EUFEMED Webinar
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Sponsors' reporting obligations on clinical trial results

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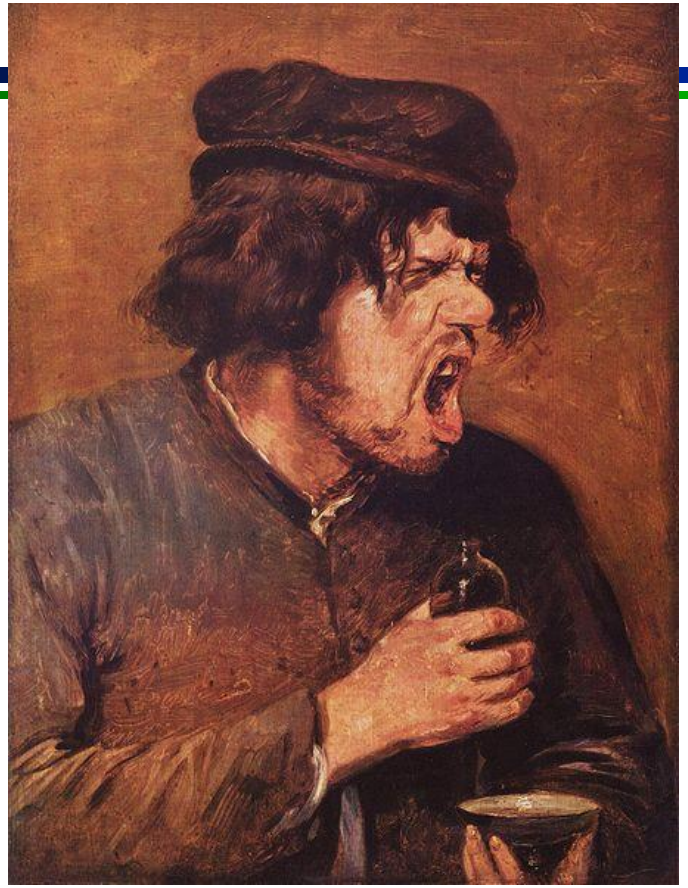
Integrated Clinical Study Report



The bitter drink
Adriaen Brouwer (1605-1638)
Städel Museum, Frankfurt/M

- **EU-CTR:**
  - The results of the clinical trial should be reported within one year from the end of the clinical trial (37)
  - The sponsor should submit a summary of the results of the clinical trial to the EU database (Art. 37,4; Annex IV)
- **Content:**
  - Based on ICH E3 Guideline
- **Purpose:**
  - Compile information on planning and conduct
  - Compile raw data, analysed data, and statistical analyses
  - Present and discuss results

Clinical Trial Report – Content (1)

- General Information, Methodology

1. *Title Page*
2. ***Synopsis, can it be used as Scientific Results Summary for CTIS ?***
3. *Table of Contents*
4. *Abbreviations*
5. *Ethics*
6. *Investigators and Administrative Structure*
7. *Introduction*
8. *Study Objectives*
9. *Investigational Plan*

9.1 Overall Study Design
9.2 Discussion of Design
9.3 Study Population
9.4 Treatments
9.5 Efficacy and Safety Variables
9.6 Data Quality Assurance
9.7 Statistical Methods Planned
9.8 Changes in Conduct / Analyses, Serious Breaches reported?

Clinical Trial Report – Content (2)

- Results and Discussion

10. Study Patients, ***Serious Breaches reported?***

11. Efficacy Results

11.1 Data Sets Analyses
11.2 Demographics
11.3 Efficacy Results
11.4 Efficacy Conclusions

12. Safety Results

12.1 Exposure
12.2 Adverse Events
12.3 Deaths and SAEs
12.4 Clinical Laboratory
12.5 Vital Signs
12.6 Safety Conclusions

13. Discussion

14. Tables, Figures, and Graphs

15. References

16. Appendices

Käthe von Porada
Max Beckmann (1884-1950)
Städel Museum, Frankfurt/M

Summary of the results of the clinical trial

ANNEX IV

CONTENT OF THE SUMMARY OF THE RESULTS OF THE CLINICAL TRIAL

The summary of the results of the clinical trial shall contain information on the following elements:

A. CLINICAL TRIAL INFORMATION:

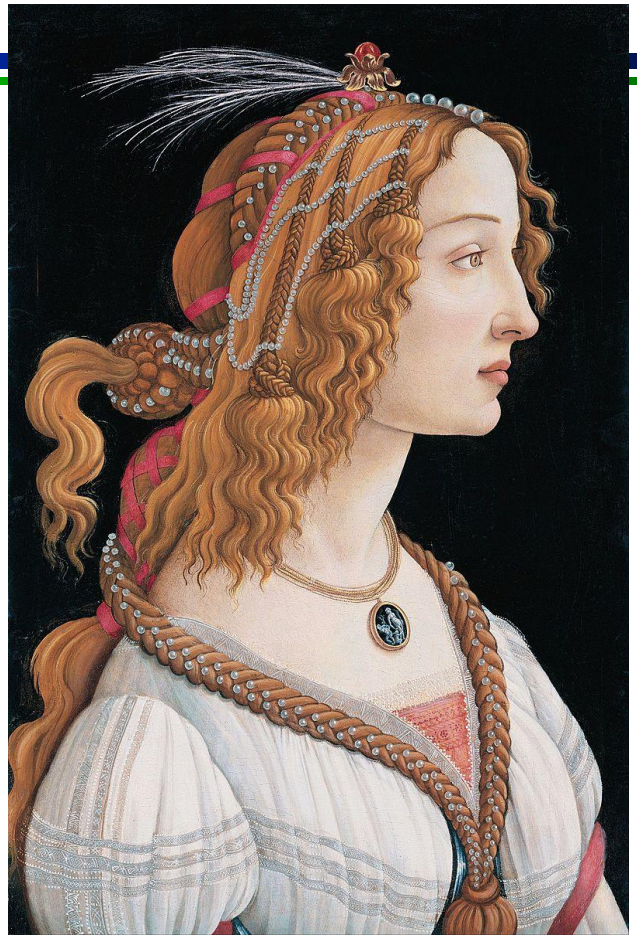
1. Clinical trial identification (including title of the trial and protocol number);
2. Identifiers (including EU trial number, other identifiers);
3. Sponsor details (including scientific and public contact points);.
4. Paediatric regulatory details (including information whether the clinical trial is a part of a Paediatric Investigation Plan);

- Clinical trial information
- Subject disposition
- Baseline characteristics
- End points
- Adverse events
- Additional information

Regulation (EU) No. 536/2014 of the European Parliament and the Council of 16. April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC
https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014R0536

Lay Summary – ‚nice to have' or ‚must have'?

- EU CTR 536/2014 calls for ‚summary of clinical trials results in a format understandable for laypersons'
- Aiming to increase transparency and trust in clinical research
- Target population: general public, interested patients, trial participants
- Mandatory for all clinical trials, including Phase I / early phase trials
- Annex V defines 10 elements of content



Simonetta Vespucci
Sandro Boticelli (1445-1510)
Städel Museum, Frankfurt/M

Regulation (EU) No. 536/2014 of the European Parliament and the Council of 16. April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC
https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014R0536

Lay Summary – Content based on EU-CTR (1)

Element 1: Clinical trial identification (study name)

Element 2: Name and contact details of the sponsor
(Who sponsored this study?)

Element 3: General information about the clinical trial
(When and where was this study done?
What was the main objective?)

Element 4: Population of subjects
(What patients/people were included in this study)

Element 5: Investigational medicinal products used
(Which medicines were studied?)

Lay Summary – Content based on EU-CTR (2)

Element 6:	Description of adverse reactions and their frequency (What were the side effects?)
Element 7:	Overall results of the clinical trial (What were the overall results of the study?)
Element 8:	Comments on the outcome of the clinical trial (How has this study helped patients and researchers?)
Element 9:	Indication if follow up clinical trials are foreseen (Are there plans for further studies?)
Element 10:	Indication where additional information could be found (Where can I find more information?)

Guidance documents for content and development of Lay Summaries

- EU Expert Group Recommendations [1] : details on content of the 10 elements, numeracy and literacy principles of lay language
- Questions & Answers document[2] to EU CTR 536/2014 (2022)
- 

Good Lay Summary Practice [3]

1. *Summary of Clinical Trial Results for Laypersons. Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use February 2018*. https://www.eu-patient.eu/contentassets/43803699d1884ff0b3dca3b7e0f6cf0b/gl_3_consult.pdf
2. *EU CTR 536/2014 Questions and Answers - Version 6. April 2022.* https://ec.europa.eu/health/system/files/2022-04/regulation5362014_qa_en.pdf
3. *Good Lay Summary Practice. 2021*. https://ec.europa.eu/health/system/files/2021-10/glsp_en_0.pdf

Good Lay Summary Practice

This guidance was developed in cooperation with the Roadmap Initiative to Good Lay Summary Practice and adopted by the Clinical Trials Expert Group (CTEG, a working group of the European Commission representing Ethics Committees and National Competent Authorities (NCA)).

Version 1

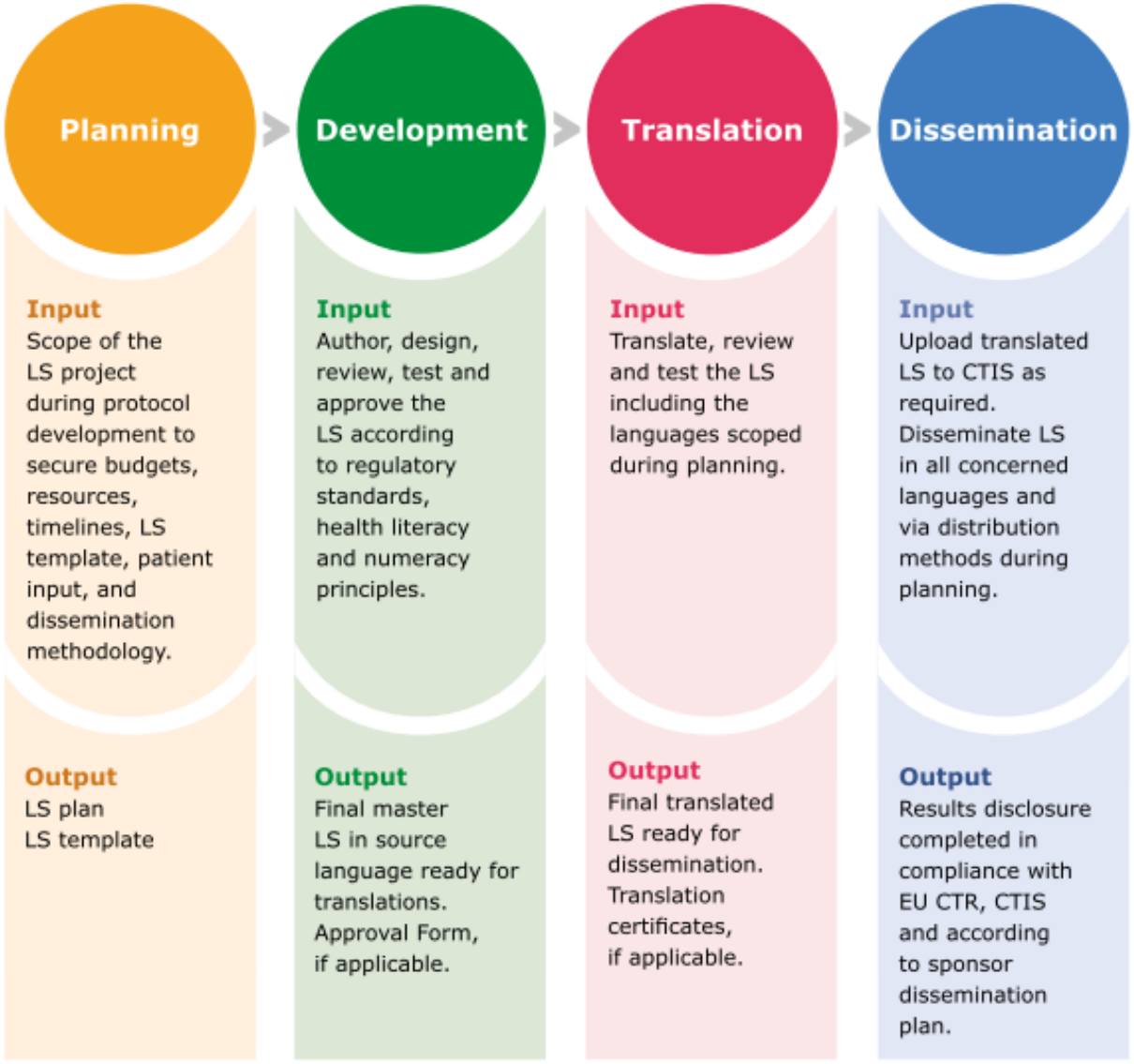
Document history:	
Date of adoption by the expert group on Clinical Trials	9 July 2021
Date of publication	4 October 2021

Good Lay Summary Practice

This "Good Lay Summary Practice" ("GLSP") provides recommendations on how to prepare, write, translate, and disseminate summaries of clinical trial results in lay language. This is a mandatory requirement laid out in Regulation (EU) No. 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use[1] ("EU CTR") and a transparency obligation to all trial participants and the interested public.

How to use this document

The GLSP is organised in two parts. Part 1 is a GLSP Quick Guide and Part 2 is the full GLSP Handbook. The GLSP Quick Guide contains core extracts from the GLSP Handbook and may serve as an overview of the recommendations offered in the Handbook. Since the intention of the GLSP is to provide practical recommendations and strive for good lay summary practices, professionals directly involved in lay summary projects are encouraged to read the full handbook to benefit from the detailed recommendations.



Lay Summaries need pre-defined planning to be successful

Required competences

- Scientific knowledge regarding e.g. clinical research methodology, disease, trial population
- Familiarity with source documents (informed consent, clinical trial report, summary of results, statistical evaluation)
- Familiarity with terminology and judgement of safety results
- Statistical knowledge
- Legal and regulatory knowledge
- Lay language communication skills
- Skills for quality control and accuracy checks
- Visual and design skills
- Skills to integrate stakeholder validation
- Willingness to work in a team and dedication to lay communication

Element 7: Results of the clinical trial

- Lay summaries report primary endpoint(s) and potentially patient-relevant secondary endpoints[1]
- Option 1: Limit results to the primary endpoint(s)
- Option 2: Include relevant secondary endpoint BUT NO CHERRY PICKING
  - Develop an overarching framework for selection of secondary endpoints to be reported in lay summaries and apply consistently to all trials
  - Preferably define patient-relevant endpoints already in trial protocol, in the latest prior to availability of interim results, but not after database lock
  - As secondary endpoints may lack statistical power, avoid placing undue emphasis on these results
  - Provide link to the Scientific Summary of the Clinical Trial Results in the EU Database

1. *EU CTR 536/2014 Questions and Answers - Version 6. April 2022.*

Element 6: Adverse reactions

- Adverse reactions must be clearly defined and presented with their frequency
- Serious adverse reactions listed first, followed by common adverse reactions
- Provide frequency in numerical terms and percentages [1]
- Lay summary presents results of a single clinical trial
  - Clinical Trial Report AE evaluation categories ≠ Lay Summary categories?
  - AE = non-serious plus serious, every SAE is also an AE, important AE according to ICH E3, AE resulting in discontinuation, SUSAR, ….
  - Causal relationship?
  - How to define ‘common’?
  - Matching with Scientific Summary of Results?

1. *Summary of Clinical Trial Results for Laypersons. Recommendations of the expert group. 2018.*

Layout and design

- Layout and design are as important as the wording
- Appearance and attractiveness have a strong impact on whether it will be read at all
  - Headings and descriptive sub-headings
  - Adequate white space
  - Columns, page breaks, colours
  - Reduction of e.g. logos
- Attractive structure helps lay summary to appear reader-friendly and accessible

‚Paradiesgärtlein'
Upper Rhenish Master (1410)
Städel Museum, Frankfurt/M, Germany

Review and user testing

- Review by different stakeholders involved in the clinical trial (patients, medical monitor, statistician, …) is recommended
- Ensure completeness and accuracy in all aspects
- This review process should at least be envisaged for the lay summary template
- Good practice to user test the lay summary with individuals who are not involved in the trial and unfamiliar with clinical research methodology
- Clear instructions on tasks expected from the test persons and feedback process are essential

Translation

- Patients' native language is an important element of fair access to information
- As a minimum, the lay summary should be provided in the languages of the countries where the trial took place[1], matching the languages used in the Informed Consent Form
- Sponsors should consider preparing an English version to allow greater accessibility across the EU and globally
- Thorough review before translation, well-managed translation process, use of glossaries and pre-defined terminology are helpful for achieving successful translation
- Proactive planning and management will facilitate the quality, timeliness, and adequacy of lay summaries to the target audience

Dissemination

- EU CTR[1]: Sponsors must upload the lay summary to the EU Database via the EU Portal
- Additional option[2]: Direct dissemination to trial participants (e.g. printed lay summary provided by the investigator)
- Delivery of the lay summary (outside of EU mandate) needs to be done in compliance with local laws, restrictions, and standards
- Sponsor should ensure dissemination in a non-promotional manner (caveat: Is Sponsor's website non-promotional?)
- Sponsor should describe principles, planning, strategies, and communication of dissemination and apply to all trials, regardless of outcome
- Sponsors should weigh benefits against risks of various dissemination methods and consider partnering with the investigator to ensure proper results communication

1. *EU-CTR 536/2014*
2. *Summary of Clinical Trial Results for Laypersons. Recommendations of the expert group. 2018*.

Sign In

The Roadmap Initiative to Good Lay Summary Practice

Over 60 participants from EU and US pharmaceutical companies, CROs, academic institutions, patient organisations, and not-for-profit organisations have formed the "Roadmap Initiative to Good Lay Summary Practice" with the aim to develop and implement a pragmatic, broadly accepted framework for Lay Summary planning, development, translation, and dissemination.

https://glsp.network/

Roadmap Initiative Updates

Get our updates by email now, register to our Newsletter.

Newsletter Registration

[Upcoming Workshop] GLSP Translation Workshop

Date: 27 June 2022 | 14:00 - 18:00 CEST

by GLSP Core Team Team | 23 May 2022

› View

Sponsor view: timelines are tight
Patient view: timelines are long

- Lay Summaries must be available in CTIS at 12 months after end of trial, i.e. at the same time as the Scientific Results Summary in CTIS (and the Integrated Clinical Trial Report according to ICH principles)
- For pediatric trials: 6 months after end of trial
- Phase I trials without therapeutic intent: extension of timelines may be requested, in the latest 30 months after end of trial

  - How does the trial protocol define ‚end of trial'?
  - Last subject - last visit - last finding?
  - Data base lock? In case a clear-cut rational is provided in the trial protocol (e.g. complex bioanalytics of parent compound and metabolites; exploratory biomarkers requiring validation of analytical assay)

Appendix, on disclosure rules, to the "Functional specifications for the EU portal and EU database to be audited ". EMA/228383/2015. 2 October 2015.

Deferral rules for confidential information

- Sponsors have options to defer the timing of publication of specific data/documents to protect commercially confidential information (CCI)
- Deferral rules and maximum timelines to defer publication of data and documents will depend on the trial category
  - Appendix, on disclosure rules, to the "Functional specifications for the EU portal and EU database to be audited - EMA/42176/2014" . EMA/228383/2015. 2 October 2015.
  - [DRAFT] Guidance document on how to approach the protection of personal data and commercially confidential information in documents uploaded and published in the Clinical Trial Information System (CTIS). EMA/212507/2021. 7 April 2022.
  - Pioppo L, Sultani M. Clinical Trial Information System (CTIS) - Bitesize talk. Deferral rules and Public website. EMA Presentation. 20 July 2022.
- Regardless if deferrals are selected by the sponsor and endorsed by the RMS/MSC , at the time of evaluation of a clinical trial application, the sponsor has the obligation to submit a document version 'for publication' and a version 'not for publication'

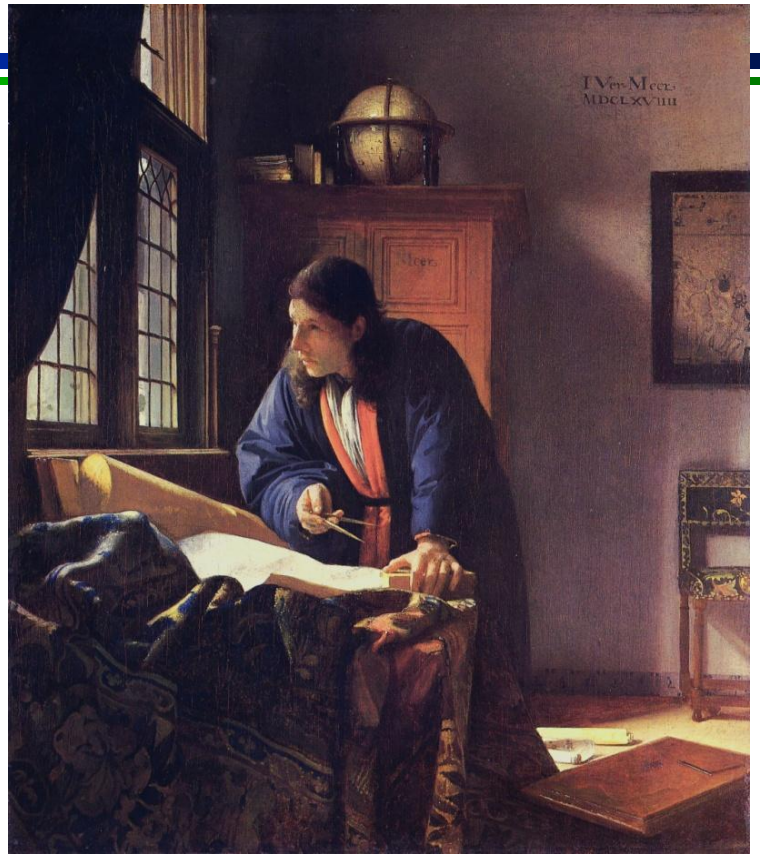
Deferral rules for confidential information

Actor	Grouping	Category 1 FIH, PK/PD, BE/BA, Bio similarity	Category 2 Phase II and III	Category 3 Phase IV
Sponsor	• Main Characteristics	Publication of final **summary of results**		
Sponsor	• Notifications	Publication of final **summary of results**		
Sponsor	• Subject information sheet	Up to **7 years** after the end of the trial in EU/EEA	Up to **5 years** after the end of the trial in EU/EEA	
Sponsor	• Protocol	Up to **7 years** after the end of the trial in EU/EEA	Up to **5 years** after the end of the trial in EU/EEA	Publication of final **summary of results**
Sponsor	• IMPD S&E sections and Investigator Brochure	Up to **7 years** after the end of the trial in EU/EEA	Up to **5 years** after the end of the trial in EU/EEA	Publication of final **summary of results**
Sponsor	• Responses to RFI	Up to **7 years** after the end of the trial in EU/EEA	Up to **5 years** after the end of the trial in EU/EEA	Publication of final **summary of results**
Sponsor	• Clinical trial results summary for an intermediate data analysis	1. 12 months after interim analysis date 2. up to **30 months** after the end of the trial in the EU/EEA		
Sponsor	• Clinical trial results summary and lay person summary	1. 12 months after the end of trial date in the EU/EEA 2. Up to **30 months** after the end of trial in the EEA		

[DRAFT] Guidance document. EMA/212507/2021. 7 April 2022.

Information that should not be considered CCI

- Information in the public domain
- Information that does not bear any innovative features
- Information that would not qualify as commercially confidential
  - General or administrative information
  - Quality-related information
  - Non-clinical-related information
  - Clinical-related information



The Geographer
Jan Vermeer (1632-1675)
Städel Museum, Frankfurt/M