Complaint to the Ombudsman – Dr Tom Jefferson

POINT 1: Rate of release of data from EMA under policy 00043

I requested Human Papilloma Virus vaccines Clinical Study Reports (Cervarix, Gardasil) and the anti-HCV molecule Sofosbivir (Sovaldi) on May 29th 2014.

My request was refused under CCI exception on the 23 June 2014

I appealed on 1 July 2014

The result of the appeal was never communicated to me but on 17 July 2014 I was sent the list of EMA holdings containing 8 Gardasil 4 CSRs and 20 Cervarix CSRs.

I was asked to prioritise their release, which I did. The first release took place on 12 September 2014.

To date (END OF Setpember 2016) there have been 80 transmissions of as many file batches: 8 **Gardasil 4** CSRs (total 10216 pages) and 5 Cervarix CSRs (12009 pages). Average batch size is 300-400 pages.

Main consequences:

Very slow release (increasingly so, as documented[1] [2])

Batching of CSRs files (300-400 pages at a time) makes it very difficult to keep track of what is going on and needs software to reconstruct a single CSR from multiple batches of files

POINT 2: Excessive unnecessary anonymization and failure to assign fake ID to line listing

This concerns individual participant data tables, in which each participant's relevant data are reported, I,e, medications [also batch numbers of ampoules of biologics - see below].

Below is a reproduction from one the listings Cervarix Trial HPV-008 – CSR main body pdf page 269/641:

Case number[a]	Subject number	Treatment group	Date of Vacc 1	Sero status at M0	Cytology and PCR results at M0	Date of M6 visit	Cytology and PCR results at M6	Other cytology and PCR results from M12 onwards	Visit leading to biopsy	Clinical diagnosis and biopsy PCR results	Protocol defined case	HPV TAA case
[redacted]		HAV	08JUN2004	N	NI: -	10DEC2004	NA: -	M12 (21JUN2005): NI: HPV-51/53 M18 (01DEC2005): NA: HPV-16/53/74 M24 (08JUN2006): NI: HPV-16/51 M30 (07DEC2006): NA: HPV-16/51/74 M36 (28MAY2007): ASC-H: HPV-16/51/74 M42 (08JAN2008): NI: HPV-16 M48 (06JUN2008): NI: -	M42	08JAN2008: PUNCH 1A CIN2 HPV-16; 17MAR2008: LEEP 1B CIN2 HPV-16; 17MAR2008: LEEP 3A CIN2 HPV-16; 17MAR2008: LEEP 3B CIN2 HPV-16/51; 17MAR2008: LEEP 3C CIN2 HPV-16	HPV-16	HPV-16
		HAV	18AUG2004	N	NI: -	16FEB2005	NA: -	M12 (17AUG2005): NI: - M18 (11JAN2006): NI: HPV-51	M42	11MAR2008: LEEP 3A AIS	HPV-16	HPV-16

As can be seen both the Case number and the Subject Number have been redacted, without assigning the participant a fake ID.

Main consequences: the impossibility of following an individual through the CSRs narrative makes interpretation impossible or difficult especially when this person is a subject of a Serious Adverse Event report narrative. In other words, this type of redaction defeats the object of transparency. Of note is that GSK appear to have used progressively more redactions, as when GSK released 30 complete CSRs directly to us in 2013, only the participant ID had been redacted.

I have complained and appealed on the basis of the public health importance of HPV vaccines and my lack of interest in both identification of participants and of reconstructing the original ID allocated. I received the following answer on 28 September 2016:

"As a preliminary note, we would like to highlight that we cannot consider your email to constitute a "formal appeal". Regulation (EC) No 1049/2001 (the "ATD Regulation") does not establish a second route of internal appeal after a confirmatory application has been submitted.

The fourth paragraph of Article 73 of Regulation (EC) No 726/2004, making explicit reference to the legal regime established by the ATD Regulation, sets out the remedies available to you should you disagree with the Agency's confirmatory decision. These remedies were highlighted in our decision letter of 10th August 2016 regarding batch 28 of your confirmatory application:

> *"should you wish to avail yourself of the remedies available under Union law against this decision, please be informed that you can bring a complaint before the European Ombudsman, pursuant to Article 228 of the Treaty on the Functioning of the European Union (TFEU). You can also institute legal proceedings before the General Court of the European Union in accordance with Article 263 of the TFEU."*

*The Agency would also like to highlight that the ATD Regulation does not permit us to modify the content of documents released in response to requests for access to documents. Article 10(3) of this Regulation clearly states that "Documents shall be supplied **in an existing** version and format".*

The General Court ruled on a number of occasions (for example in Case Dufour v ECB, T-436/09, ECR, EU:T:2011:634, paragraph 149; and in Case Typke v Commission, T-214/13, ECR, EU:T:2015:448) that if an application for access to documents requires the creation of a new document, even if this new requested document would be based on information already appearing in existing documents held by the institution, such application does not come within the parameters of Regulation No 1049/2001. Therefore, the Agency is not permitted to modify an existing document but only to apply redactions to it in order to protect information covered by the exceptions set out in Article 4 of the ATD Regulation. This is the reason why the Agency cannot apply anonymisation (i.e. replacing information with another) to the documents that are subject to your request for access to documents but can only redact certain information contained therein.

We completely understand that you may encounter difficulties in your work as a consequence of the redaction of patient identification numbers or case numbers. The Agency is also fully aware of the existing public attention regarding HPV vaccines.

However, in accordance with Article 4(1)(b) of the ATD Regulation and the European Union legislation regarding the protection of personal data read in conjunction with Regulation (EC) No 45/2001, the Agency has to redact all protected personal data in order to avoid that the disclosure of the document would undermine the privacy and integrity of any individual.

In accordance with applicable EU data protection legislation, information is considered personal data in so far as it refers to "an identified or identifiable individual person" and that an "identifiable person" is one that can be identified, directly or indirectly, "in particular by reference to an identification number or to one or more factors specific to his or her physical, […] identify" (Article 2(a) of Regulation (EC) No 45/2001). The position of the Agency is that coding of an individual trial participant (i.e. allocation of a random number to each patient) would not eliminate the risk of a possible re-identification of the concerned individual and therefore the public disclosure of this information could not be justified on the basis of current data protection legislation.

In this regard, we would like to highlight that the replacement of patient direct identifiers (such as names) with patient IDs is a known pseudonymisation technique. This technique is explained in the Opinion 05/2014 on anonymisation techniques of the Article 29 Data Protection Working Party (please see page 20). It is considered a pseudonymisation technique because the unique number that is allocated to the research subject (unique for the data set) allows for the linking of this number to an individual patient. In other words the link between the research subject and the number does exist and is not undermined by its pseudonymisation. Therefore from this perspective, the Agency considers that the data sets that are submitted to the EMA for the regulatory review are not fully anonymised and are therefore not adequate for

release to third parties in accordance with the ATD Regulation or other forms of public release. The risk of releasing pseudonymised data sets is clearly highlighted in the Opinion 05/2014 on anonymisation techniques of the Article 29 Data Protection Working Party which reads:

"A specific pitfall is to consider pseudonymised data to be equivalent to anonymised data. The Technical Analysis section will explain that pseudonymised data cannot be equated to anonymised information as they continue to allow an individual data subject to be singled out and linkable across different data sets. Pseudonymity is likely to allow for identifiability, and therefore stays inside the scope of the legal regime of data protection. This is especially relevant in the context of scientific, statistical or historical research."

As you may know the patient IDs that are allocated to subject enrolled in clinical trials are not just random codes. The patient ID numbers are typically made up in a sequence of numbers and letters that are associated with three elements, the study, the study site and the patient. Therefore, it is understood that by releasing the patient numbers that were allocated at the time of randomisation one would release information about the geographical location of the patient. It is widely recognised that in addition to the direct identifiers, the geographical location is one of the data elements that poses high risk of re-identification.

In addition these unique numbers are considered to constitute direct identifiers. The uniqueness should be understood as the possibility to associate the number/code with only one research subject in a given data set. This is documented in the literature, for example we can refer you to the decision rule for classifying identifiers (figure B-3) which is available in the Appendix B of the IOM report: Sharing Clinical Trial Data: Maximizing benefits, minimizing risks.

For all the reasons mentioned above, the EMA is redacting the patient ID numbers from the documents that are released to the public in accordance with the ATD Regulation. The Agency conducts this exercise in light of the sensitive nature of the information at stake, the applicable rule on processing of health data laid down in Article 10 of Regulation (EC) 45/2001 and regulatory guidelines including for example the provisions of the Recommendations on the handling of requests for access to Periodic Safety Update Reports (PSURs) "the minimum personal data to be deleted to ensure anonymisation of the information would require the deletion of information on 1) Date of birth; 2) (Reporting) country; 3) Patient identification code". Furthermore, the Recommendations provide that "it should never be possible to identify a natural person from the information disclosed".

The position adopted by EMA takes into account the advice of the European Data Protection Supervisor (EDPS) regarding the extent to which information received for the purpose of pharmacovigilance, including adverse reactions should be considered personal data in accordance with Article 2(a) of Regulation (EC) 45/2001.

We hope that you can understand the EMA's position on this sensitive matter".

As I've pointed out to EMA redactions of this type make the release of data a cosmetic exercise. The situation gets worse when EMA redact batch numbers from vials of biologics such as vaccines making it impossible to assess whether a particular effect observed (for example a suspected adverse event is due to a spefici batch of that vaccine.

POINT 3: Lack of availability of a list of CSRs and other important material held by EMA

My group and I have complained[3] in private and in public several times about the lack of visibility of what is available under policy EMA 0043. EMA have failed to respond in any way.

Main consequences: sizeable increase in work load trying to identify availability or blanket (blind) requests for data and unnecessary burden on requestor and EMA.

References

1. Doshi P, Jefferson T. Open data 5 years on: a case series of 12 freedom of information requests for regulatory data to the European Medicines Agency. Trials (2016) 17:78 DOI 10.1186/s13063-016-1194-7. http://trialsjournal.biomedcentral.com/articles/10.1186/s13063-016-1194-7

2. Peter Doshi & Tom Jefferson. Access to clinical trial data from the European Medicines Agency. http://blogs.biomedcentral.com/on-medicine/2016/02/11/access-clinical-trial-data-european-medicines-agency/

3. Tom Jefferson and Peter Doshi: Thanksgiving special—menus needed at the EMA's restaurant. BMJ Blogs

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