results of this trial from 2011 to 2015. Details were provided and all 4 clinical papers had also been linked to disclosure on clinicaltrials.gov and were publically accessible with full trial results published online in July 2015 and in print in September 2015. In addition Bayer added the results synopsis to the EudraCT database in May 2016. (Result posting on the EU Clinical Trial Database EudraCT was only required since 21 July 2014 with studies with EudraCT number and end of study before 21 July 2013: result synopsis submission to EudraCT was required by 21 Dec 2016).

Bayer therefore submitted that Trial #15302 was not within the scope of disclosure according to the requirements of the Joint Position. As such, Bayer disagreed that any breach of Clauses 21.3 of the Second 2012 Edition of the Code had occurred. In addition, Bayer had demonstrated full disclosure of the trial results for Trial #15302 and as such there was no breach of Clause 9.1 or Clause 2 of the Second 2012 Edition.

GENERAL COMMENTS FROM THE PANEL

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 the CMRO study was published and the complaint proceedings commenced. The Panel noted that the study concluded that of the completed trials associated with 34 new medicines licensed to 24 different companies in 2013, results of 90% had been disclosed within 12 months and results of 93% had been disclosed by 31 July 2015.

The Panel noted that the CMRO publication in question was an extension of previously reported data from two studies, one related to new medicines approved in Europe in 2009, 2010 and 2011 (Rawal and Deane 2014) which found that over three-quarters of all these trials were disclosed within 12 months and almost 90% were disclosed by the end of the study. That 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 leading to 15 cases. The second study found that the results of 90% had been disclosed within 12 months and results of 92% had been disclosed by 31 July 2014. 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 present case was not the subject of external complaint. The study itself formed the basis of the complaint.

The Panel considered that the first issue to be determined was whether the matter was covered by the ABPI Code. If the research 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 such activities came within the scope of the Code such as activities relating to UK health professionals or activities carried out in the UK.

Clause 13.1 of the 2016 and 2015 editions of the Code stated that companies must disclose details of clinical trials in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature.

The relevant supplementary information stated that this clause required the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patient enrolment) and the results of completed trials for medicines licensed for use and commercially available in at least one country. Further information was to be found in the current Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases and the current Joint Position on the Publication of Clinical Trial Results in the Scientific Literature, both at www.ifpma.org.en/ethics/clinical-trials-disclosure.html. Companies must include on the home page of their website, information as to where details of their clinical trials could be found.

The Panel noted that the first Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases was agreed in 2005 by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), the European Federation of Pharmaceutical Industries and Associations (EFPIA), the Japanese Pharmaceutical Manufacturers Association (JPMA) and the Pharmaceutical Research and Manufacturers of America (PhRMA). The announcement was dated 6 January 2005.

The Panel noted that Article 9, Clinical Research and Transparency, of the most recent update of the IFPMA Code of Practice (which came into operation on 1 September 2012) included a statement that companies disclose clinical trial information as set out in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases (2009) and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature (2010). As companies had, in effect, agreed the joint positions their inclusion in the IFPMA Code should not have made a difference in practice to IFPMA member companies but meant that IFPMA member associations had to amend their codes to reflect Article 9. Pharmaceutical companies that were members of national associations but not of IFPMA would have additional disclosure obligations once the national association amended its code to meet IFPMA requirements. The disclosures set out in the joint positions were not required by the EFPIA Codes.

The Panel noted that even if the UK Code did not apply many of the companies listed in the study were members of IFPMA and/or EFPIA.

The Panel considered that it was good practice for clinical trial results to be disclosed for medicines which were first approved and commercially available after 6 January 2005 (the date of the first joint position). This was not necessarily a requirement of the ABPI Codes from that date as set out below.

As far as the ABPI Code was concerned, the Panel noted that the first relevant mention of the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005 was in the supplementary information to Clause 7.5 of the 2006 Code:

> ***'Clause 7.5 Data from Clinical Trials***
>
> *Companies must provide substantiation following a request for it, as set out in Clause 7.5. In addition, when data from clinical trials is used companies must ensure that where necessary that data has been registered in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005.'*

Clause 7.5 of the 2006 Code required that substantiation be provided at the request of health professionals or appropriate administrative staff. Substantiation of the validity of indications approved in the marketing authorization was not required. The Panel considered this was not relevant to the complaint being considered which was about disclosure of clinical trial results. The Joint Position 2005 was mentioned in the supplementary information to Clause 21.5 but this did not relate to any Code requirement to disclose clinical trial results.

In the 2008 ABPI Code (which superceded the 2006 Code and came into operation on 1 July 2008 with a transition period until 31 October 2008 for newly introduced requirements), Clause 21 referred to scientific services and Clause 21.3 stated:

> 'Companies must disclose details of clinical trials.'

The relevant supplementary information stated:

> ***'Clause 21.3 Details of Clinical Trials***
>
> *This clause requires the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information can be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005 (http://clinicaltrials.ifpma.org).*
>
> *Details about clinical trials must be limited to factual and non-promotional information. Such information must not constitute promotion to health professionals, appropriate administrative staff or the public.'*

In the 2011 Code (which superceded the 2008 Code and came into operation on 1 January 2011 with a transition period until 30 April 2011 for newly introduced requirements), the supplementary information to Clause 21.3 was updated to refer to the 2008 IFPMA Joint Position.

In the Second 2012 Edition (which came into operation on 1 July 2012 with a transition period until 31 October 2012 for newly introduced requirements), changes were made to update the references to the joint position and to include the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature. Clause 21.3 now stated:

> *'Companies must disclose details of clinical trials in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature.'*

The relevant supplementary information stated:

> ***'Clause 21.3 Details of Clinical Trials***
>
> *This clause requires the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information can be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical*

Trial Registries and Databases 2009 and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature 2010, both at http://clinicaltrials.ifpma.org.

Details about clinical trials must be limited to factual and non-promotional information. Such information must not constitute promotion to health professionals, appropriate administrative staff or the public.'

The Panel noted that in the 2014 ABPI Code the disclosure requirements which had previously been stated in Clause 21 had been moved to Clause 13. In addition, the supplementary information stated that companies must include on their website information as to where details of their clinical trials could be found. The 2014 Code came into effect on 1 May 2014 for newly introduced requirements following a transition period from 1 January 2014 until 30 April 2014. These requirements were to be found in Clause 13.1 of the 2015 Code. The relevant supplementary information had been amended in the 2015 Code to replace the year of the relevant joint positions with the word 'current', to add a reference to the medicine being licensed and 'commercially available' and to update the website address. The 2015 Code came into effect on 1 May 2015 for newly introduced requirements following a transition period from 1 January 2015 until 30 April 2015. Similarly the 2016 Code came into effect on 1 May 2016 for newly introduced requirements following a transition from 1 January 2016 to 30 April 2016. The study at issue was posted online on 25 November 2016.

The Panel examined the Joint Position on the Disclosure of Clinical Trial Information which was updated on 10 November 2009 and superseded the Joint Position 2008. With regard to clinical trial registries the document stated that all trials involving human subjects for Phase I and beyond at a minimum should be listed. The details should be posted no later than 21 days after the initiation of enrolment. The details should be posted on a free, publicly accessible, internet-based registry. Examples were given. Each trial should be given a unique identifier to assist in tracking. The Joint Position 2009 provided a list of information that should be provided and referred to the minimum Trial Registration Data Set published by the World Health Organisation (WHO). The Joint Position 2009 referred to possible competitive sensitivity in relation to certain data elements and that, in exceptional circumstances, this could delay disclosure at the latest until after the medicinal product was first approved in any country for the indication being studied. Examples were given.

The Panel noted that the matter for consideration related to the disclosure of clinical trial results.

With regard to the disclosure of clinical trial results the Joint Position 2009 stated that the results for a medicine that had been approved for marketing and was commercially available in at least one country should be publicly disclosed. The results should be posted no later than one year after the medicine was first approved and commercially available. The results for trials completed after approval should be posted one year after trial completion – an adjustment to this schedule was possible to comply with national laws or regulations or to avoid compromising publication in a peer-reviewed medical journal.

The Joint Position 2009 included a section on implementation dates and the need for companies to establish a verification process.

The Joint Position 2005 stated that the results should be disclosed of all clinical trials other than exploratory trials conducted on a medicine that was approved for marketing and was commercially available in at least one country. The results generally should be posted within one year after the medicine was first approved and commercially available unless such posting would compromise publication in a peer-reviewed medical journal or contravene national laws or regulations. The Joint Position 2008 was dated 18 November 2008 and stated that it superseded the Joint Position 2005 (6 January and 5 September). The Joint Position 2008 stated that results should be posted no later than one year after the product was first approved and commercially available in any country. For trials completed after initial approval these results should be posted no later than one year after trial completion. These schedules would be subject to adjustment to comply with national laws or regulations or to avoid compromising publication in a peer reviewed medical journal.

The Joint Position on the Publication of Clinical Trial Results in the Scientific Literature was announced on 10 June 2010. It stated that all industry sponsored clinical trials should be considered for publication and at a minimum results from all Phase III clinical trials and any clinical trials results of significant medical importance should be submitted for publication. The results of completed trials should be submitted for publication wherever possible within 12 months and no later than 18 months of the completion of clinical trials for already marketed medicines and in the case of investigational medicines the regulatory approval of the new medicine or the decision to discontinue development.

Having examined the various codes and joint positions, the Panel noted that the Joint Position 2005 excluded any clinical trials completed before 6 January 2005. The position changed on 18 November 2008 as the Joint Position 2008 did not have any exclusion relating solely to the date the trial completed. The Joint Position 2009 was similar to the Joint Position 2008 in this regard.

The Panel noted that deciding which Code, and thus which joint position applied, was complicated. It noted that the 2011 Code which, taking account of the transition period, came into operation on 1 May 2011, was the first edition of the Code to refer to the Joint Position 2008.

The Panel concluded that from 1 November 2008, (allowing for the transition period) until 30 April 2011 under the 2008 Code companies were required

to follow the Joint Position 2005. From 1 May 2011 until 30 April 2012 under the 2011 Code and 1 May 2012 until 31 October 2012 under the 2012 Code companies were required to follow the Joint Position 2008. Since 1 November 2012 companies were required to follow the Joint Position 2009. The Panel considered that since the 2008 Code companies were, in effect, required to comply with the joint position cited in the relevant supplementary information. The relevant supplementary information gave details of what was meant by Clause 21.3 (Clause 13.1 in the 2014, 2015 and 2016 Codes). The Panel accepted that the position was clearer in the Second 2012 Edition of the Code. The Panel noted that the 2011 Code should have been updated to refer to the Joint Position 2009.

For medicines first licensed and commercially available in any country from 1 November 2008 until 30 April 2011 the results of clinical trials completed before 6 January 2005 would not have to be posted.

From 1 May 2011 there was no exclusion of trials based solely on completion date and so for a product first licensed and commercially available anywhere in the world after 1 May 2011 the applicable joint positions required relevant clinical trial results to be posted within a year of the product being first approved and commercially available or within a year of trial completion for trials completed after the medicine was first available.

Noting that the CMRO study referred to licensed products the Panel considered that the trigger for disclosure was the date the product was first approved and commercially available anywhere in the world. This would determine which version of the Code (and joint position) applied for trials completed prior to first approval. The next consideration was whether the trial completed before or after this date. For trials completing after the date of first approval, the completion date of the trial would determine which Code applied. The Panel considered that the joint positions encouraged disclosure as soon as possible and by no later than one year after first availability or trial completion as explained above. The Panel thus considered that its approach was a fair one. In this regard, it noted that the matter for consideration was whether or not trial results had been disclosed, all the joint positions referred to disclosure within a one year timeframe and companies needed time to prepare for disclosure of results. The Panel considered that the position concerning unlicensed indications or presentations of otherwise licensed medicines etc would have to be considered on a case by case basis bearing in mind the requirements of the relevant joint position and the legitimate need for companies to protect intellectual property rights.

The Panel referred to the decision tree in the previous cases (for example Case AUTH/2654/11/13 *et al*) which had been updated in 2015 and published in Case AUTH/2763/5/15. The Panel updated the 2015 decision tree to include the 2016 Code.

The Panel considered that companies would be well advised to ensure that all the clinical trial results were disclosed as required by the codes and joint positions. The Panel considered that there was no complaint about whether the results disclosed met the requirements of the joint positions so this was not considered. In the Panel's view the CMRO publication at issue and thus the matter for consideration was only about whether or not trial results had been disclosed and the timeframe for such disclosure. The CMRO publication focussed on the disclosure of evaluable trial results and the Panel only considered those evaluable trials.

The Panel noted that its consideration of these cases relied upon the information provided by the respondent companies. The CMRO publication did not identify the studies evaluated; it only provided quantitative data. The Panel noted that the study related to products approved for marketing by the EMA in 2013 and searched for the data between 1 May and 31 July 2015. The study was published online on 25 November 2016. It appeared that the authors of the CMRO publication had contacted various companies for additional information.

The Panel noted that the date the product was first licensed and commercially available anywhere in the world might pre-date EMA approval.

PANEL RULING

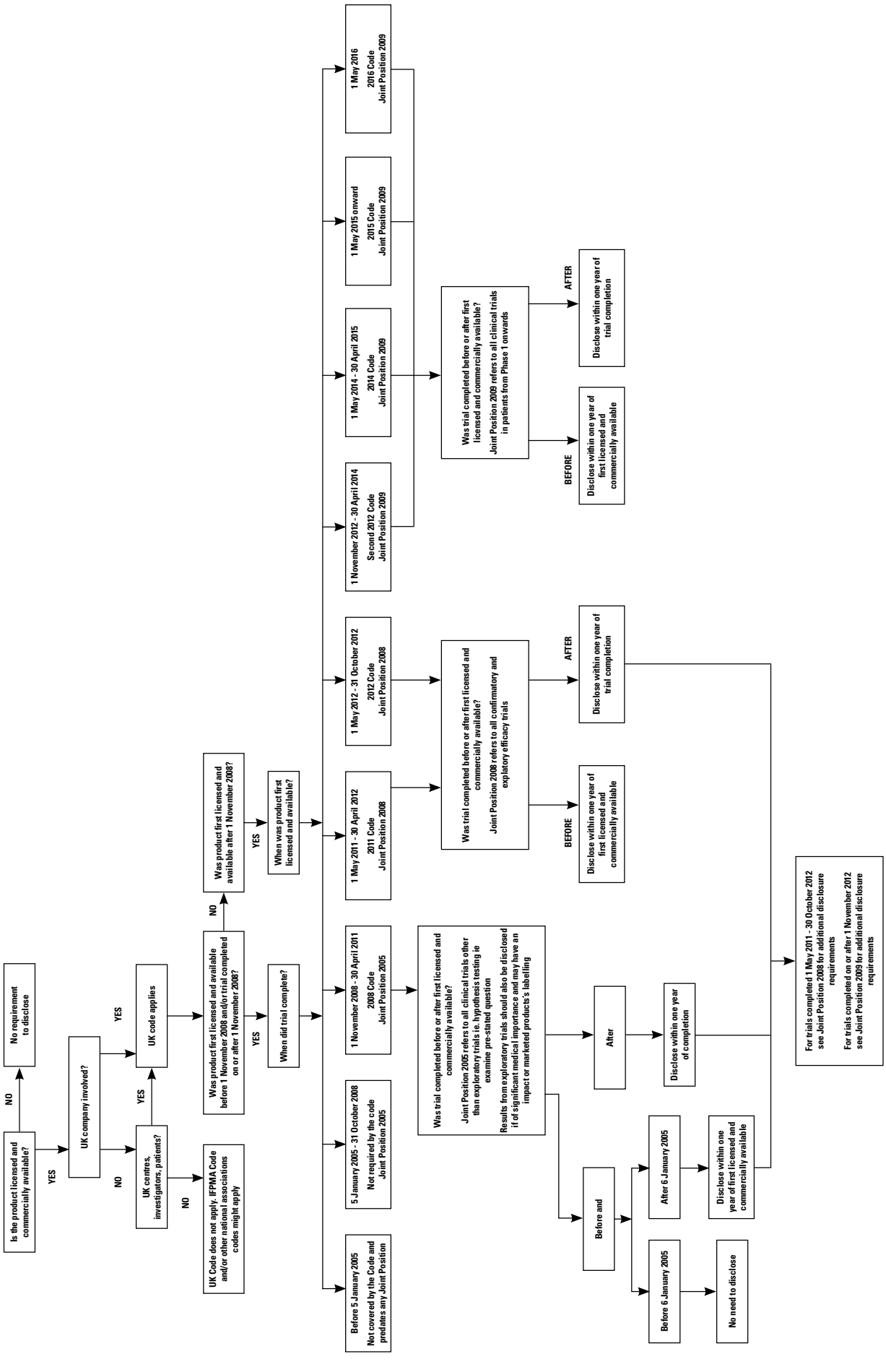
The Panel noted the CMRO publication in that one evaluable Phase I trial had not been disclosed within the 12 month timeframe. The disclosure percentage at 12 months measured from the later of the first date of regulatory approval or trial completion date was 88%. The disclosure percentage at 31 July 2015 of trials completed by the end of July 2015 was 88%. A footnote (company communication) stated that the undisclosed phase I trial was originally out of scope of disclosure requirements and results would be posted on EudraCT.

The Panel noted Bayer's submission that the trial in question (NCT00667537) was conducted in the UK on 6 patients to explore the bio-distribution, pharmacokinetics, and dosimetry of radium 223; it was neither a confirmatory clinical trial nor an exploratory efficacy trial and it completed on 3 December 2008.

The Panel noted Bayer's interpretation of the 2009 Joint Position which stated 'Additional trials that fall within the scope of this revised Joint Position and are initiated 6 months after the publication date of this Joint Position should be included in a public clinical trial registry'. It was Bayer's understanding that the trial in question (NCT00667537) qualified as an 'additional trial' under the 2009 Joint Position as it was not required to be disclosed under the 2008 Joint Position and that 'additional trials' were only subject to disclosure requirements if the trial was initiated [emphasis added] 6 months after the publication of the 2009 Joint Position. In the Panel's view, Bayer had mixed up requirements regarding clinical trial registries with those of clinical trial results databases. The complaint related to the disclosure of clinical trial results. The 2009 Joint Position clearly stated that the posting

Decision Tree

Updated Decision tree developed by the Panel



of clinical trial results should occur in compliance with the timelines and conditions defined in that Joint Position.

The Panel noted that Xofigo was first licensed and commercially available in May 2013 and this, as stated in the Panel's general comments above, was the trigger date for disclosure. In May 2013, the Second 2012 Code and thus the Joint Position 2009 applied which meant that for all licensed and commercially available medicines, all clinical trials from Phase I onward needed to be disclosed regardless of their completion date. Disclosure had to be within 1 year of the product first being licensed and commercially available or within one year of the trial's completion whichever was later.

The Panel noted on the information before it results from the trial should have been posted on a publicly accessible, internet-based clinical trials database by May 2014. As this had not happened the Panel ruled a breach of Clause 13.1. The delay in disclosure meant that high standards had not been maintained and a breach of Clause 9.1 was ruled.

The Panel noted Bayer's submission that there had been four clinical publications drawn from the results of the trial from 2011 to 2015. Details were provided and all four clinical papers had also been linked to disclosure on clinicaltrials.gov and were publicly accessible with full trial results published online in July 2015 and in print in September 2015. In addition Bayer added the results synopsis to the EudraCT database in May 2016. As the data had been disclosed the Panel considered there was no breach of Clause 2 and ruled accordingly.

Complaint received **29 November 2016**

Cases completed **14 March 2017**