

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA Clinical Data Publication: experience to date and future direction

Continued Evolution of Data Sharing- PSI conference 2018

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An agency of the European Union





Policy 0070:

- 2 October 2014, Clinical Data Publication

What is it:

- Publication of clinical data supporting CHMP Assessments

Benefits:

- **Transparency**, continued EMA commitment
- Proactive publication enables **public scrutiny**: establishes trust, confidence
- **Better public information**: Public access enables application of new knowledge in future research, increases efficiency of medicine development, learning from experience
- **Avoids clinical trials duplication**: limits unnecessary patient exposure
- **Enhanced scientific knowledge**/value of secondary analysis: sharing scientific knowledge, contribution to public health





Phase I

- Clinical reports = clinical overview, clinical summary, clinical study reports, protocol & amendments, sample case report form, documentation of statistical methods
- **EMA is working on Phase I implementation**

Phase II

- Individual patient data (IPD)
- **Later stage**



EUROPEAN MEDICINES AGENCY
Clinical data



Online access to clinical data for medicinal products
for human use

<https://clinicaldata.ema.europa.eu>

Type of published procedure

Initial marketing authorisation	36
Extension of indication	18
Line extension	0
Total number of published procedures	54



Published documents

Anonymisation Report	54
Module 2.5	63
Module 2.7.1-2.7.4	160
Module 5.3 (CSR)	3,002
Total number of documents	3,279
Total number of pages	1,308,244



- Policy 0070 states that **adequate personal data protection needs to be ensured** and that full compliance with applicable EU legislation needs to be achieved.
- Directive 95/46/EC excludes anonymised data from the scope of data protection legislation. To anonymise any data, the data must be processed in such a way that **it can no longer be used to identify a natural person** by using “**all the means likely reasonably to be used**” by either the controller or a third party.
- EDPS acknowledges that for Policy 0070 there are constraints which make the **very low likelihood of possible re-identification of the data subject** the only consistent safeguards for the protection of personal data.

Two options are available to establish if the data are anonymised:

- 1) Demonstration of effective anonymisation based on **three criteria**:
 - ✓ Possibility to single out an individual.
 - ✓ Possibility to link records relating to an individual.
 - ✓ Whether information can be inferred concerning an individual.

- 2) **Evaluation of the risk of re-identification** against a pre-defined threshold .

1. Determination of direct identifiers and quasi-identifiers;
2. Identification of possible adversaries and plausible attacks on the data;
3. Evaluation of the actual risk of re-identification (and determination of the risk of re-identification threshold);
4. Data utility considerations;
5. Choice of anonymisation methodology and level of anonymisation;
6. Evaluation that the actual risk of re-identification is below threshold set after data have been anonymised.

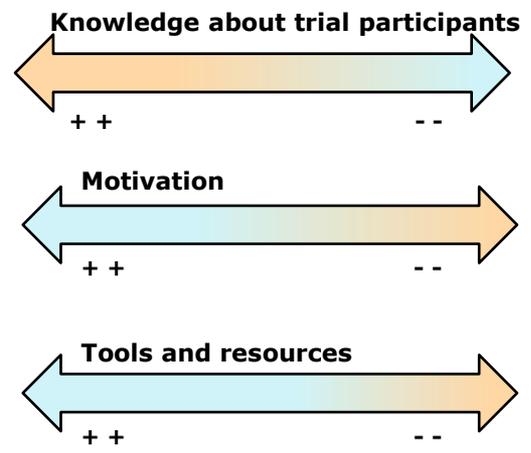
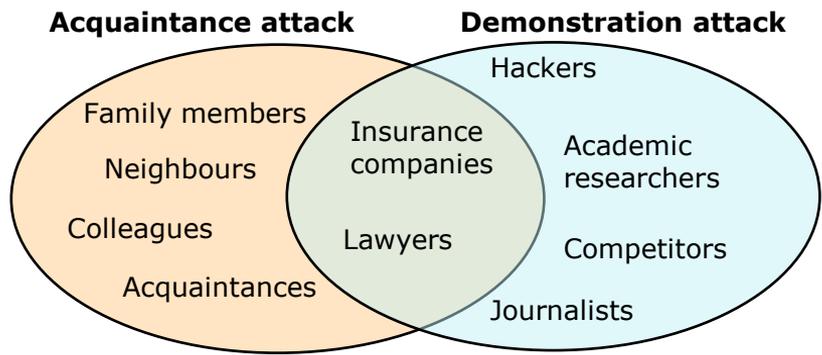


What can impact the level of anonymisation required? (1/2)

- *Context of data disclosure;*
- *Prevalence of disease;*
- *Study characteristics (i.e. sample size, number of sites, number of countries);*
- *Frequency of trials participants with same value on a set of quasi identifiers (i.e. group size);*
- *Number of quasi identifiers per trial participants (e.g. narratives);*
- *Data utility considerations.*

What can impact the level of anonymisation required? (2/2)

- *Plausible attackers*



Other aspects to consider:

- Knowledge that a specific subject is in the data set;
- Time, cost and effort: to what extent?
- Breach of law.



- Qualitative risk threshold to be set (e.g. low, very low);
- No calculation of re-identification risk;
- Risk assessment based on subjective evaluation;
- Analytical approach?
- Redaction as preferred technique;
- Study categorisation driven by sample size;
- Heterogeneity in the anonymisation performed.

- Quantitative risk threshold to be set (0.09);
- Calculation of re-identification risk;
- Transformation as additional technique (e.g. pseudo-anonymisation, offset dates, randomisation, generalisation of medical history to MedDRA HLT, HLGTT and SOC);
- Less conservative assumptions (attacker knowledge, data set considered);
- Different methodologies applied.



The subject received the 1st study therapy infusion on PPD [REDACTED] 2013.

On Day 11 (PPD [REDACTED] 2013), 10 days post the 1st infusion day, the Investigator reported a non-serious adverse event of Grade 1 abdominal distension, which was considered by the Investigator to be related to the study therapy. The subject received treatment with simethicone. No action was taken with regard to the study therapy.

On Day 18 (PPD [REDACTED] 2013), 3 days post the 2nd infusion day, the Investigator reported non-serious adverse events of Grade 2 diarrhea and Grade 1 flatulence, which were considered by the Investigator to be related to the study therapy. The subject received treatment with loperamide and paregoric. The next planned study therapy infusion was delayed due to the event of diarrhea. On Day 29 (PPD [REDACTED] 2013), the subject started treatment with oral meprednisone at a total daily dose of 60 mg given once a day for diarrhea. On Day 30 (PPD [REDACTED] 2013), the subject's stool culture showed normal results. On Day 33 (PPD [REDACTED] 2013), the event of diarrhea resolved and the subject received the last dose of oral meprednisone (60 mg/day). On Day 37 (PPD [REDACTED] 2013), the study therapy was resumed.

On Day 51 (PPD [REDACTED] 2013), the 4th infusion day, the Investigator reported non-serious adverse events of Grade 1 increased alanine aminotransferase (ALT) and Grade 1 increased aspartate aminotransferase (AST) (refer to lab table below), which were considered by the Investigator to be related to the study therapy. The subject did not receive any treatment.

On Day 79 (PPD [REDACTED] 2013), 14 days post the 5th infusion day, the events of increased ALT and increased AST were worsened to Grade 2 (refer to lab table below). The next planned study therapy infusion was delayed due to the events of increased ALT and increased AST. On Day 81 (PPD [REDACTED] 2013), the subject started treatment with oral meprednisone at a total daily dose of 60 mg given once a day for the events of increased ALT and increased AST.

On Day 84 (PPD [REDACTED] 2013), the events of increased ALT and increased AST improved to Grade 1. On Day 90 (PPD [REDACTED] 2013), the event of increased AST resolved. On the same day (Day 90), the dose of oral meprednisone was tapered to 40 mg/day and then to 20 mg/day on Day 95 (PPD [REDACTED] 2013). On Day 97 (PPD [REDACTED] 2013), the event of increased ALT resolved. The dose of oral meprednisone was tapered to 10 mg/day on Day 99 (PPD [REDACTED] 2013) and to 5 mg/day on Day 104 (PPD [REDACTED] 2013). The subject received oral meprednisone (4 mg/day) until Day 109 (PPD [REDACTED] 2013). On Day 114 (PPD [REDACTED] 2013), the study therapy was resumed.

On Day 133 (PPD [REDACTED] 2013), 11 days post the 7th infusion day, the Investigator reported a non-serious adverse event of Grade 1 diarrhea, which was considered by the Investigator to be related to the study therapy. The subject continued to receive treatment with loperamide and paregoric. No action was taken with regard to the study therapy. On Day 138 (PPD [REDACTED] 2013), the event of diarrhea worsened to Grade 2. The next planned study therapy infusion was delayed due to the event of diarrhea. On Day 139 (PPD [REDACTED] 2013), the subject received treatment with oral meprednisone at a total daily dose of 40 mg given once a day for diarrhea. On Day 142 (PPD [REDACTED] 2013), a stool culture showed normal results. On the same day (Day 142), the subject received the last dose of oral meprednisone. On Day 143 (PPD [REDACTED] 2013), the event of diarrhea resolved. On Day 148 (PPD [REDACTED] 2013), the study therapy was resumed.

On Day 148 (PPD [REDACTED] 2013), the 8th infusion day, the Investigator reported non-serious adverse events of Grade 1 increased ALT and Grade 1 increased AST (refer to lab table below), which were considered by the Investigator to be related to the study therapy. The subject did not receive any treatment, and no action was taken with regard to the study therapy.

On Day 167 (PPD [REDACTED] 2013), the events of increased ALT and increased AST worsened to Grade 2 (Day 167 lab results not available). The subject was restated on treatment with oral meprednisone at a total daily dose of 60 mg given once daily. The next planned study therapy infusion was delayed due to the events of increased ALT and increased AST.

On Day 174 (PPD [REDACTED] 2013), the event of increased ALT worsened to Grade 3 and the event of increased AST improved to Grade 1 (Day 174 lab results not available). On Day 177 (PPD [REDACTED] 2013), the event of increased AST worsened to Grade 3 (Day 177 lab results not available). The treatment with oral meprednisone was switched to intravenous (IV) methylprednisolone at a total daily dose of 65 mg given

Subject: 100097

Demographics and Baseline Characteristics

- Country: [COUNTRY]
- Sex: Male
- Baseline weight(kg): [WEIGHT]
- Study site identifier: 0510774
- Description of planned arm: Daratumumab 8 mg/kg
- Baseline height(cm): [HEIGHT]
- Race: [RACE]
- Description of actual arm: Daratumumab 8 mg/kg
- Baseline ECG score: 0
- Age(yrs): 34

Disposition Information

- Treatment discontinuation: 2013-10-27 Progressive Disease
- Study discontinuation: 2014-05-25 Death

Summary of Study Medication

Total Dose Received (mg/kg)	Date of First Exposure to Treatment	Date of Last Exposure to Treatment	Duration of Treatment (Months)
9.30	2013-09-29	2013-10-27	0.95

NARRATIVE TEXT

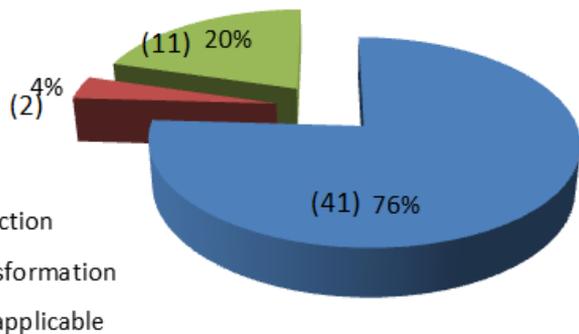
Subject 100097, a 34-year-old [RACE] male initially diagnosed in [REDACTED] with stage III multiple myeloma, was randomized to receive daratumumab at a dose level of 8 mg/kg in Part 1, Stage 1 of the study. At study entry, his relevant ongoing medical history included Anemias NEC, aspartate aminotransferase level increase, Medical history, Medical history, Joint disorders, Respiratory, thoracic and mediastinal disorders, blood creatinine level increase, Investigations, Metabolism and nutrition disorders, Metabolism and nutrition disorders, Psychiatric disorders, and Blood and lymphatic system disorders. His baseline ECG score was 0. At screening, his vital signs included body temperature of 36.6°C, pulse rate of 80 beats per minute (bpm), and blood pressure of 136/80 mm Hg. Plasma cells obtained from the baseline bone marrow biopsy were 95%.

The subject received a total of 5 lines of prior systemic therapy as follows: Line 1 consisted of bortezomib and dexamethasone; Line 2 consisted of cyclophosphamide, GCSF, melphalan, and ASCT; Line 3 consisted of dexamethasone and lenalidomide; Line 4 consisted of bortezomib, carmustine, cyclophosphamide, dexamethasone, and melphalan; Line 5 consisted of bortezomib. Line 5 consisted of bortezomib, lenalidomide in Line 3, an alkylator in Line 4, and bortezomib in Line 5.

Concomitant medications reported at study entry included doxazosin and acyclovir.

On [REDACTED], the subject's platelet count was $71 \times 10^9/L$ (Grade 2) (range: $150-350 \times 10^9/L$), then on [REDACTED], the subject's platelet count decreased further to $39 \times 10^9/L$ (Grade 2).

On Study Day 1 (29 Sep 2013), nonserious adverse events of Grade 3 chills (reported term: rigors) and Grade 1 non-cardiac chest pain were reported. The investigator considered both events as IRRs and as very likely related to the study drug. Pre-infusion vital signs included body temperature of 36.8°C, pulse rate of 80 bpm, and blood pressure of 126/81 mm Hg. The subject was administered pre-infusion medications as per protocol. Approximately 90 minutes after the start of the infusion, his vital signs included body



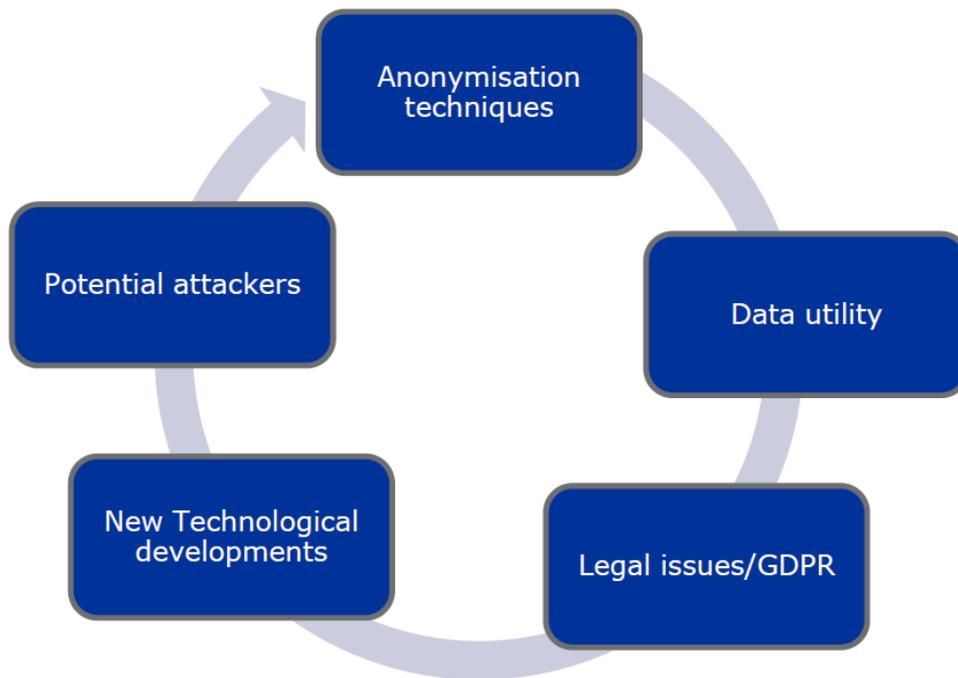
Redaction vs. Transformation

- Call for expression of interests from experts launched on April 2017;
- Composed of 20 members with a broad range of expertise, ensuring a diverse representation of the various stakeholders (e.g. data protection lawyers, experts in anonymisation standards, patient representatives);
- First TAG meeting took place on 29-30 November 2017.

Objectives:

- To learn from the **experience gained** with the publication of the first clinical reports and to assess best practices in the field of anonymisation, assess patient re-identification and any privacy risk, taking into account EU law on data protection;
- To understand the **challenges** encountered by **pharmaceutical industry** while anonymising the reports for publication;
- To **investigate** if **data transformation** resulting from the anonymisation techniques used can lead to a different interpretation of the study results;
- To investigate the **scientific utility** of the clinical data published as a function of the methodology used by the Applicant/MAH in the anonymization of the reports, and establish whether **secondary analysis** of clinical data can be successfully undertaken using the data published by the Agency;
- To follow **new technological developments** that might impact on the anonymization of clinical reports and establish adequate measures to keep the risk of re-identification to an adequate level.

Next steps:



- Good engagement from MAHs (100 dossiers published);
- Anonymisation poses a challenge for all parties involved in the anonymisation of clinical reports;
- Confidence will be gained with the experience (public release, potential adversaries, threshold);
- Inputs from TAG will help defining best practices in anonymisation.



Any questions?

Further information

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