Voydeya: A Real Life Example of EMA Policy 0070 in Rare Disease

04 December 2024

Raquel Billiones, PhD and Alison McIntosh, PhD

for the CORE Reference Team

EUROPEAN MEDICAL WRITERS ASSOCIATION

REFERENCE

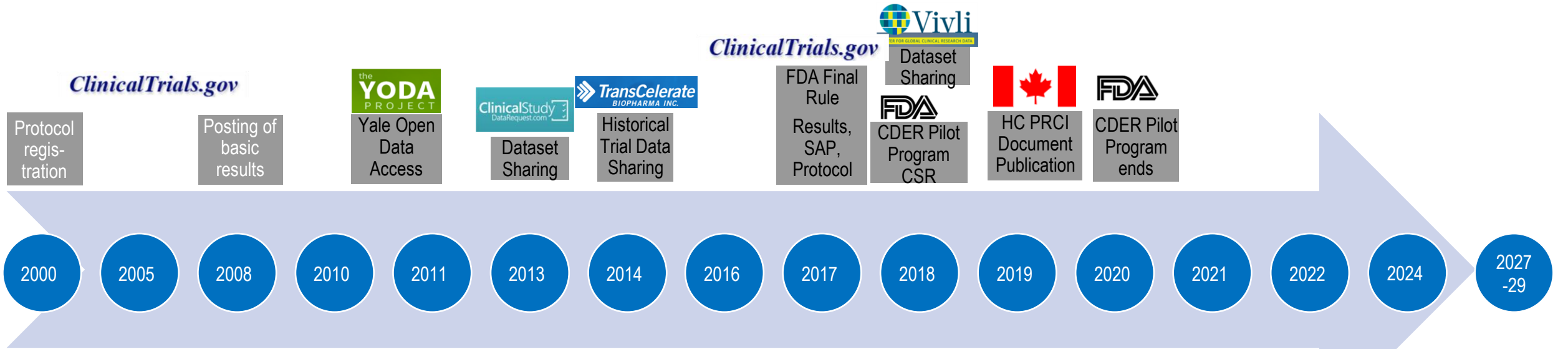
EUROPEAN MEDICAL WRITERS ASSOCIATION

AMERICAN MEDICAL WRITERS ASSOCIATION
The Resource for Medical Communicators

Clinical Trial Data: Transparency and Disclosure

Presenter: Dr Alison Mcintosh

Clinical Trial & Data Transparency Timeline



WHO International CT Registry Platform

ICTRP

ICMJE Protocol registration

EMA Policy 0043 Access to documents

EMA Policy 0043 Access to documents

EU CT Register Protocol Registration

EU CTR 536/2014

EMA Policy 0070 Document Publication

EMA Policy 0070 Document Publication

Clarity and Openness in Reporting E3-based

EU MDR 2017/745 EU IVDR 2017/746

EMA Policy 0070 Suspension

EMA Policy 0070 Suspension

ICMJE Data sharing statement

EMA Transparency Measures COVID-19 Document Publication

EMA Transparency Measures COVID-19 Document Publication

EU CTIS Document Publication

EU CTIS Document Publication

EMA Policy 0070 Restart

EUDAMED Document Publication

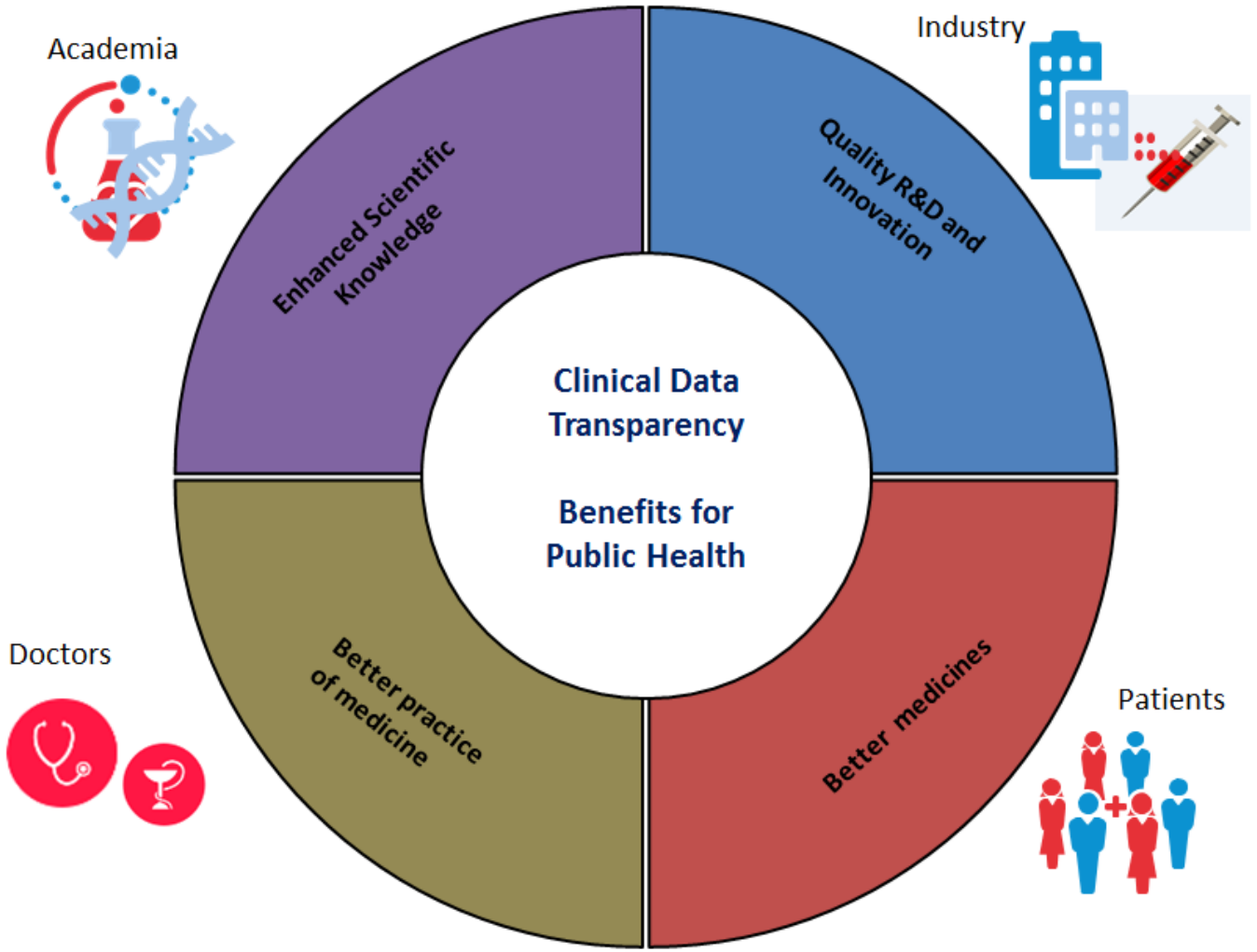
EUDAMED Document Publication

INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

EUROPEAN MEDICAL WRITERS ASSOCIATION

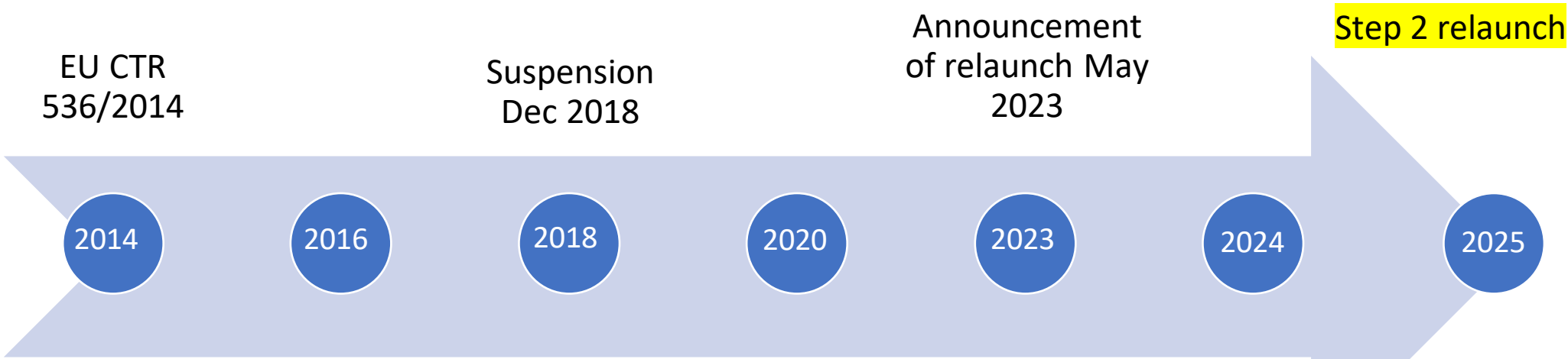
Billiones. The clinical research transparency journey. Medical Writing Volume 33 (3), 6-7; September 2024

Why Disclose?



Source: From EMA website; reused and adapted with permission

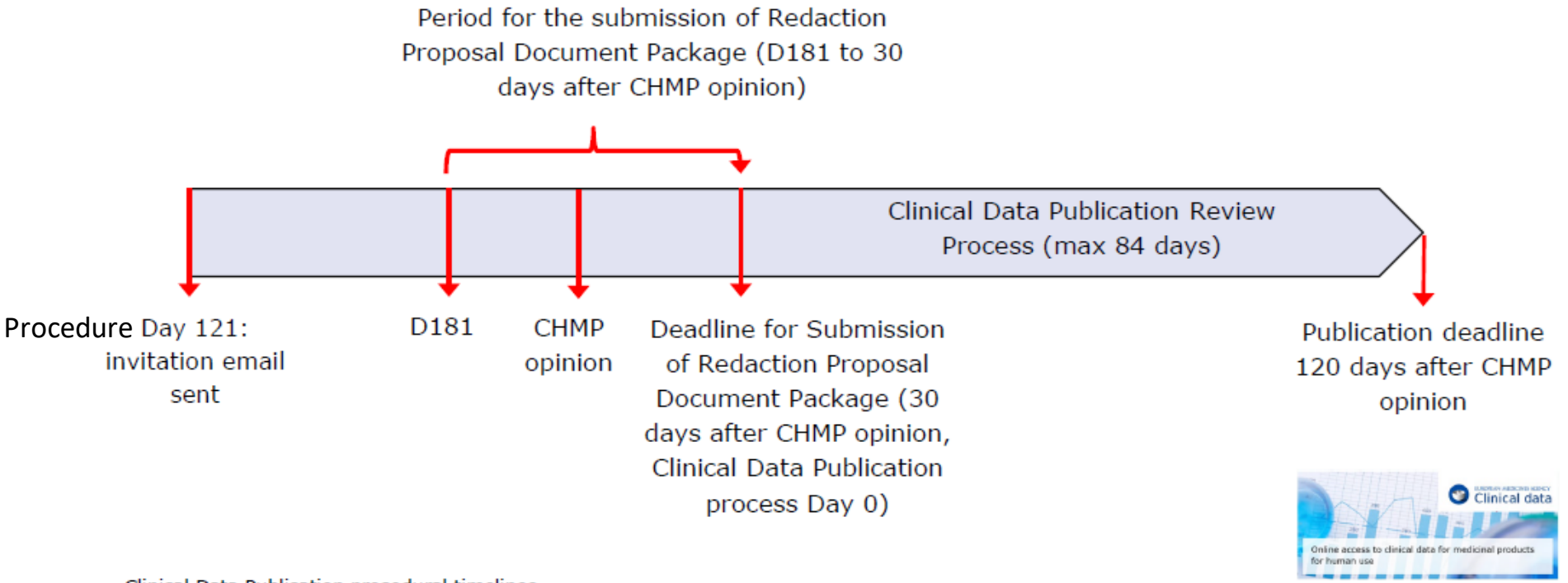
EMA Policy 0070 Timeline



EMA Policy 0070 Relaunch

EUROPEAN MEDICINES AGENCY

Clinical data publication timeline (iMAA and line extension applications)



5 Clinical Data Publication procedural timelines

https://www.ema.europa.eu/en/documents/presentation/presentation-cdp-procedural-timelines_en.pdf

EMA Clinical Data Website (since 20 October 2016)

EMA website: https://clinicaldata.ema.europa.eu

Account needed

General information purposes

- Read on screen (no save, download or print)
- Search
- For everyone

Academic and other non-commercial research purposes

- Download
- Search
- Print

EU residents only

Policy 0070: Brief Introduction to Anonymisation Report (AnR)

Presenter: Dr Alison Mcintosh

Anonymisation Report (AnR) Template

- New for Policy 0070 Relaunch

AnR Form Template (released 24 May 2024)
AnR Form Instructions (released 24 May 2024)

Both can be downloaded from
https://www.ema.europa.eu/en/human-regulatory-overview/marketing-authorisation/clinical-data-publication/support-industry-clinical-data-publication

CORE Reference Webinar 07 June 2024

- Included general introduction to Policy 0070 Anonymisation Report (AnR) Template
  - See https://www.core-reference.org/news-summaries/core-reference-seminar-emwa-valencia-may-2024-and-webinar-07-june-2024/
  - See https://www.core-reference.org/media/1088/core-reference-seminar-emwa-valencia-may-2024-and-webinar-07-june-2024-slides.pdf
  - Refer to webinar slides 21 – 37 or presentation video at 30 – 58 minutes

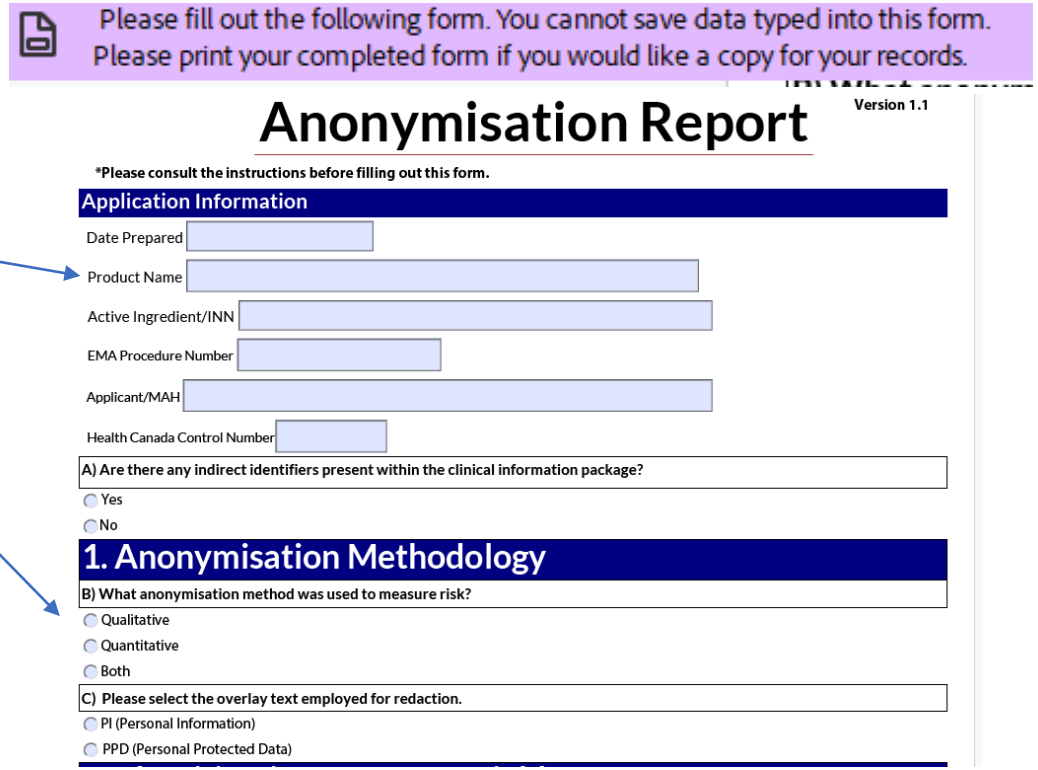
Brief Recap

- AnR template used for all clinical data publication submissions (EMA/Health Canada or both)
- AnR describes
  - Anonymisation strategy adopted for each individual document package
  - Data protection consideration taken into account when deciding on the anonymisation strategy
- Structured Data Fields
  - Limited free text sections
- Clinical Data Publication (CDP) Questions and Answers (Q&As) updated and released 26 Jul 2023 (Rev 3): Section 3 covers info regarding anonymisation reports
    - https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/questions-answers-qas-external-guidance-policy-0070-clinical-data-publication-cdp_en.pdf

AnR Template Structure

Heading Structure

Section	Heading
(A)	Application information
1 (B,C)	Anonymisation Methodology
2	Identification of Data variables
2.1 (D)	Direct Identifiers
2.2 (E)	Indirect Identifiers
3 (F-M)	Risk Assessment
4 (N-Q)	Data Utility
5 (R)	Deviations
6	Attestations


Please fill out the following form. You cannot save data typed into this form.
Please print your completed form if you would like a copy for your records.

Anonymisation Report

Version 1.1

*Please consult the instructions before filling out this form.

Application Information

Date Prepared

Product Name

Active Ingredient/INN

EMA Procedure Number

Applicant/MAH

Health Canada Control Number

A) Are there any indirect identifiers present within the clinical information package?

Yes

No

1. Anonymisation Methodology

B) What anonymisation method was used to measure risk?

Qualitative

Quantitative

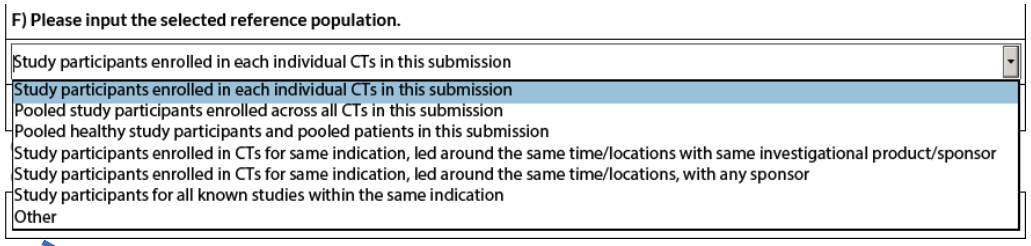
Both

C) Please select the overlay text employed for redaction.

PI (Personal Information)

PPD (Personal Protected Data)

Information in this section provides greater context for the chosen anonymisation strategy

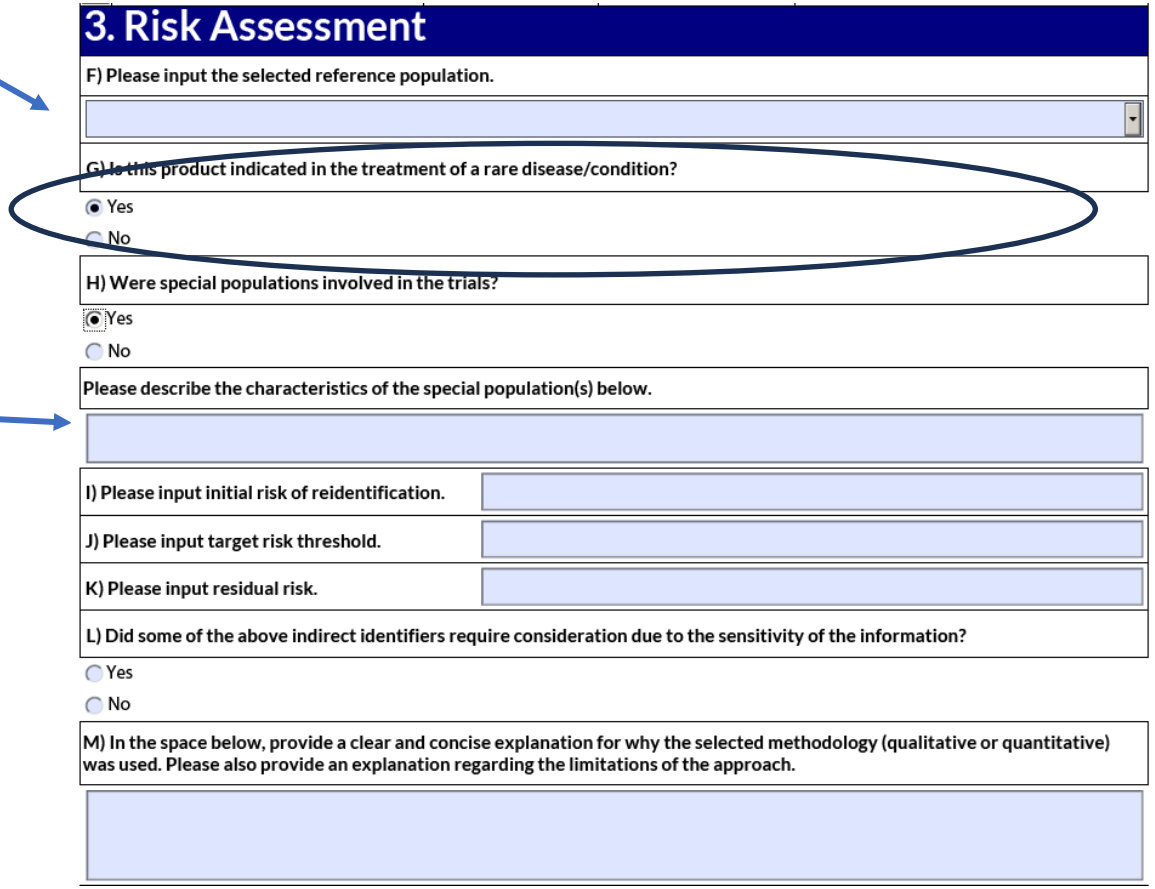


The selection of the appropriate reference population determines the total patient group size and the level of anonymisation that is necessary to reduce the risk of patient re-identification. (Pull down menu selection)

Select 'Yes' or 'No' if the product is intended to treat rare disease populations/conditions.

If yes then must describe the characteristics of the population(s) in the free text box that appears

Special population: e.g., pediatric, geriatric, pregnant or breastfeeding women. In the context of anonymisation, special populations might warrant special attention as they often represent a specific subset of participants as well as not necessarily sharing all key characteristics of the general reference population



Rare disease: a life-threatening, seriously debilitating or serious and chronic condition affecting a small number of patients.
The definitions of a rare disease in Canada and the EU both indicate a prevalence of fewer than 5 in 10,000 persons.

Input the initial risk of reidentification approximated. In general, a qualitative value such as high, moderate, low can be included, as applicable. For quantitative approaches, maximum risk observed prior to anonymisation should be provided, as applicable.

3. Risk Assessment Guidance

- Template Instructions:

  "Section M: In the space below, provide a clear and concise explanation for why the selected methodology (qualitative or quantitative) was used. Please also provide an explanation regarding the limitations of the approach"

- Instruction sheet further guidance:

  "Provide greater context on chosen anonymisation techniques (i.e redaction, transformation, recoding etc.) with reference to the different sections of the clinical documents (i.e. demographic tables, summaries, narratives etc.) and why that specific approach was deemed the most suitable with respect to the risk assessment conducted as well as the technical means available"

Real-life Example EMA Policy 0070: Voydeya

Presenter:

Raquel Billiones, PhD

Alexion (AstraZeneca Rare Disease Unit)

Voydeya information presented here are available in the public domain under

Home - Clinical Data Publication - clinicaldata.ema.europa.eu

Views and opinions are those of the presenter and do not necessarily reflect those of EMWA or Alexion

Real-life Example EMA Policy 0070: Voydeya

- Danicopan, a small molecule, oral
- Initial MAA
- New chemical entity
- Orphan drug designation

Search - Clinical Data Publication - clinicaldata.ema.europa.eu

Name	Active substance	MAH Name	Product Status	Publication Date	Procedure Type
Voydeya	Danicopan	Alexion Europe	Authorised	26/06/2024	Initial Marketing Authorisation

Showing 1 to 1 of 1 entries

Previous 1 Next

Product name
Voydeya

MAH
Alexion Europe

Active substance
Danicopan

ATC code
L04AJ09

Number of Documents
160

Procedure type
Initial Marketing Authorisation

Publication year
2024

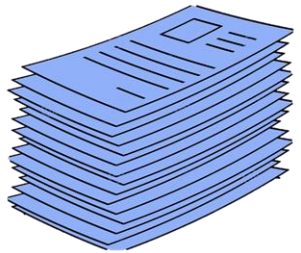
Product Status
Authorised

Type
O

Article 58
No

EMA procedure number
EMEA/H/C/005517/0000

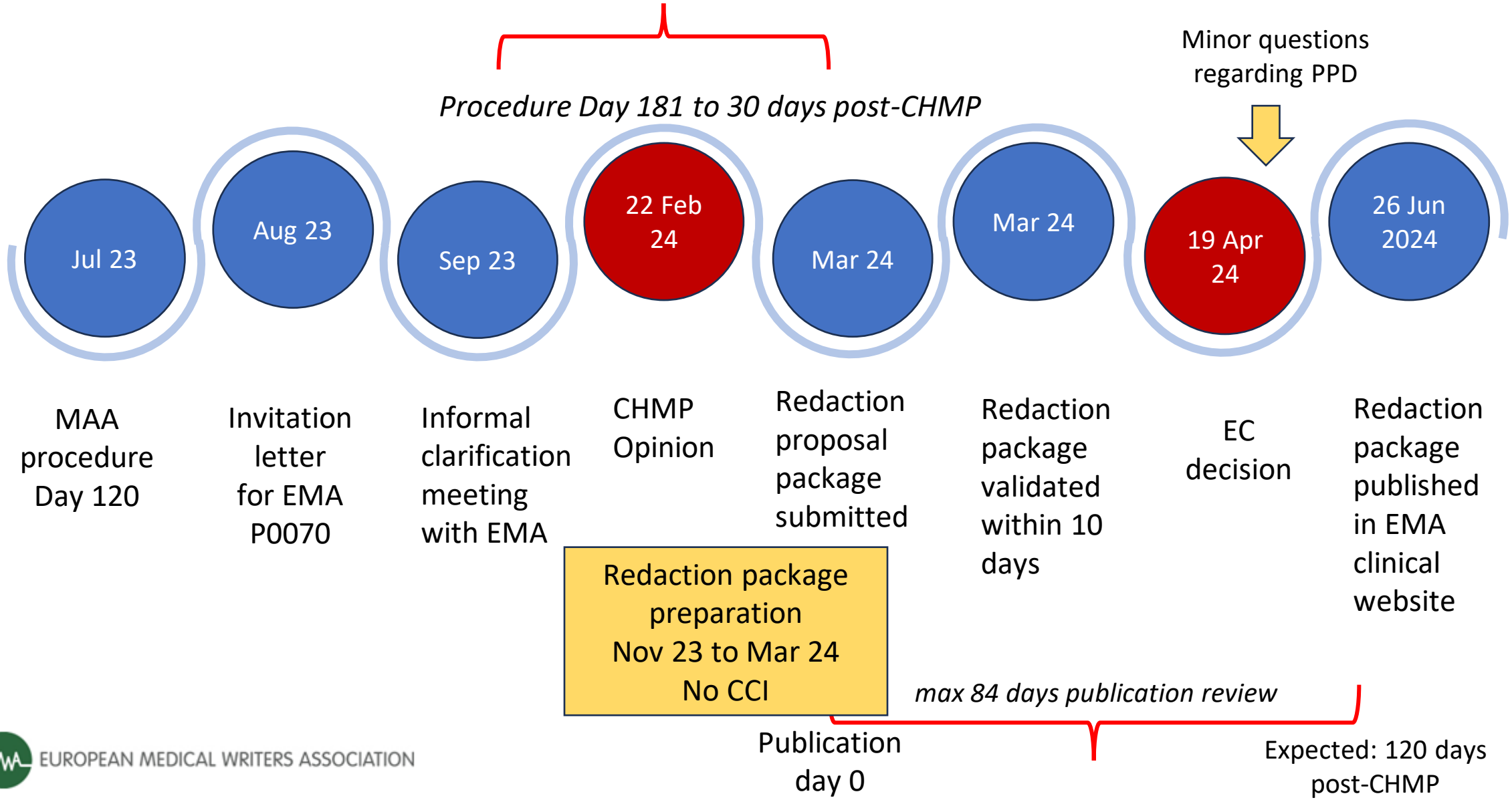
Challenges



- 25 clinical studies
- 160 documents in scope
- Anonymisation for PPD only; no CCI
- Crossfunctional endeavour

- Indicated for paroxysmal nocturnal hemoglobinuria, a rare disease
- Small number of patients in many sites and countries
- Finding the balance between personal data protection and data utility

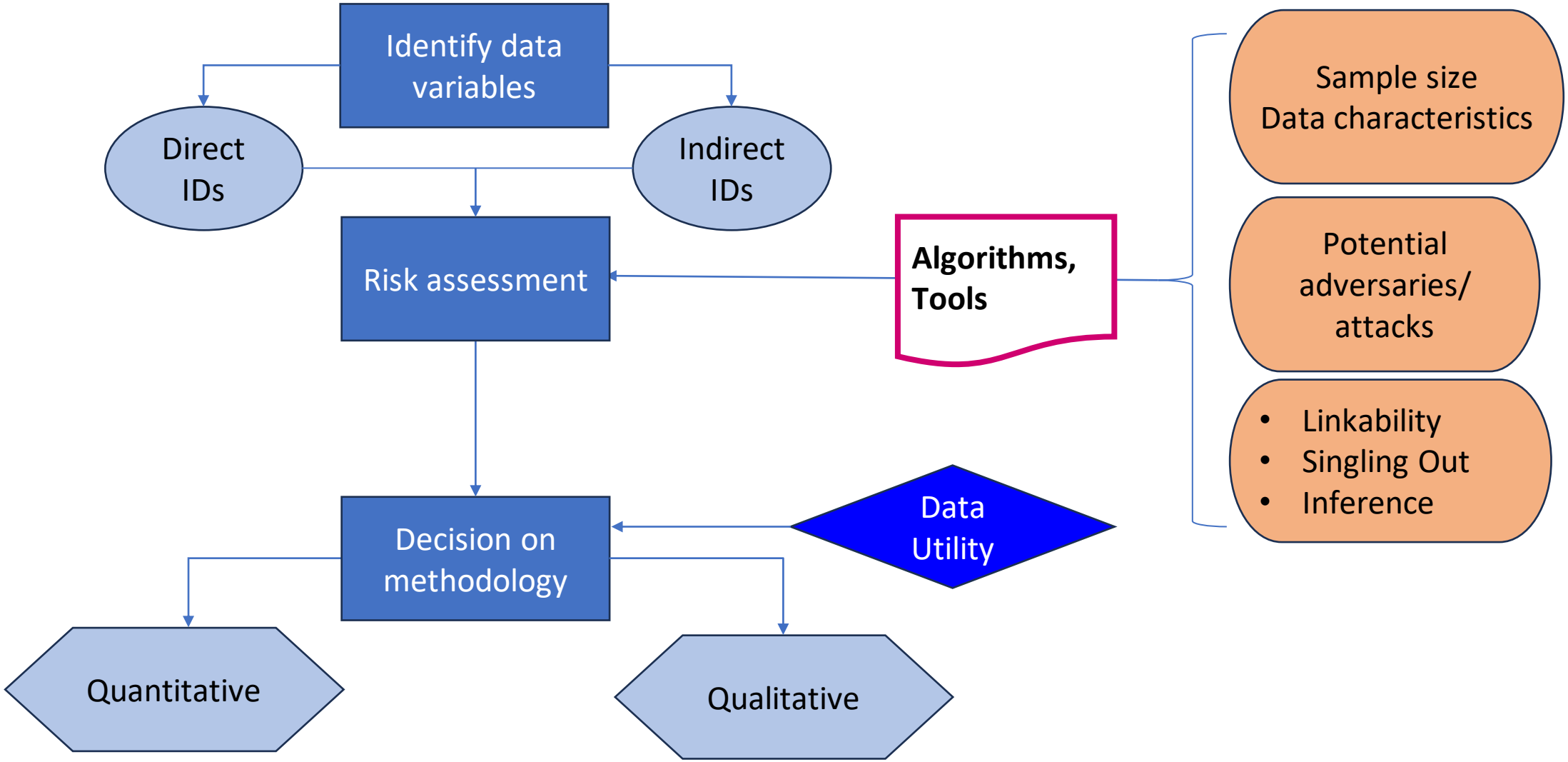
Voydeya Timeline for EMA Policy 0070

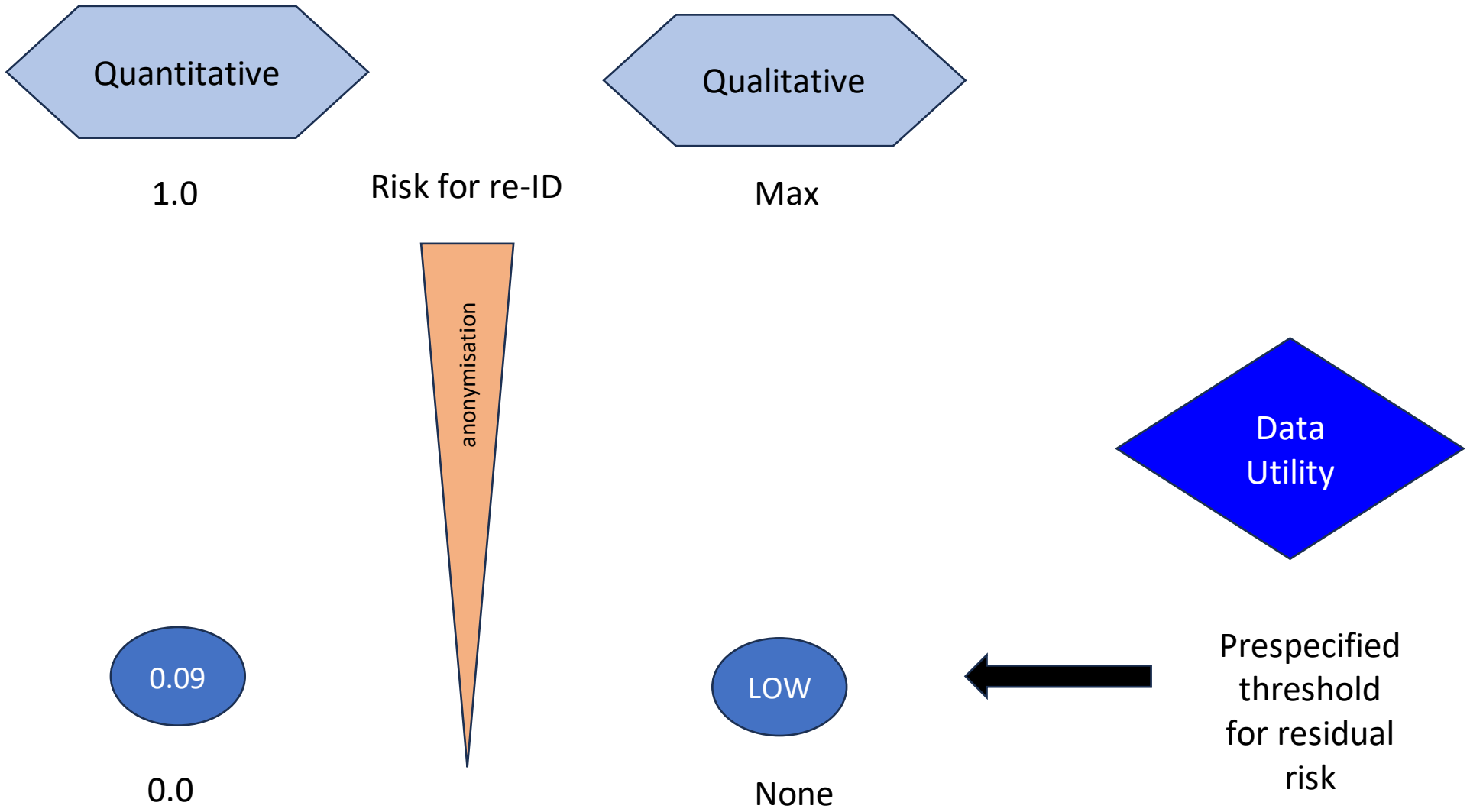


Redaction Package Preparation

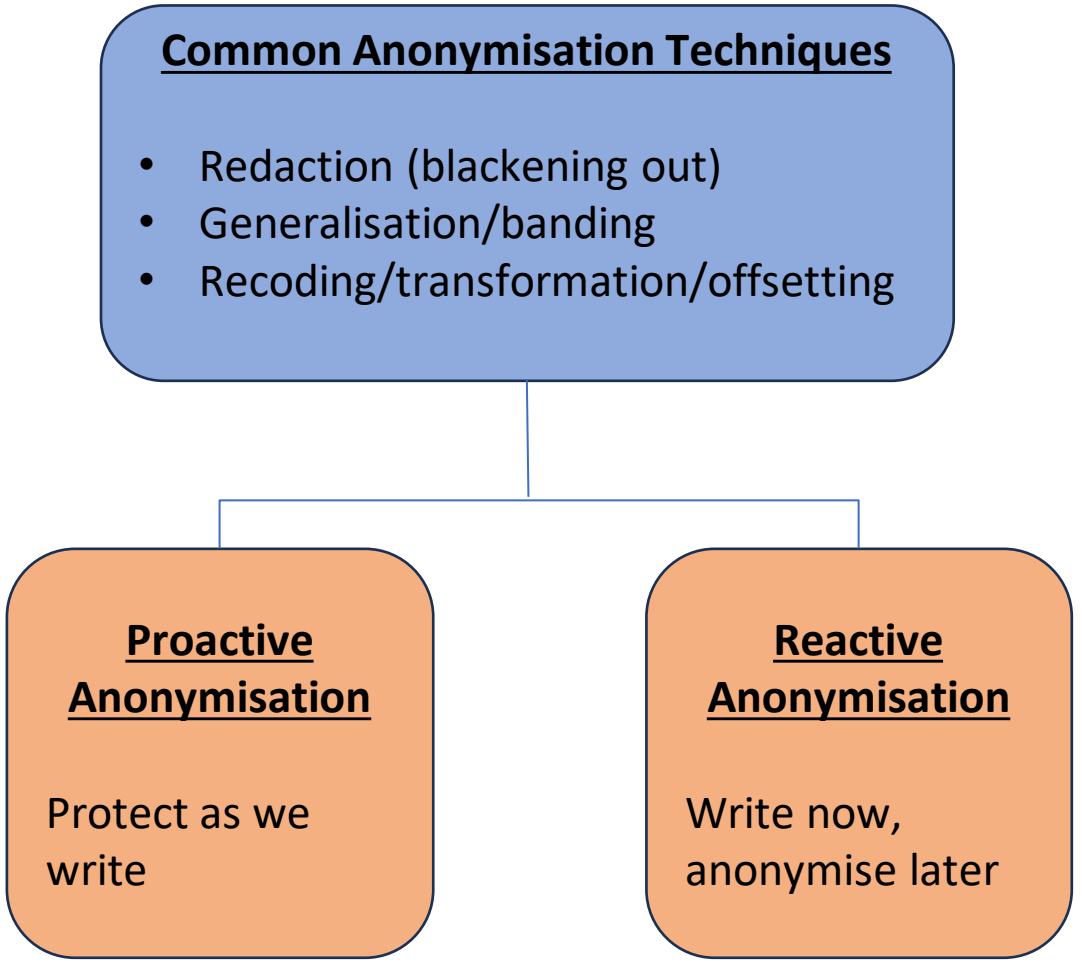
- Identify documents that are in scope
- Risk assessment and methodology decision
- Anonymisation
- Prepare anonymisation report

- Mod 2.5
- Mod 2.7.1, 2.7.2, 2.7.3, 2.7.4
- Mod 5.0
  - All CSRs and selected Appendices
    Section 14 Tables & Figures
    Section 14.3.3 Narratives
    Section 16.1.1 Protocol +Amendments
    Section 16.1.2 Sample CRF
    Section 16.1.9 SAP
  - Mod 5.3.5.3 ISS Outputs


Identify data variables
Direct IDs
Indirect IDs
Risk assessment
Algorithms, Tools
Sample size
Data characteristics
Potential adversaries/ attacks
Linkability
Singling Out
Inference
Data Utility
Decision on methodology
Quantitative
Qualitative


Quantitative
Qualitative
1.0
Risk for re-ID
Max
anonymisation
Data Utility
0.09
LOW
Prespecified threshold for residual risk
0.0
None

Common anonymisation techniques



Voydeya Anonymisation Report

EMA – Health Canada Common Template

1. **Anonymisation Methodology**
2. **Identification of Data Variables**
   - **2.1 Direct Identifiers**
   - **2.2 Indirect Identifiers**
3. **Risk Assessment**
4. **Data Utility**
5. **Deviations**

Direct IDs: info that permits direct recognition or communication with the corresponding individuals (name, initials, address, phone numbers, patient ID)

Indirect (quasi) IDs: variables representing an individual's background information that can indirectly identify individuals (dates, demographics, medical history, AEs, etc.)

1. Anonymisation Methodology

A) Are there any indirect identifiers present within the clinical information package?

- (•) Yes
- ( ) No

1. Anonymisation Methodology

B) What anonymisation method was used to measure risk?

- ( ) Qualitative
- ( ) Quantitative
- (•) Both

[If Both] Please list the studies within the submission distinguishing between the qualitative and quantitatively anonymised studies (or documents.)

ACH471-001 - Quantitative - PoSA=0.067
ACH471-002 - Quantitative - PoSA=0.091
ACH471-005 - Qualitative
ACH471-006 - Quantitative - PoSA=0.083
ACH471-009 - Quantitative - PoSA=0.063
ACH471-010 - Quantitative - PoSA=0.077
ACH471-011 - Quantitative - PoSA=0.071
ACH471-012 - Quantitative - PoSA=0.063
ACH471-013 - Quantitative - PoSA=0.091
ACH471-014 - Quantitative - PoSA=0.09[illegible]
ACH471-016 - Quantitative - PoSA=0.091
ACH471-017 - Quantitative - PoSA=0.091
ALXN2040-HV-101 - Qualitative
ALXN2040-HV-102 - Quantitative - PoSA=0.053
ALXN2040-HV-119 - Quantitative - PoSA=0.091
ALXN2040-PNH-301 - Quantitative - PoSA=0.077
ACH471-100 - Qualitative
ACH471-101 - Quantitative - PoSA=0.083
ACH471-102 - Qualitative
ACH471-103 - Qualitative
ACH471-201 - Qualitative
ACH471-204 - Quantitative - PoSA=0.077
ACH471-205 - Quantitative - PoSA=0.091
ALXN2040-20-0013 - Qualitative
PMX-0025 - Qualitative
PMX-0038 - Qualitative
Clinical-overview - Qualitative

- **25 clinical studies**
- **Sample size range: 8 to 84**
- **Both quantitative and qualitative risk assessments**
- **Preserve data utility**

Quantitative
Phase 3 study
N=84
PoSA = 0.077

Qualitative
Phase 2 study
N=10

*PoSA = possibility of suspected attack

2. Identification of Data Variables

2.1 Direct Identifiers

D) In the table below, please list the direct identifiers present in the clinical information package. Only include identifiers that are present in the document package.

	Category	Participant/ Personnel	Anonymisation	Comments
+ -	Participant/Subject ID	Participant	Yes (Recoded)	
+ -	Participant/Subject ID	Participant	Yes (Redacted)	Exception: redacted in documents containing pooled study data (Module 2, ISE, ISS, PMX-0025, PMX-0038)
+ -	Handwritten Text	Personnel	Yes (Redacted)	
+ -	Name/Initials/Signature	Personnel	No (Retained)	Specific to the corporate office (i.e., not related to an individual)
+ -	Name/Initials/Signature	Personnel	Yes (Redacted)	Specific to an individual
+ -	Contact Details (Email, Phone & Fax)	Personnel	Yes (Redacted)	Specific to an individual
+ -	Contact Details (Email, Phone & Fax)	Personnel	Yes (Redacted)	Exceptions: Sponsor Signatory and Principal Investigator have been retained in the Clinical Study Reports only.
+ -	Other Direct Identifier	Personnel	Yes (Redacted)	DocuSign Envelope Identification number, IP address

- **Retained**
  - Names of PI and Sponsor in CSRs
  - Corporate addresses & contact details
- **Recoded/Transformed**
  - Patient ID
- **Redacted**
  - Names, signature (wet ink, eSig, IP address)
  - Contact details of an individual

2. Identification of Data Variables

2.2 Indirect Identifiers

Category	Participant/ Personnel	Anonymisation	Comments
Demographics - Sex/Gender	Participant	Yes (Redacted)	
Demographics - Sex/Gender	Participant	No (Retained)	ACH471-002, ACH471-005, ACH471-006, ACH471-010, ACH471-012, ACH471-017, ALXN2040-PNH-301
Demographics - Ethnicity	Participant	Yes (Redacted)	
Demographics - Ethnicity	Participant	No (Retained)	ACH471-101
Demographics - Age	Participant	Yes (Generalized)	Age group bands were utilized
Demographics - Age	Participant	Yes (Redacted)	ALXN2040-HV-101, ACH471-005, ACH471-100, ACH471-103, ACH471-201, Module 2 documents, ISE, ISS, PMX-0025, PMX-0038
Demographics - Race	Participant	Yes (Redacted)	
Demographics - Race	Participant	Yes (Other)	ACH471-001: White was kept, all other low frequency races were redacted
Demographics - Race	Participant	No (Retained)	ALXN2040-HV-101, ALXN2040-HV-119
Demographics - BMI	Participant	Yes (Redacted)	
Demographics - Height	Participant	Yes (Redacted)	
Demographics - Body Weight	Participant	Yes (Redacted)	

Sex/Gender

- Redacted by default
- Retained in Phase 1 study (all males), study with n > 80

Age

- Generalised (age groups)
- Redacted in studies with outliers

Race/Ethnicity

- Redacted
- Retained in single race study
- Kept “White”, redacted minority groups or recoded as “other”

Singling out or uniqueness

2. Identification of Data Variables

2.2 Indirect Identifiers

Category	Participant/ Personnel	Anonymisation	Comments
Adverse Event Terms	Participants	No (Retained)	
Adverse Event Terms	Participants	Yes (Redacted)	Exceptions: terms within a rare disease population that are identified as visibly identifiable, rare, newsworthy, or has a negative association.
Records - Medical History	Participant	No (Retained)	
Records - Medical History	Participant	Yes (Redacted)	Exceptions: terms identified as visibly identifiable, rare, newsworthy, have a negative association, or disclose the sex of the participant in a study where sex is redacted.
Records - Concomitant Medications	Participant	No (Retained)	
Records - Concomitant Medications	Participant	Yes (Redacted)	Exceptions: when medications are linked with rare and/or sensitive information, or have a negative association, which could result in harm to the participant in the case of successful re-identification. Also redacted when it would disclose the sex of the participant in a study where sex is redacted.
Demographics - Body Weight	Participant	Yes (Redacted)	
Date/Day - Relative Day	Participant	No (Retained)	
Date/Day - Calendar Date	Participant	Yes (Offset)	Specific to a participant.
Date/Day - Calendar Date	Participant	Yes (Redacted)	Exception: redacted in documents containing pooled study data (Module 2 documents, ISE, ISS, PMX-0025, PMX-0038)

Adverse events / medical history

- Retained
- Redacted if “sensitive”

Concomitant medications

- Retained
- Redacted if “sensitive”
- Redacted if info is inferential
  - Conmeds that “give away” sex, geographic location

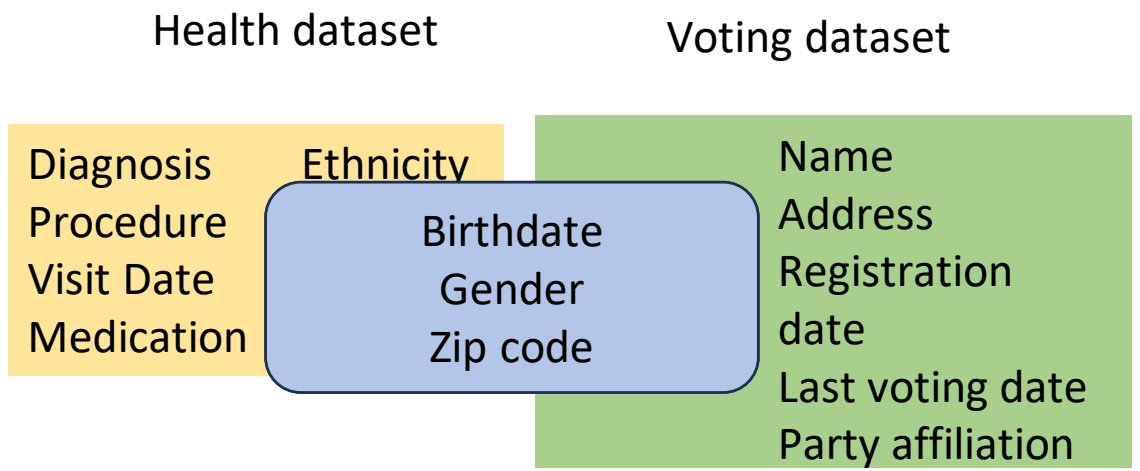
Inference

Dates

- Retained if relative day (eg, Study Day 1)
- Redacted / Transformed if calendar date

2. Identification of Data Variables (Examples not from Voydeya)

Linkability of different variables



Sweeney, 1979 on linkage

3. Risk Assessment

3. Risk Assessment

F) Please input the selected reference population.

Study participants enrolled in each individual CTs in this submission

G) Is this product indicated in the treatment of a rare disease/condition?

(◉) Yes
( ) No

H) Were special populations involved in the trials?

(◉) Yes
( ) No

Please describe the characteristics of the special population(s) below.

An older population was included; for instance, in the phase 3 study ALXN2040-PNH-301, over 25% of patients were aged 65-84.

I) Please input initial risk of reidentification.	1 and High
J) Please input target risk threshold.	0.091 and Low
K) Please input residual risk.	Section 1.B states the quantitative results; Low for qualitative studies

L) Did some of the above indirect identifiers require consideration due to the sensitivity of the information?

(◉) Yes
( ) No

Please list the categories of identifiers which were deemed sensitive by the applicant.

Those identifiers assessed as sensitive as per the qualitative approach and related to study participants were redacted. These included: adverse event terms, medical history terms, and concomitant medication. This sensitive information (e.g., adverse event that was unique in population at large, or a rare disease diagnosis) was qualitatively assessed by experts and redacted only when the risk of re-identification was high as these identifiers were visibly identifiable, rare, newsworthy, or have a negative association, which could result in harm to the participant in the case of successful re-identification. Redactions were also implemented for terms that indicated the sex of the participant when sex was redacted in that study. Lastly, redactions were implemented for sensitive terms, which occurred infrequently.

Where a concomitant medication was linked with such a rare and/or sensitive information, or indicated the sex of the participant when sex was redacted in that study, the concomitant medication was also redacted. This also occurred infrequently.

Sensitive information (redacted)

AEs, medical history terms, and concomitant medication which are

- unique in the population
- rare disease diagnosis (other than the indication)
- newsworthy
- have a negative association

Identified by the software!!!

4. Data Utility

4. Data Utility

N) List the variables with the highest data utility (up to five).	Gender, age, adverse events, medical history

O) How was data utility loss mitigated for these variables?

Alexion utilized a validated software to measure risk and anonymize the clinical documents for this submission. The software calculates a re-identification risk value for each participant enrolled in the clinical trial based on K-anonymity. Alexion thoroughly considered the balance of data utility and privacy when applying the anonymization method to this submission. Data utility was maximized by including a quantitative risk assessment, appropriate reference population selection, and the anonymization of personal data using randomization and offsetting. When the risk assessment did not allow the application of specific anonymization methods due to the limitation of the sample size of the study, redaction was applied to protect participant privacy. Summary information included in this submission was retained.

Therefore, where possible (i.e., in quantitatively-assessed studies), age was banded and gender was retained. Adverse events were a priority for retention as was medical history; both were qualitatively assessed by experts and retained except in unique instances where the term was assessed to be a high-risk identifier (i.e., visibly identifiable, rare, newsworthy, or has a negative association), or the term indicated the sex of the participant when sex was redacted in that study. All adverse events were retained on the summary level.

P) Have aggregate tables been appropriately retained?

- (•) Yes
- ( ) No

Gender
Age
AEs
Medical history

Data with highest utility
Retained or banded

Exceptions are sensitive data and outliers REDACTED

Narrative # 01

Participant ID	8593-663				
Narrative Type(s)	☐ Death ☐ SAE ☒ Discontinuation due to AE ☒ AE of Special Interest ☐ Pregnancy				
Demography (Age/Sex/Race)	18-60 years/Female/PPD				
Treatment Assignment and Dose	TP1: danicopan 150 mg tid TP2: danicopan 150 mg tid				
C5i background therapy	Ravulizumab IV 3300 mg (TP1 and TP2)				
Status at Data Cutoff	TP2				
Preferred Term (Verbatim Term)	**Onset Day**	**Seriousness**	**Status of Event/ Day of Resolution**	**Relationship to Study Intervention as Determined by Investigator**	**Action Taken with Study Intervention**
Hepatic enzyme increased (elevated liver enzymes)	Study Day 43 (TP1)	Nonserious	Not recovered/Not resolved/ NA	Related	Drug withdrawn

Abbreviations: AE = adverse event; C5i = complement component 5 inhibitor (eculizumab or ravulizumab); ID = identification number; IV = intravenous; NA = not applicable; SAE = serious adverse event; tid = 3 times per day; TP1 = Treatment Period 1; TP2 = Treatment Period 2

The participant was diagnosed with PNH in 2005. The participant received the first dose of blinded study intervention (danicopan) on Study Day 1 (TP1). The participant completed TP1, and did not complete TP2.

Medical history (year of onset/year of resolution) included: cytomegalovirus test positive (unknown/ongoing), PPD (unknown/ongoing), cerebral venous sinus thrombosis (2008/unknown), and asthenia (2021/2021).

Concomitant medications on Study Day 1 included: folic acid, acenocoumarol, omeprazole, ciprofloxacin, vitamin B12 NOS (not otherwise specified), and meropenem.

Narrative # used in lieu of patient ID

Recoded

Age band, sex retained, race redacted

Recoded: Study Day in lieu of calendar date

Generalised: Year instead of calendar date

Sensitive data

★ Proactive anonymisation

★ Reactive anonymisation

EUROPEAN MEDICAL WRITERS ASSOCIATION

CORE REFERENCE

Anonymisation (Dummy data, not from Voydeya)

Before

ID#	Initials	Location	Age (Y)	Gender	Race	History
001	JP	Zurich	30	Female	White	Cancer
002	AM	London	24	Female	White	Viral infection
003	RB	Copenhagen	28	Female	Black	TB
004	JM	Manchester	27	Male	Asian	Cardiovascular
005	TR	Amsterdam	24	Female	Native Am	Heart-related
006	SB	Geneva	23	Male	White	TB
007	ST	Berlin	19	Male	White	Cancer
008	RC	Zurich	29	Male	White	Cardiovascular
009	GL	Munich			Black	
010	LB	London	19	Male	Other	Viral infection

Recoding | Redaction | Generalisation | Banding | Retain | Generalisation | Retain

After

ID#	Initials	Location	Age (Y)	Gender	Race	History
185	PPD	Switzerland	20 < Age ≤ 30	Female	White	Cancer
281	PPD	UK	20 < Age ≤ 30	Female	White	Viral infection
383	PPD	Denmark	20 < Age ≤ 30	Female	Other	TB
427	PPD	UK	20 < Age ≤ 30	Male	Other	Cardiovascular
587	PPD	Netherlands	20 < Age ≤ 30	Female	Other	Heart-related
651	PPD	Switzerland	20 < Age ≤ 30	Male	White	TB
725	PPD	Germany	Age ≤ 20	Male	White	Cancer
155	PPD	Switzerland	20 < Age ≤ 30	Male	White	Cardiovascular
823	PPD	Germany	Age ≤ 20	Male	Other	Cardiovascular
250	PPD	UK	Age ≤ 20	Male	Other	Viral infection

Medical Writing Learnings

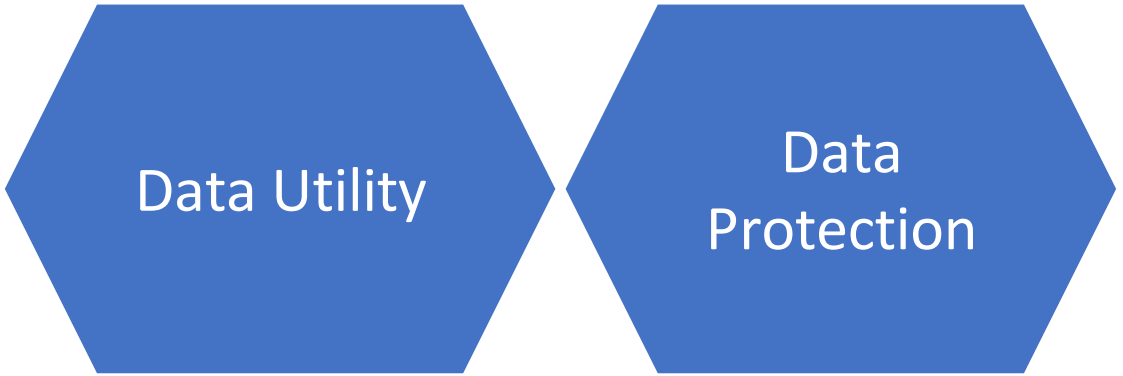
Phase 3 CSR was written with disclosure & data protection in mind (proactive anonymisation)

- **No CCI**
- **No patient ID, demographics were used in the CSR body.**
- **Direct and indirect IDs only used in Section 14.3.3 Narratives**
- **CSR body required very minimal redaction.**

Additional reactive anonymisation

- **Patient IDs were recoded.**
- **Age was banded.**
- **Redaction was limited to information that are unique, sensitive, inferential.**

Similar approach in Clinical Modules



A big thank you to the cross-functional team who developed the Voydeya disclosure package

- **CT Transparency**
- **Medical Writing**
- **Regulatory Affairs**
- **Biostatistics**
- **Legal Counsel**