Learning Objective

By end of today's session you will know about:

- An Overview About EudraCT Regulations
- Insights About the Major Differences Between the Widely used Global Databases (EudraCT and ClinicalTrials.gov)
- Practical Considerations for Functional Areas

Overview About EudraCT Regulations

EudraCT - An Overview

Sponsor submit CT dossier (CTA + substantial amendment + end of trial notifications + clinical study report) to NCA

Sponsor

NCA

- ✓ Request EudraCT number
- ✓ Prepare CTA
- ✓ Substantial amendment (if any)
- ✓ End of trial notification
- ✓ Clinical study report

EudraCT Database

- ✓ Upload of:
- ✓ CTA
- ✓ Substantial amendment (if any)
- ✓ End of trial notification

Create and post results

EUCTR public website
CTAs and Results available publicly

Regulatory Bodies and Laws

Regulatory Bodies

- European Medicine Agency
- Member States (NCA) of the EU

Laws/Acts/Regulations

- Commission Guideline 2012/C 302/03
- Directive 2001/20/EC
- Pediatric Regulation (EC) No 1901/2006 (Art 41,45,46)
- Regulation (EC) No 726/2004

EudraCT V10: A Significant Step Towards Transparency

Registry
EudraCT v.8
08 Mar 2011

- ✓ Protocol related information
- ✓ Trials initiated after 01 May 2004
- ✓ Trials conducted only in EU/EEA unless they are part of Pediatric investigational plan (PIP)
- ✓ No data entry done by Sponsors
- ✓ Data automatically pulled from CTA Form submitted by sponsor to NCAs
- ✓ Trials publicly available:
  All Phase 2 to 4 and Phase 1 in children

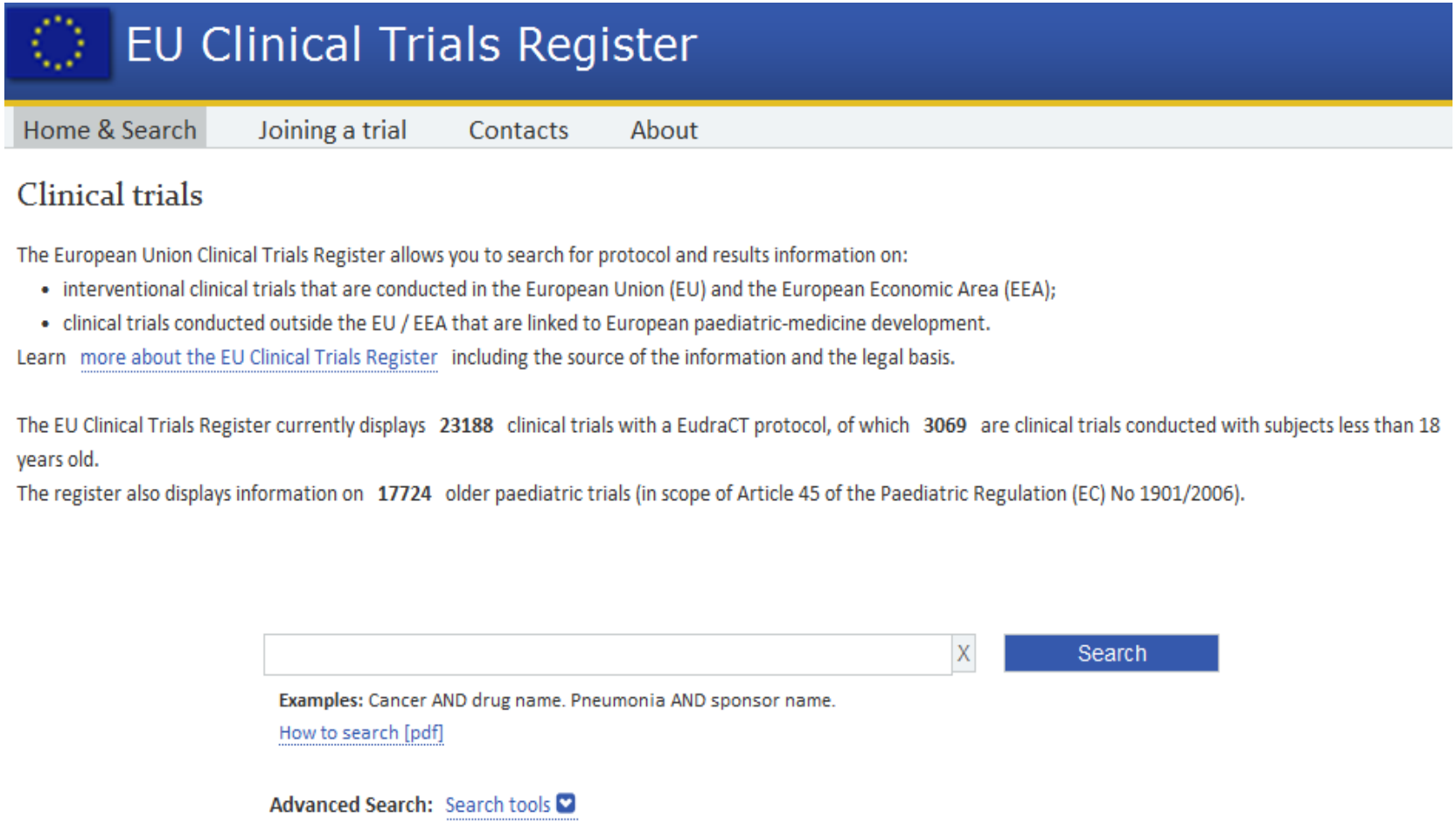
Results Database
EudraCT v.10
Implementation date:
21 Jul 2014

- ✓ Results of Phase 1 to 4 interventional trials
- ✓ Provision for registration of trial conducted outside EU/EEA* (PIP trials and Pediatric trials)
- ✓ Manual data entry by sponsors or XML
- ✓ Retrospective submission of results till 01 May 2004
- ✓ Results publicly available:
  All Phase 2 to 4 and Phase 1 in children

Result Submission Timelines: Prospective and Retrospective

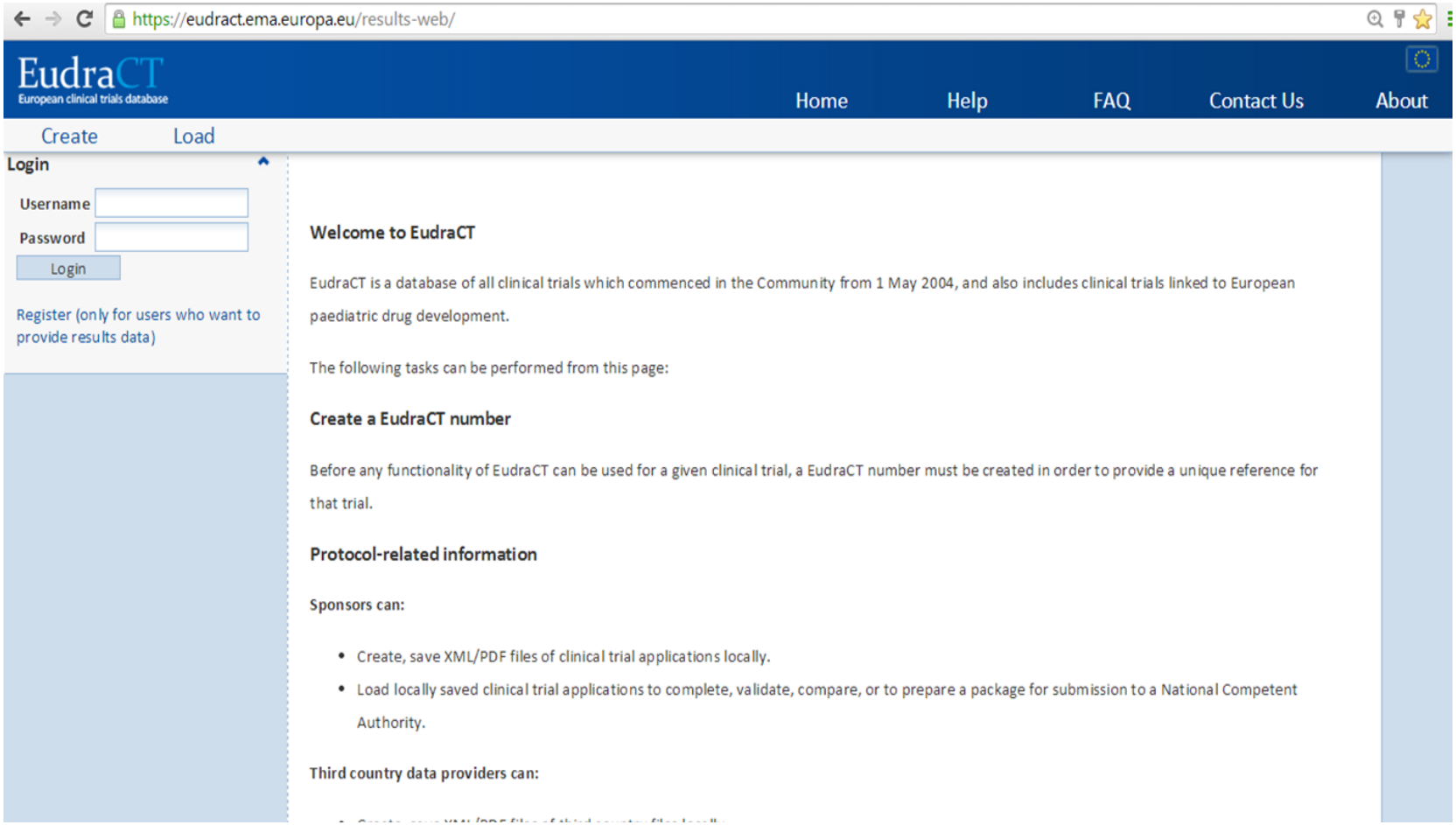
	21 Jul 14	LSLV + 6 months	LSLV + 12 months	21 Jul 2016
	0	+ 6	+ 12	+ 24
	EudraCT finalisation	EudraCT + 6 months	EudraCT + 12 months	EudraCT + 24 months
Prospective/ Routine Timelines		Pediatric trials acc. Regulation (EC) No 1901/2006 + Art 41, + Art 46 trials completed on 21 Jul 2014 or after	Adult trials acc. 2001/20/EC completed on 21 Jul 2014 or after	
Retrospective Timelines 			Pediatric trials Art. 41 + Art. 46 Completed before 21 Jul 2014	Pediatric trials Art. 45 Completed before 21 Jul 2014 (if not already submitted to EMA)
			Adult trials acc. 2001/20/EC completed **from 21 Jul 2013 to 21 Jul 2014**	Adult, acc. 2001/20/EC completed **before 21 Jul 2013**
Report Type		Full data set	Full data set	Full Data Set or ICH E3 synopsis or CT.gov result preview or publications, with copyright

EUCTR Public Website



https://www.clinicaltrialsregister.eu/ctr-search/search

EudraCT Database (Version 10)



https://eudract.ema.europa.eu/results-web/

Major Differences Between the two Major Global Databases (EudraCT and ClinicalTrials.gov)


EudraCT
Vs
ClinicalTrials.gov

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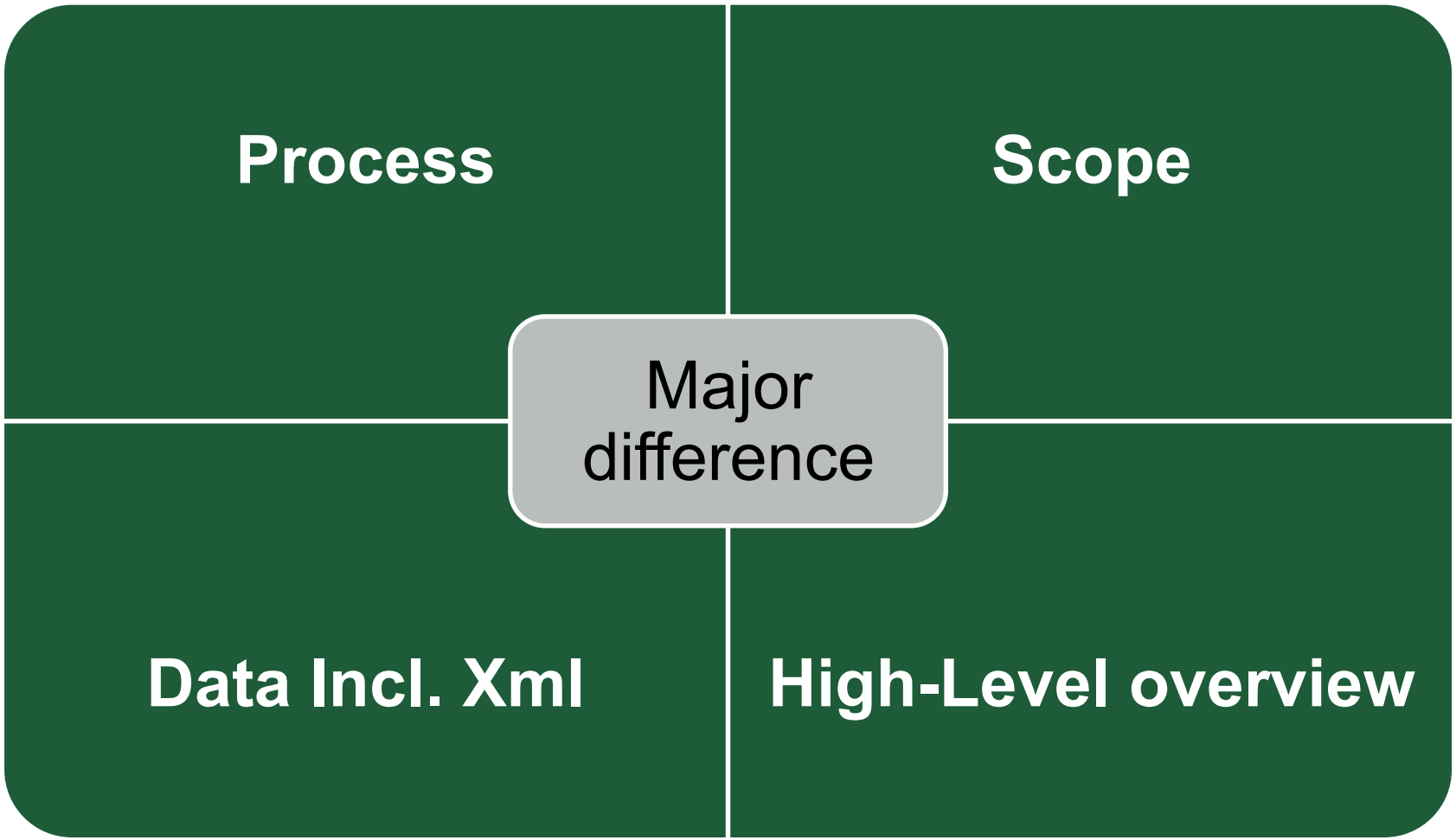
Process
Scope
Major difference
Data Incl. Xml
High-Level overview

EudraCT Vs ClinicalTrials.gov

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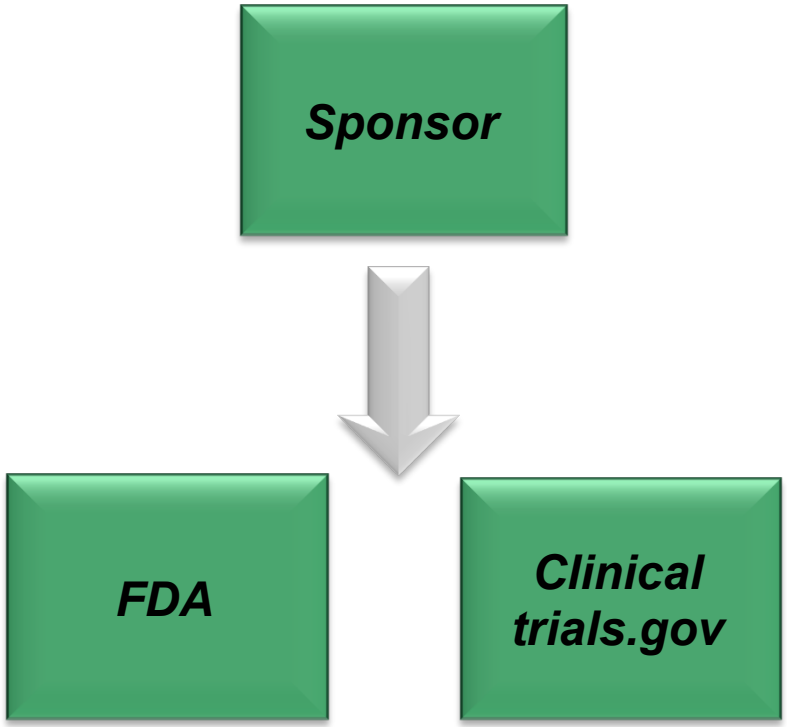
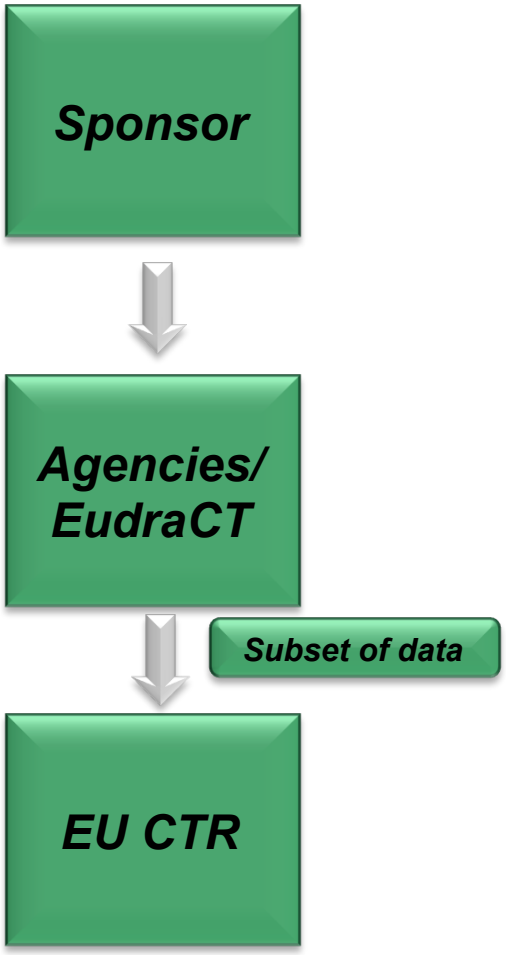
Process

US (ClinicalTrials.gov)



EU (EudraCT)



EudraCT Vs ClinicalTrials.gov

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Scope

US (ClinicalTrials.gov)

- CT.GOV was designed from the outset and remains as a Web-based resource that provides patients, their family members, health care professionals, researchers, and the public with easy access to information on publicly and privately supported clinical studies. Trial information is directly provided and updated to CT.GOV by the sponsor or principal investigator of the clinical study.

EU (EudraCT)

- In regards to protocol registration, the purpose of the EudraCT database is to allow the various European Economic Area (EEA) agencies to take a decision on whether to approve the study
- Secondary purpose is to submit the data to the EU CTR.

EudraCT Vs ClinicalTrials.gov

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High-Level overview

	EudraCT	ClinicalTrials.gov
Mandatory scope	Phase 1 to 4, **unapproved** and approved products	Phase 2 to 4, approved products
Voluntary posting	No voluntary posting possible	Voluntary posting accepted: All types of trials
Publicly available	Phase 1 (Pediatric trials), Phase 2 to 4	All posted studies
Timelines	Pediatric trials: **LSLV + 6 months** Adult trials: LSLV + 1 year	All trials: LSLV + 1 year
Countries and sites	Enrolment per country Enrolment in the EU	Countries, sites + recruitment status

EudraCT Vs ClinicalTrials.gov

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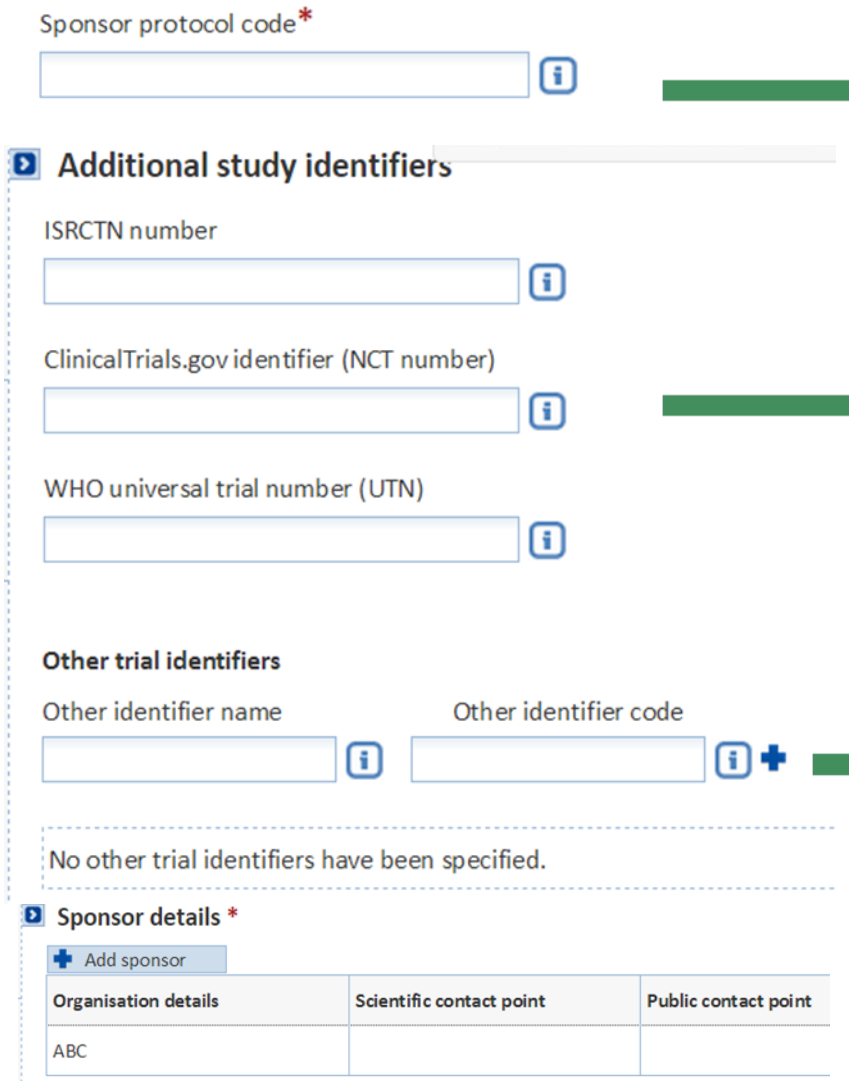
Data Differences :Trial Information (1/6)



Study code on the protocol

Information on ClinicalTrials.gov

Additional sponsor study number assigned

Contact point (scientific & public)

EudraCT Vs ClinicalTrials.gov

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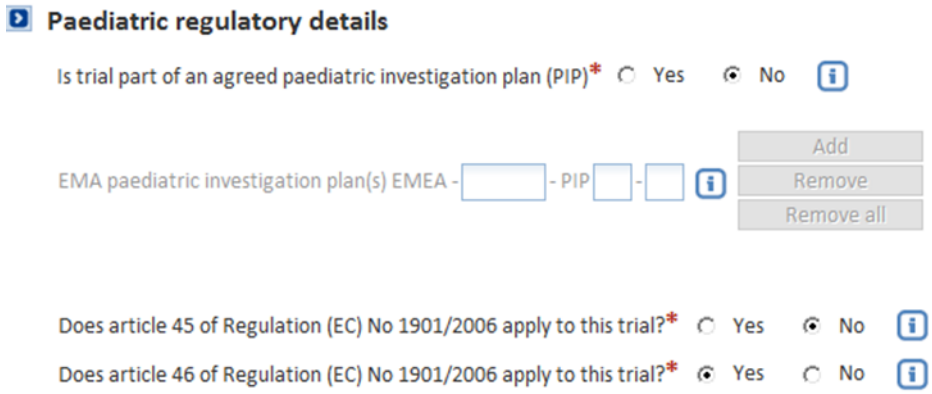
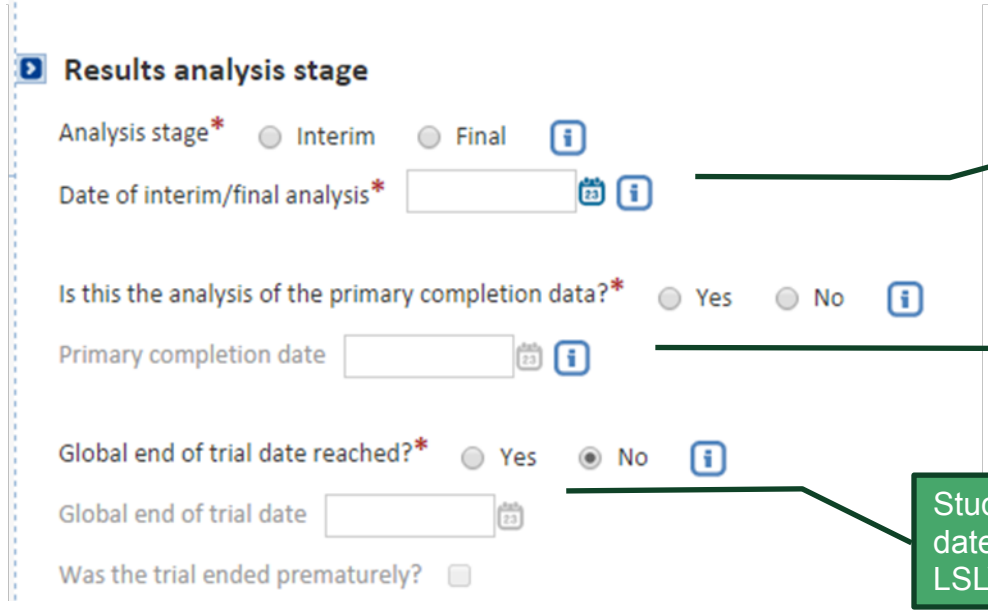
Data Differences :Trial Information (2/6)



- ✓ Mandatory info to decide the scope and to post result on EudraCT
- ✓ To be to be confirmed by study **team** during review cycle



Cut-off data point for the reported analysis or date of database lock

Primary completion date is the date that the final subject was examined or received an intervention for the purposes of final collection of data for the **primary end point**.

Study completion date is in CSR i.e. LSLV

EudraCT Vs ClinicalTrials.gov

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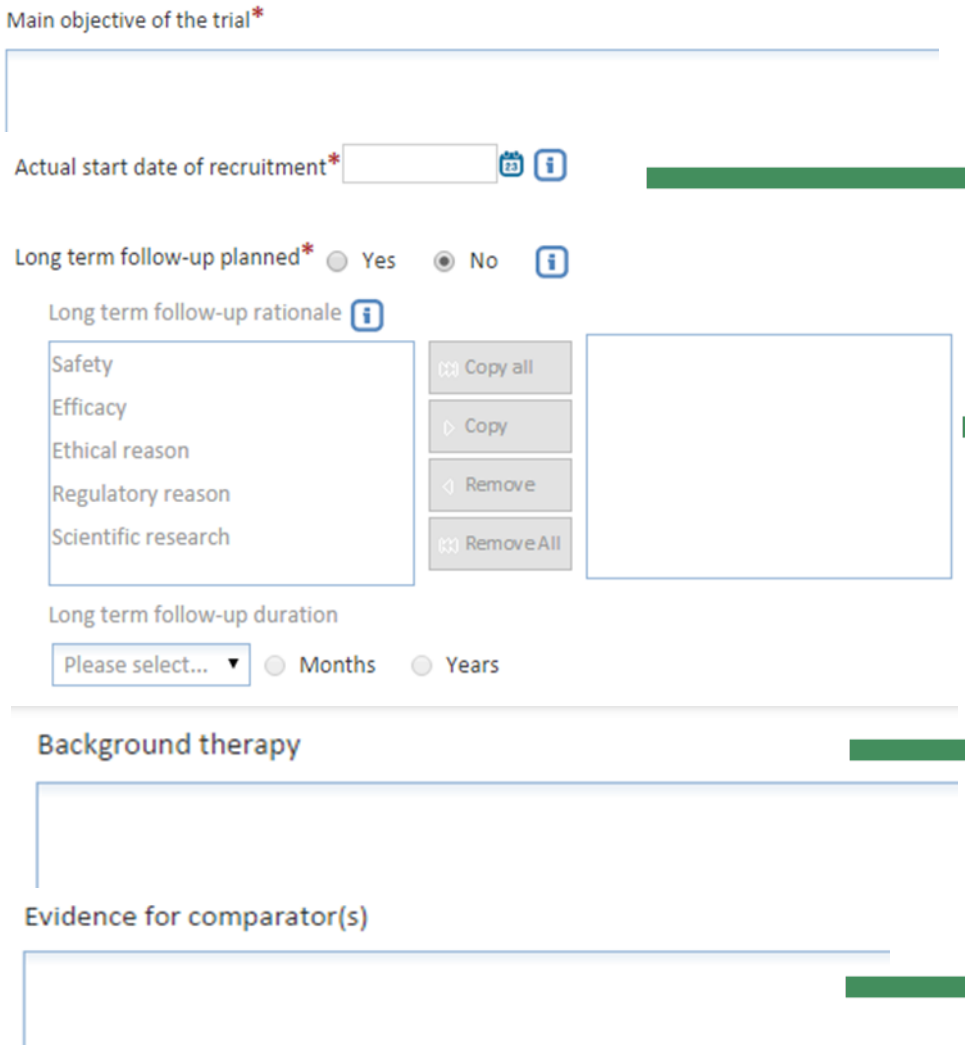
Data Differences :Trial Information (3/6)



Primary objective(s) only

Study start date FSFV

- ✓ Long term monitoring of subjects planned after the end of treatment
- ✓ To confirmed or added by study team the review cycle

Treatments other than experimental or comparator drugs.
Non-mandatory, can be left blank

Rationale and evidence for the use of the comparators used in the trial.
Non-mandatory, can be left blank

EudraCT Vs ClinicalTrials.gov

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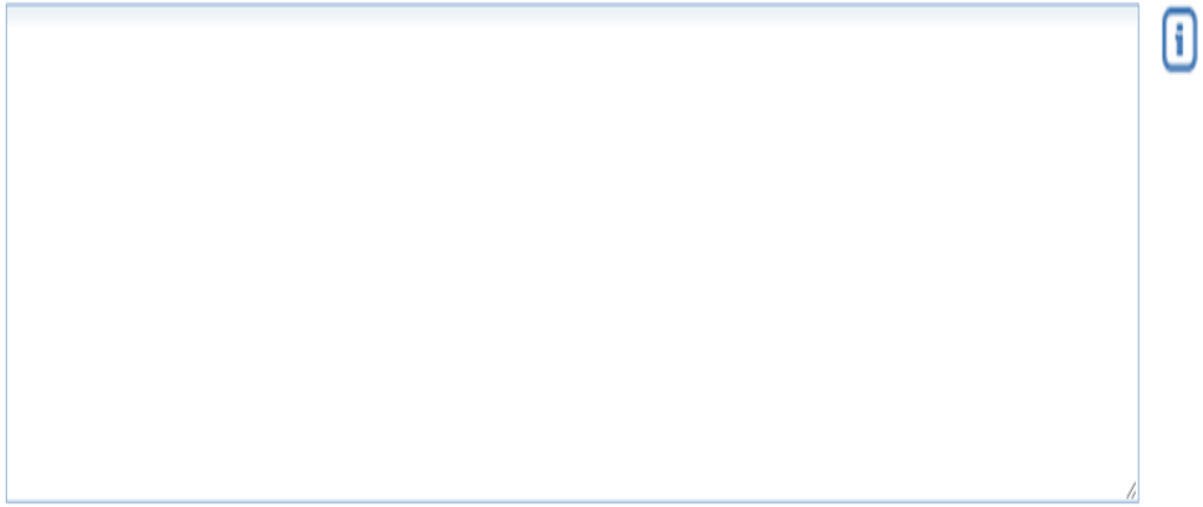
Data Differences :Trial Information (4/6)

Protection of trial subject: Mandatory field

- Protection of trial subjects*



- ✓ Enter a description for any specific measures that were put in place to protect trial subjects, e.g. measures to minimize pain and distress
- ✓ To be to be confirmed by **Study team** during review cycle

EudraCT Vs ClinicalTrials.gov

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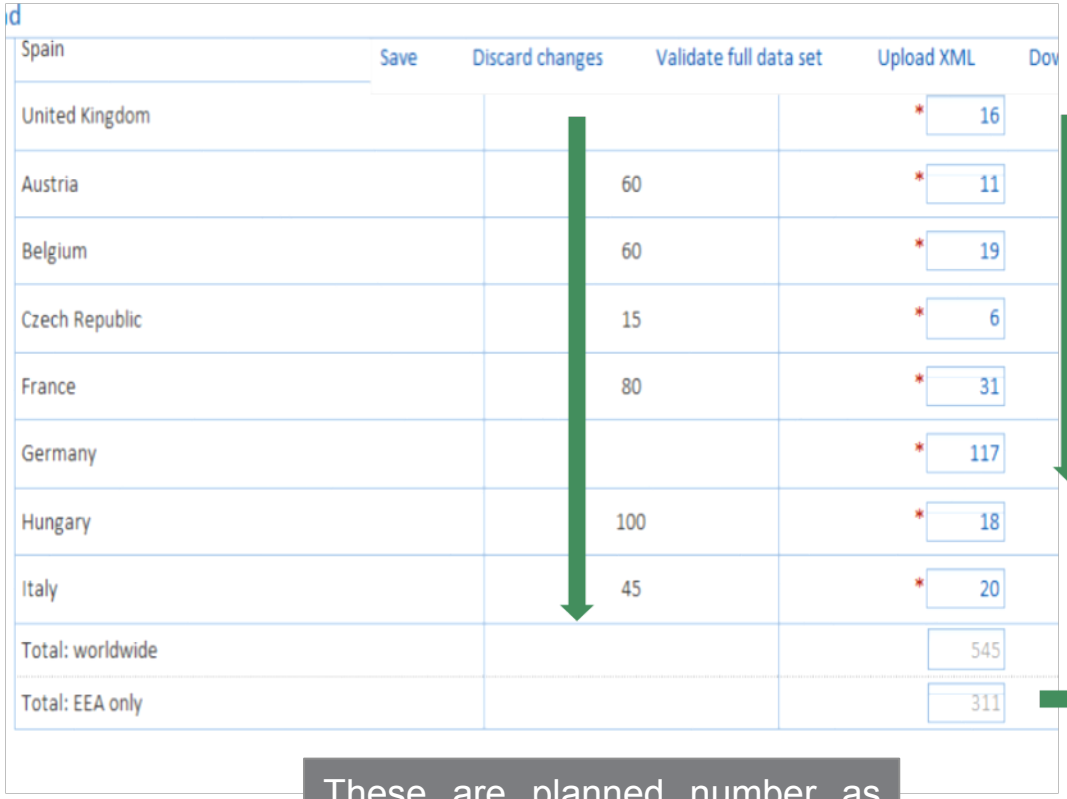
Data Differences :Trial Information (5/6)

Population of trial subjects (Country wise): Mandatory field



Spain	Save	Discard changes	Validate full data set	Upload XML	Dov
United Kingdom				* 16	
Austria			60	* 11	
Belgium			60	* 19	
Czech Republic			15	* 6	
France			80	* 31	
Germany				* 117	
Hungary			100	* 18	
Italy			45	* 20	
Total: worldwide				545	
Total: EEA only				311	

These are planned number as per CTA submitted (Auto-populated or non-editable)

- ✓ Randomized vs. enrolled: Actual randomized subjects country wise entered as we need to keep the total number consistent with no. of subject started in disposition table
- ✓ Statistician needs to confirm/ complete during review cycle (depending upon availability of info in the CSR appendices)

Total population in EEA is auto-calculated (not requested by CT.gov),

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Data Differences :Trial Information (6/6)

Age group break down for trial: Mandatory field

Age group breakdown for trial

Age range	Planned number of subjects	Actual number of subjects enrolled
In utero		*
Preterm newborn infants (gestational age < 37 wks)		*
Newborns (0-27 days)		*
Infants and toddlers (28 days-23 months)		*
Children (2-11 years)		*
Adolescents (12-17 years)		*
Adults (18-64 years)	26	*
From 65 years -		
From 65-84 years		*
85 years and over		*

- ✓ Age breakdown as per these pre-sepcified categories is mandatory (not requested by CT.gov)
- ✓ Actual number of subjects as per these pre-specified categories
- ✓ Statistician needs to confirm/ complete during review cycle (depending upon availability of info in the CSR appendices)

These are planned number of subject per age category as per CTA submitted (Auto-populated or non-editable)

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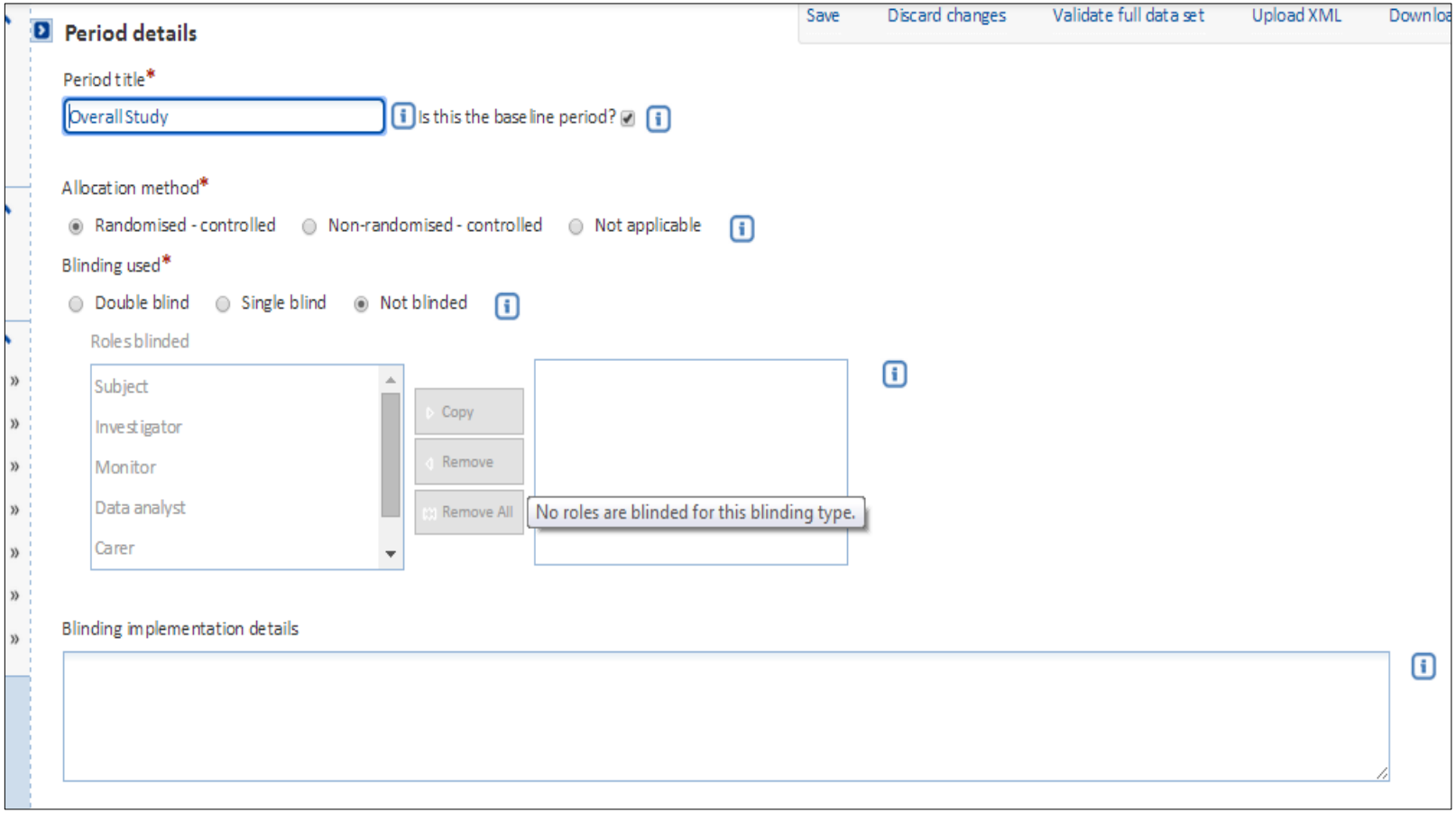
Data Differences :Subject Disposition (1/2)

- ✓ Period details



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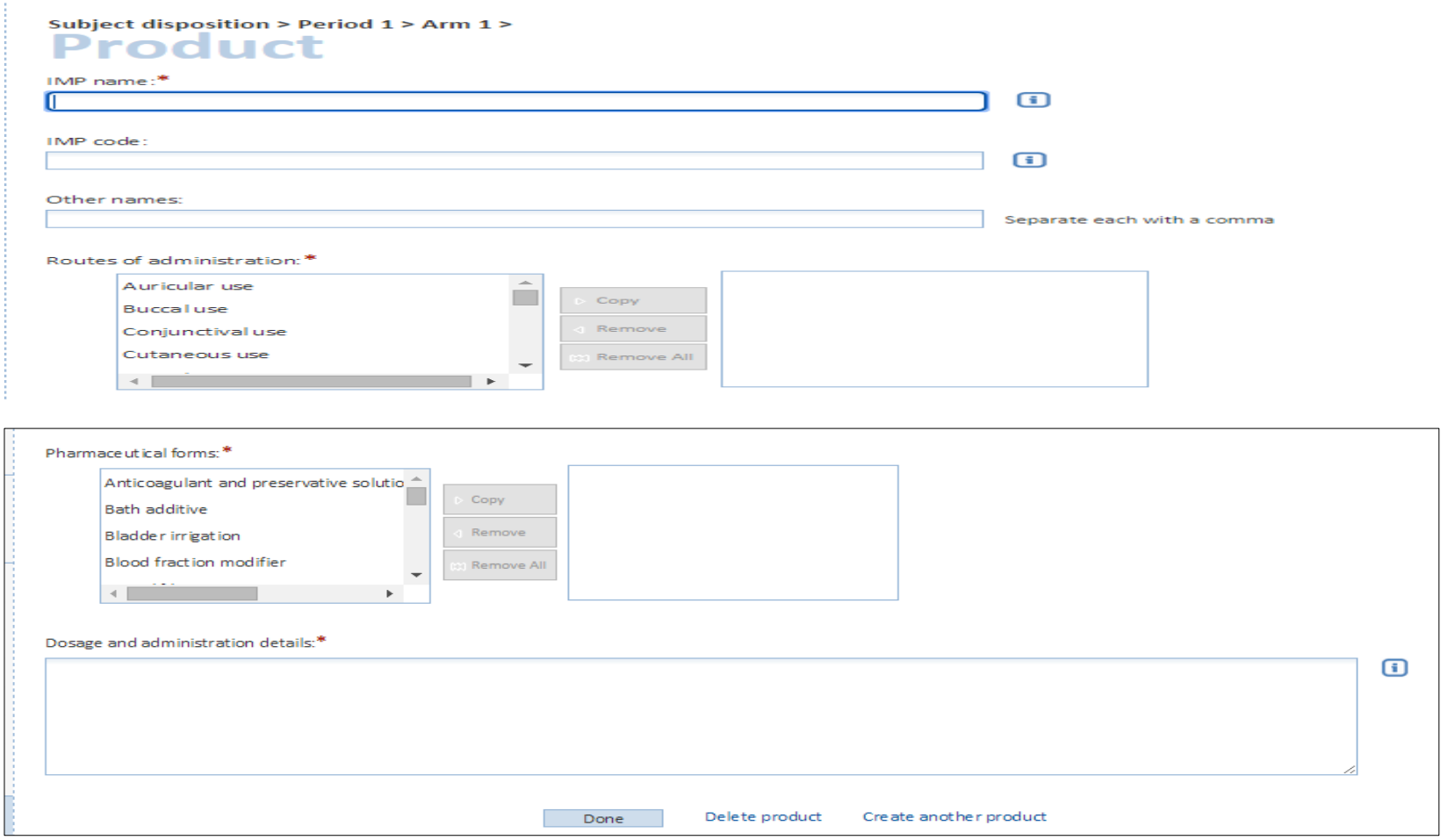
Data Differences :Subject Disposition (2/2)

- ✓ Product details



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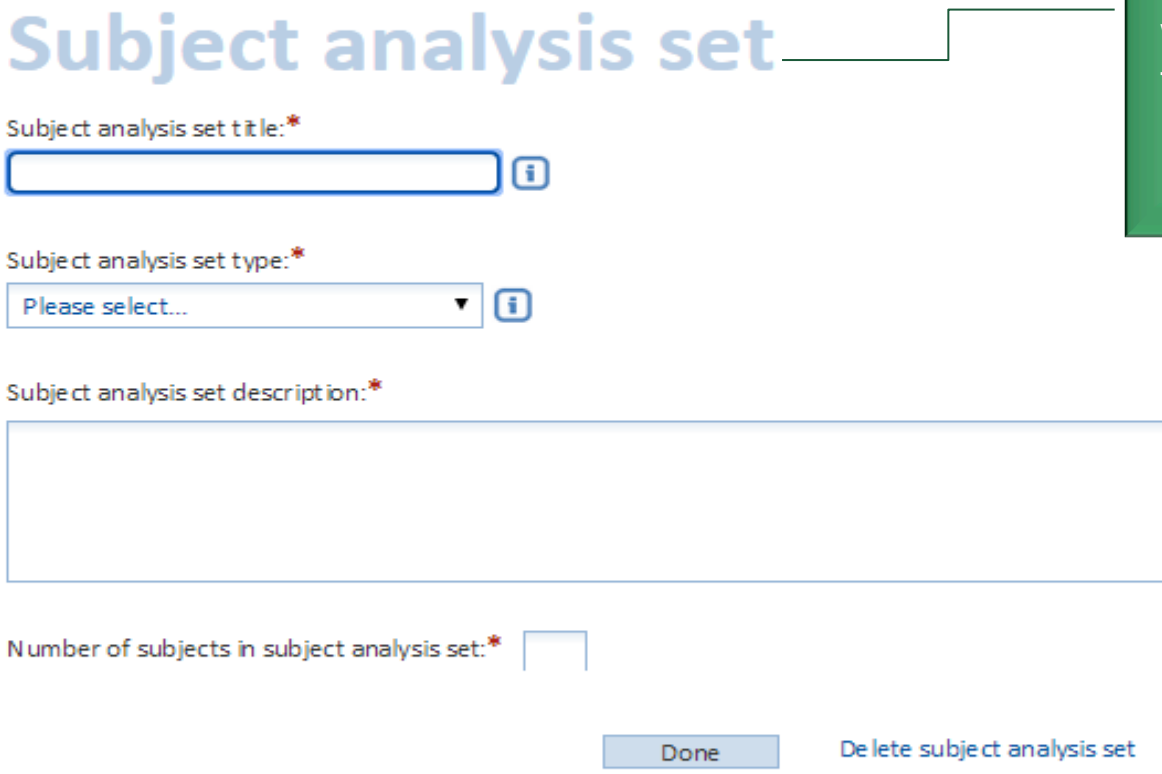
Data Differences :Baseline/Endpoint

- ✓ Subject Analysis set



Add a subject analysis set if you wish to report on groups different from the reporting groups defined in the subject disposition section.

EudraCT Vs ClinicalTrials.gov

Data Differences :Adverse Events :General Information

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Reporting group title:*

Reporting group description:

For this reporting group, provide the following totals:

Subjects exposed:*

Subjects affected by serious adverse events:*

Subjects affected by non-serious adverse events:*

Total number of deaths (all causes):*

Total number of deaths resulting from adverse events:

- ✓ These fields are mandatory
- ✓ Statistician needs to confirm/complete during review cycle (depending upon availability of info in the CSR appendices)
- ✓ 'Total number of deaths': This field is mandatory and also not required by CT.gov

This field is not mandatory and also not required by CT.gov

EudraCT Vs ClinicalTrials.gov

Data Differences : Serious Adverse Events

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Values for serious adverse event per reporting group *

Reporting groups	Subjects affected number	Subjects exposed number	Occurrences all number	Occurrences causally related to treatment number	Fatalities number	Fatalities causally related to treatment number
ABC						

SAE table should have:

- Total number of subjects affected and exposed
- Total number of occurrences
- Total number of occurrences casually related to treatment
- Number of deaths due to SAE
- Number of deaths due to SAE casually related to treatment

- ✓ Mandatory and not requested by CT.gov.
- ✓ Statistician needs to confirm/complete during review cycle (depending upon availability of info in the CSR appendices)

Ideal Scenario: Statistician to generate SAE tables with this information for direct uploading (XML)

EudraCT Vs ClinicalTrials.gov

Data Differences : Non-Serious Adverse Events

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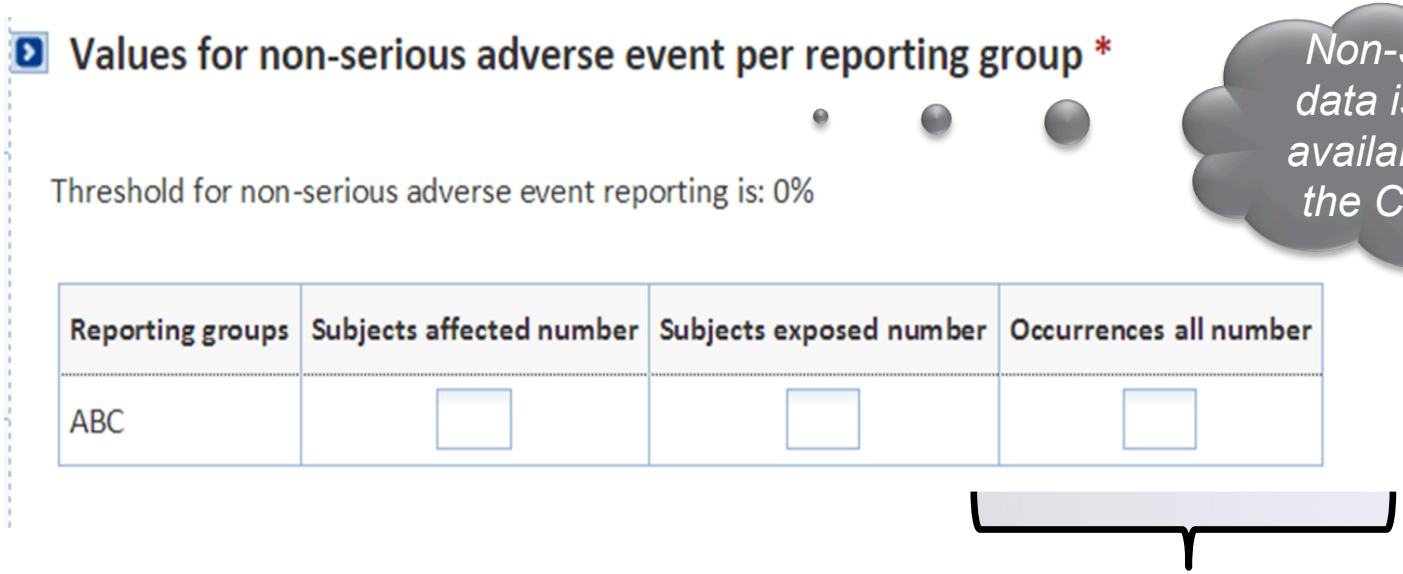

Non-SAE data is not available in the CSRs

Non-SAE table should have:

- Total number of subjects affected
- Total number of subjects exposed
- Total number of occurrences

- ✓ Mandatory field
- ✓ Statistician needs to confirm/complete during review cycle (depending upon availability of info in the CSR appendices)

Ideal Scenario: Statistician to generate Non-SAE tables with this information for direct uploading (XML)

EudraCT Vs ClinicalTrials.gov

Data Differences : Amendments and Interruptions

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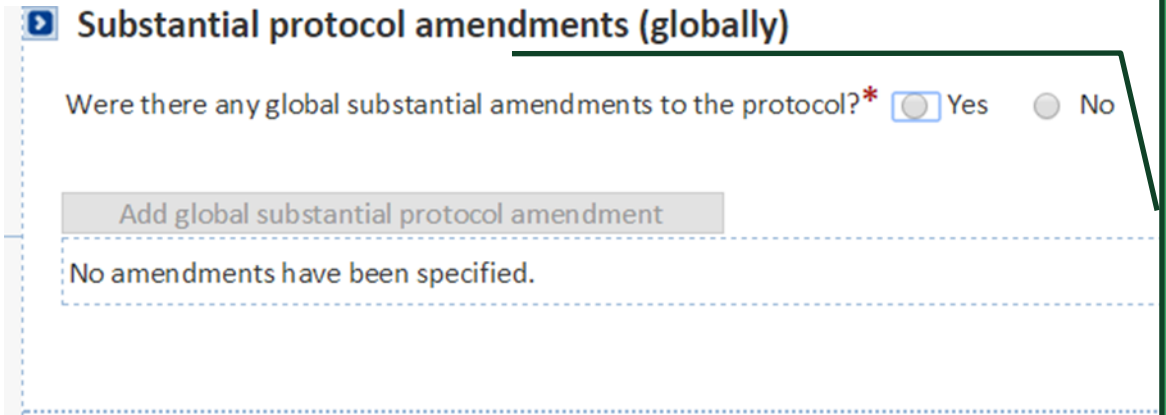
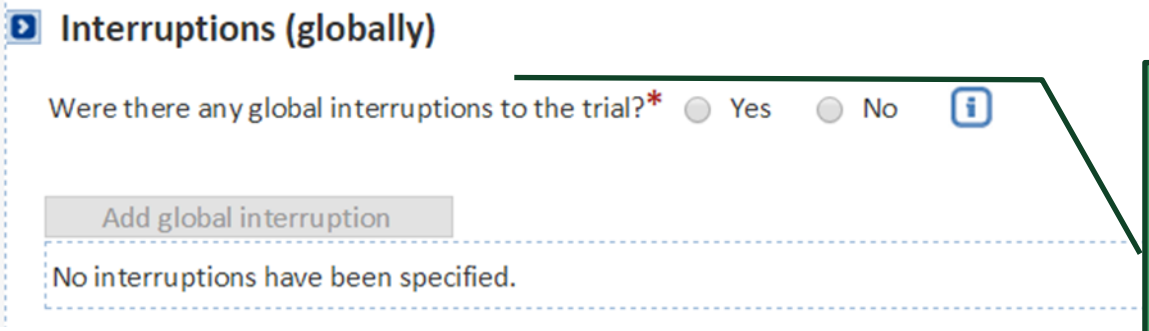


- ✓ Description and a reason for the main changes to the protocol
- ✓ Substantial amendment date was first approved by a regulatory authority
- ✓ Character limit: 2000
- ✓ Medical monitor to confirm/update based on the all substantial amendments



- ✓ Description and reason for the interruption
- ✓ Date when the interruption took effect
- ✓ Character limit: 2000
- ✓ Medical monitor to confirm/update based on the all substantial amendments

Source of information: CTR Section, “Changes in the conduct of the study”

EudraCT Vs ClinicalTrials.gov

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Xml Differences

- Due to completely different XML file structures, an organization's clinical IT group will face double the programming efforts if they want to generate XML files that will upload trial data automatically to EudraCT and CTGOV.
- While an organization might attempt to transform the CTGOV- XML to the EudraCT XML file, this is not recommended as missing information will always be found and the need to manually edit the XML files.

The better approach is to have one common data set that covers the requirements for both registries, and then generate separate XML files for EudraCT and CTGOV.

Key requirements for Xml

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Trial Information:

- # Study number with CSR report number and date of report
- # AE selection criteria – e.g. Treatment-emergent
- # Population to be reported
- # XML output – EMA/FDA/ PharmaCM

AE Information:

- #Timeframe
- #Frequency Threshold
- #Dictionary name and version
- #Event count to be included or not
- #Assessment type
- #Reporting Groups – Title, Description

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Practical Considerations for Functional areas

Prepare Functional Areas

*Take home message

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Clinical Team

- ✓ Increase the visibility and importance of EudraCT within functions
- ✓ Drive trials forward to ensure reporting deadlines are met (Availability of CSR specially in pediatric trial as timelines are very stringent)
- ✓ Provide timely and accurate trial related information
  - Study. timelines, EudraCT number, countries, etc.
  - Information about 3rd country trials under pediatric regulations
  - Communication regarding important trial milestones

Legal

- ✓ To keep sponsor informed about any updates in agreement in contract with license or alliance partners, as to which party has responsibility for registration of studies and posting the results to plan accordingly
- ✓ To review the posting text from legal point of view and provide comments/suggestions (If any)

Prepare Functional Areas

*Take home message

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Regulatory Affairs

- ✓ Confirmation on the global end of trial dates for in-scope studies as EUCTR public database is not up to date
- ✓ Information about 3rd country trials under pediatric regulations
- ✓ Complete three standard questions under pediatric regulations which are mandatory for posting the results on EudraCT
  - ✓ Is this trial is part of an agreed PIP?
  - ✓ Does Article 45 regulation apply to this trial?
  - ✓ Does Article 46 regulation apply to this trial?

Statistician

- ✓ AEs tables/Xml files as per EudraCT requirements
- ✓ Demographic data (Age) as per pre-specified categories for EudraCT
- ✓ Subject disposition country wise as per EudraCT requirements
- ✓ Accuracy check of the data source used for posting
- ✓ Statistical analysis information as in EudraCT Statistical analysis is mandatory for Primary OMs

References

- Guidance on posting and publication of result-related information on clinical trials in relation to the implementation of Article 57(2) of Regulation (EC) No 726/2004 and Article 41(2) of Regulation (EC) No 1901/2006 – October 2012
- Technical guidance on the format of the data fields of result-related information on clinical trials submitted in accordance with Article 57(2) of Regulation (EC) No 726/2004 and Article 41(2) of Regulation (EC) No 1901/2006 - January 2013
- https://www.clinicaltrialsregister.eu/ctr-search/search
- https://eudract.ema.europa.eu/docs/guidance/Trial%20results_Modalities%20and%20timing%20of%20posting.pdf
- https://eudract.ema.europa.eu/docs/technical/EudraCT_result_related_data_Dictionary.xls
- https://eudract-training.ema.europa.eu/
- https://eudract.ema.europa.eu/document.html
- http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/10/WC500174796.pdf (European Medicines Agency policy on publication of clinical data for medicinal products for human use adopted on 02 Oct 2014)
- https://arisglobal.com/wp-content/uploads/2014/09/EudraCT-Results-Reporting-WhitePaper.pdf

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Thank you...

Questions

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Back-up Slides

EudraCT V10: In Scope and Out of scope Activities

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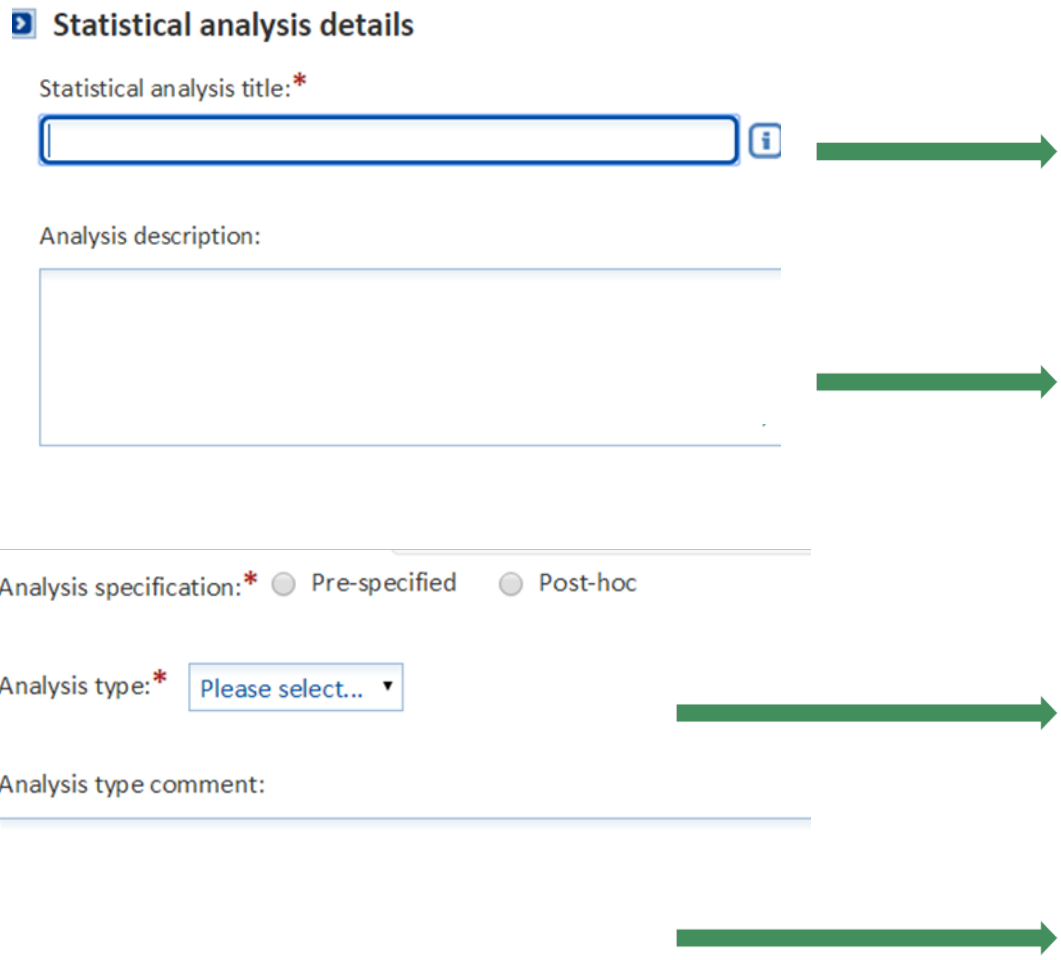
In Scope Activities

- Interventional trials (Approved and unapproved products)
- Phase 1 to 4
- Trials completed on or after 01 May 2004
- ICH E3 synopsis posting
  - Pediatric trials Art. 45 if not already submitted to EMA
  - Non-pediatric trials completed between 01 May 2004 to 20 Jul 2013 with at least one site in EU/ EEA
- Full dataset posting
  - All Pediatric trials acc. 2001/20/EC, Art 41 and Art 46 and Non -pediatric trials acc to 2001/20/EC completed on or after 21 Jul 2014
  - All pediatric trials, Art 41 and Art 46 completed before 21 Jul 2014

Out of Scope Activities

- Non-interventional studies (NIS)
- Investigator sponsored trials (ISTs)
- Trials completed before 01 May 2004
- Non-pediatric trials outside EU/ EEA

Statistical Analysis (1/3)



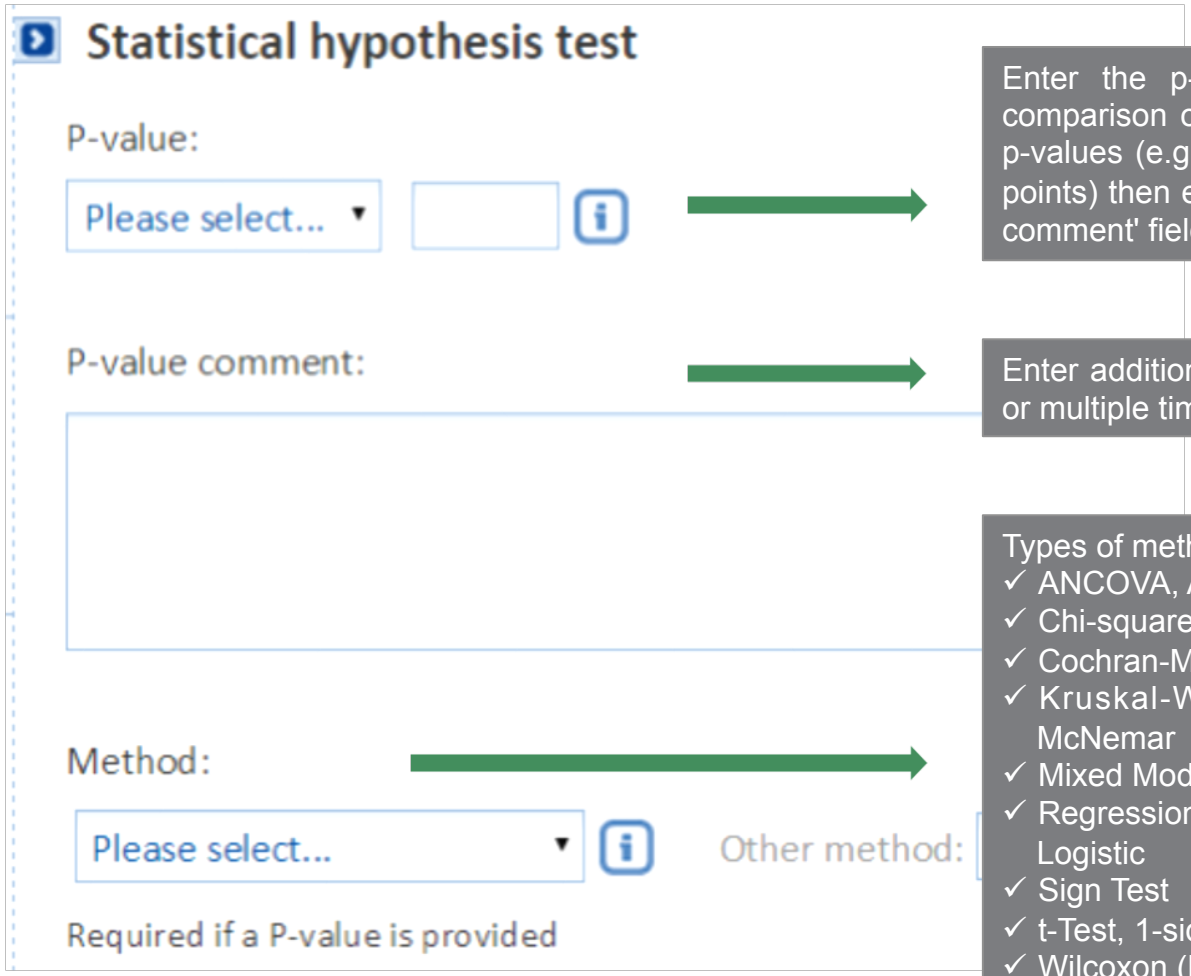
- ✓ **Statistical analysis results for primary endpoints are mandatory only**. If not available (for e.g., in premature termination), a justification is required
- ✓ Bio stats needs to confirm/complete full statistical analysis section during review cycle

- ✓ Details about null hypothesis, power calculation, adjustments for covariates, handling of missing data or adjustments for multiple comparisons
- ✓ Source section in CSR: 'Determination of sample size'

Drop down options includes:
Non-inferiority, superiority, equivalence and others

Enter additional details about the analysis, including definition of non-inferiority margin

Statistical Analysis (2/3)

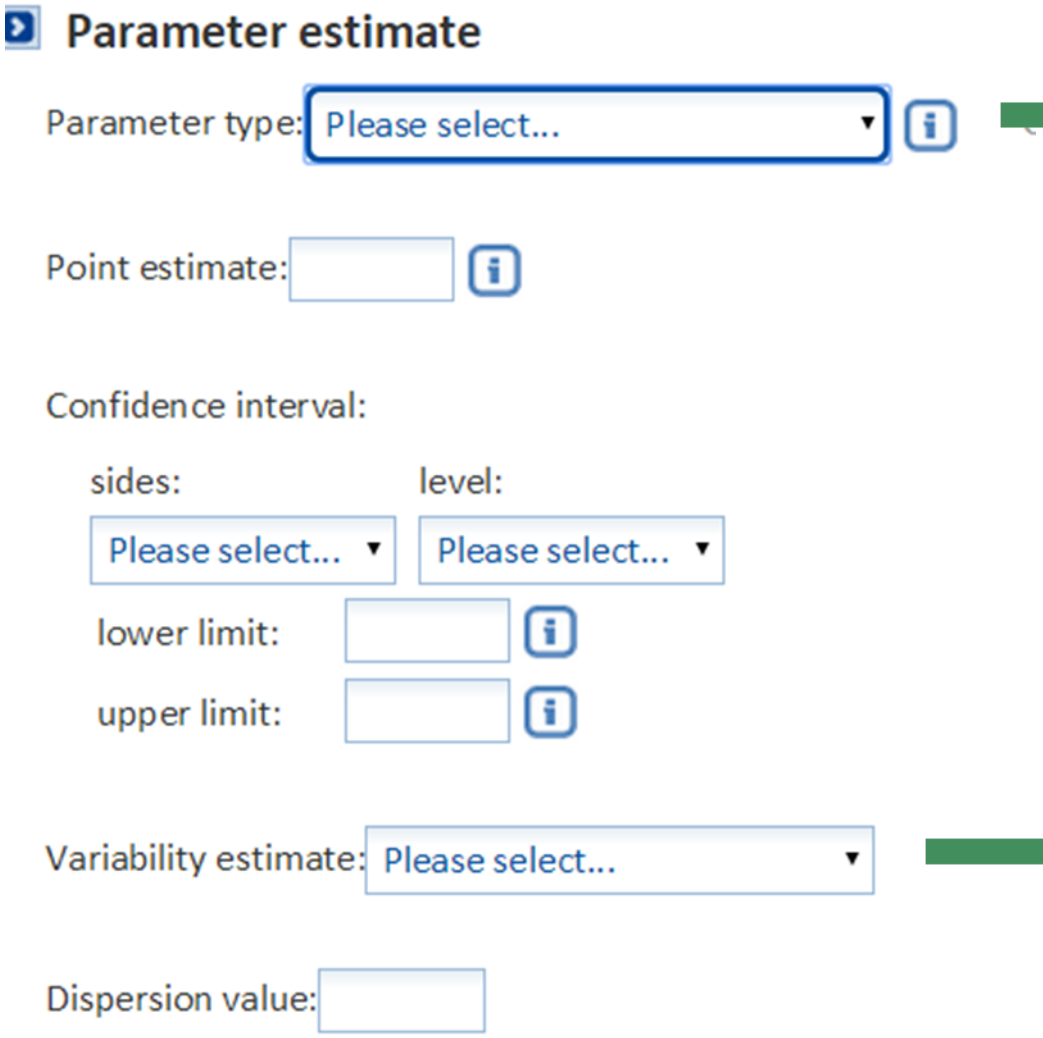


Enter the p-value that corresponds to the primary comparison of the analysis. If you want to report other p-values (e.g. for multiple comparisons or multiple time points) then enter the additional p-values in the 'p-value comment' field.

Enter additional p-values (e.g. for multiple comparisons or multiple time points) in the 'p-value comment' field.

Types of methods:
- ✓ ANCOVA, ANOVA
- ✓ Chi-squared, Chi-squared, Corrected
- ✓ Cochran-Mantel-Haenszel, Fisher Exact
- ✓ Kruskal-Wallis, Log Rank, Mantel Haenszel, McNemar
- ✓ Mixed Models Analysis
- ✓ Regression, Cox, Regression, Linear, Regression, Logistic
- ✓ Sign Test
- ✓ t-Test, 1-sided, t-Test, 2-sided
- ✓ Wilcoxon (Mann-Whitney)
- ✓ Other (Please specify)

Statistical Analysis (3/3)



Types of parameters:
- ✓ Cox Proportional Hazard
- ✓ Hazard Ratio (HR), Hazard Ratio log
- ✓ Mean Difference (Final Values), Mean Difference (Net), Median Difference (Final Values), Median Difference (Net)
- ✓ Odds Ratio (OR), Odds Ratio log
- ✓ Risk Difference (RD)
- ✓ Risk Ratio (RR), Risk Ratio log
- ✓ Slope
- ✓ Other (Please specify)

Types of variability estimate:
- ✓ Standard deviation
- ✓ Standard error of the mean