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INSTITUTE OF **A**PPLIED **B**IOSCIENCES INΣΤΙΤΟΥΤΟ ΕΦΑΡΜΟΣΜΕΝΩΝ ΒΙΟΕΠΙΣΤΗΜΩΝ CENTRE for RECEARCH and TECHNOLOGY-HELLAS



Institute of Applied Biosciences (INAB) Centre for Research and Technology, Hellas (CERTH)

Real-World Data Management Systems

Development of **standardized** and **centralized** data repositories and management systems for **Real World Evidence**

enabling multi-center projects on clinical association studies

Web-based applications

Provide data availability and security in a user friendly way Simplicity, data reliability, easiness in use and flexibility as necessary conditions User – friendly, adjusted to user requirements

Real - world evidence (RWE) biomedical research is an increasingly important component of INAB | CERTH activities

OBJECTIVES

- A. collect and transform clinically relevant RWD into evidence
- B. correlate data in order to provide accurate information about the diagnosis, prognostic assessment and management
- C. facilitate biological, translational and clinical research

Organize and analyze clinically relevant data from the **daily** practice, by gathering homogenized high-quality datasets, thus Improving the quality and delivery of medical care

APPROACH _

1. Standardization & Harmonization

Agreement on common policies and procedures with standards-based approaches, paving the way for standardized registration of RWD

2. Simplicity & Flexibility

Design in expandable modules allowing the rapid introduction of additional data categories and extension of data domain when and if needed

3. Data Availability & Usability

Unified access to clinically relevant structured data while fulfilling the data quality assurance requirements

4. Data Protection

EU General Data Protection Regulation (GDPR) Technical and Organizational measurements for data protection and data security

APPROACH _

Combine information into a data integration framework

Data integrity, data accuracy and quality assessment

User-friendly integration of ontologies, terminologies and standards

Data correlations and statistical analysis

Quality control and curation mechanisms

Data analytics, Data mining and knowledge discovery Data protection, security, privacy and availability

DATA MODEL

Describe all the relevant information to form an accurate and complete representation of patient diagnosis and disease course

DATA MODEL _



DATA MODEL ____



DATA MODEL

— Characteristics

- Meet the requirements for an accurate description of diagnosis, prognostic assessment and management of patients
- □ Adjusted to project-based requirements (extended / expanded)
- Expressing the complexity of disease

DATA MODEL

— Data Requirements

Collect all information about the data that will be stored in the database.

- > What are the types of data and the data categories of the different data entities?
- > Which fields will be included in each data category?
- > What is the data type and format of each field that will be stored in the database?
- > Are there specific values allowed for the defined fields?
- > What are the rules and relationships among different types of data?
- Which data are required?
- > How will the data be assessed?

User scenarios and workflows



Detailed description of data

- Detailed list of data categories, entities, terminologies
- Definition of data types, data format and allowed values
- Configuration of data relationships and rules
- Consistency and integrity constraints

DATA MODEL

1. Detailed list of data categories, entities, terminologies

- Main data

Data category	Column name					
	Patient id					
Registration data	Registration center					
	Hospital					
	Physician					
Demographic	Gender					
data	Year of birth					
	Age					
	Date of diagnosis					
Diagnosis data	Age at diagnosis					
	Diagnosis					
	PS at time of diagnosis					

Treatment data

Date of first treatment				
First treatment type				
Response to first treatment				

—Lab data

Data category	Column name
	Blood test date
	Haemoglobin (g/dL)
	WBC
	ANC
	Platelets
	Serum albumin (g/dL)
Blood test	Serum creatinine
	Alkaline phosphatase
	Alkaline phosphatase (ULN)
	Serum urea
	Serum calcium
	Peripheral Blood plasma cells
	%
	Date of bone marrow test
Dama	Aspirate method
Bone	BM infiltration in aspirate
marrow test	Trephine method
1631	BM infiltration in trephine
	BM Flow examination

DATA MODEL

2. Definition of data types, data format and allowed values

Field	Data type	Data format	Unit	Value constraints
Diagnosis	text	List		CLL,MBL,SLL
Date of diagnosis	date	DD/MM/YYYY		>1980
Rai stage at diagnosis	text	List		0,1,11,111,1V
Binet stage at diagnosis	Text	List		A,B,C
Comorbidities at diagnosis	text	List		YES,NO
Blood count date	date	DD/MM/YYYY		less than or equal to current date
Hb	decimal	#0.0-100.0	g/dL	0.0-100.0
WBC (x10^9/I)	decimal	#0.00-1000.00	(x10^9/l)	0.00-1000.00
Treatment status	Text	List		Treated,Untreated
Response to first treatment	Text	List		CR,CRi,Nodular PR,PR,PR with lymphocytosis,Progressive,Stable
Date of last follow-up	Date	DD/MM/YYYY		less than or equal to current date
Survival status	Text	List		Alive,Dead

DATA MODEL

3. Configuration of data relationships and rules



DATA MODEL

4. Consistency and integrity constraints

Required information

Field
Patient ID
Diagnosis
Date of diagnosis
Rai stage at diagnosis
Binet stage at diagnosis
Treatment status

Data redundancy control

Examples:

The Patient id must uniquely characterize one patient A patient has only 1 RAI stage at diagnosis time A patient cannot have 2 visits with the same date

Depended / Essential information

Examples:

If patient is reported DEAD, then Date of death is a required field

If patient is reported Treated, then Start date of treatment and treatment type are required fields

Additional constraints and rules for the **comparison of related fields** Examples

Start date of treatment cannot be before Date of diagnosis

Treatment-related data are not applicable for Untreated patients

A patient with enlarged lymph nodes at time of diagnosis cannot be reported with RAI stage: 0

DATA PROTECTION

GDPR compliance



- Data are collected solely for specific and legitimate purposes
- Data are adequate and related to the purpose of collection
- Data are processed and treated lawfully and fairly in a transparent manner

Pseudonymized identifier for each patient

Data anonymization procedures

The correspondence with original records will be stored only at the local level.

Fully anonymized data used for statistical analysis, Aggregated results are reported.

🥑 ISO 27001:2013

for Information Security Management System

ISO 22301:2019 for Business Continuity Management System

Appropriate technical and organizational measures - data confidentiality, availability and integrity - data protection and security

SYSTEM DESIGN

Database development



Database system specifically designed for clinical and biological data

Main characteristics

- Data Integrity
- Data Consistency
- Redundancy Control
- Data Availability
- Data Correlations

Data security

- □ User management
- Project Management
- Activity Logs
- Back up mechanisms
- Maintenance procedures

Interoperability

Reporting system



USER MANAGEMENT



✓ Role-based access

Role assignment: Restricted or Extended Access Privileges

USER MANAGEMENT

User role examples of center-based access

Principal investigator of center (PI)

Overall access, review registration and management procedures

Data administrator (DA)

Overall read & write privileges

Data moderator (DM)

Restricted read & write permissions to selected data categories

Read - only user

Restricted read permissions to selected features

User role example of project-based access

General Pl

Read-only access to data from all centers in a project

Role-assignment example

Cytogenetics-lab User

Access only to cytogenetic data

USER MANAGEMENT

User Authentication

CLL The INAI		hronic Lymphocytic Leuke	mia	
Log	gin			
±	Username			
a	Password			
	Let me in 🞝			not login, contact us at biodb@inab.certh.gr
 developed and host Institute of Applied 	ted in Biosciences (INAB) Centre for Resear	rch and Technology Hellas (CERTH)	INA3	CERTH CENTRE FOR RESEARCH & TECHNOLOOY HELLS

Strictly personal user accounts - credentials

Login Page

USER MANAGEMENT

User Account Activation

Login Credentials

Username Temporary Password

 Terms and Policies agreement
 Set up new password



The USER agrees that all of the above terms are essential. The continuation of the activation process means the unconditional acceptance of the above terms of use.

I have read and accepted the terms of use



Enter your old password: Old pass Enter a new password: New Pas	
Enter a new password: New Pas	sword
	Sword
/erify new password: Verify Pa	assword
Change password	

Procedure 1. Enter your credentials and set a new password 2. Click the link to view and read institutes policies in order to proceed 3. Confirm you have read and agree with the policies 4. Click change password to submit changes Password instructions New password must be different than the previous one The length of new password must be at least 6 characters The length of new password must be less than 20 characters New password must contain at least 1 uppercase character [A-Z] New password must contain at least 1 lowercase character [a-z] New password must contain at least 1 numeric character [0-9] New password must contain at least 1 of the allowed symbols [.-.1@#]

Set up Password

USER MANAGEMENT

User Account Activation

Confirm and login to activate account:





EAN **CLLdb** database version 2.0 | 2020-03-27 The INAB database for Chronic Lymphocytic Leukemia Search cases Register new case Retrospective data registration - Data retrieval - Documentation - Contact + Contact Welcome to the INAB CLL database, a data registration and management system for the collection and analysis of clinicobiological data of patients with Chronic Lymphocytic Leukemia, developed and hosted in Institute of Applied Biosciences (INAB), Center for research and logy Hellas (CERTH) Data management tools Real-time data management Search GR01 cases, review case summary and / or register new cases in CLLdb Retrospective data upload Upload template files with new GR01 cases, retrieve data validation and homogenization report. Retrospective data import Review uploaded datasets and import data into CLLdb Data retrieval tools Query tool Search GR01 cases, review case summary and / or register new cases in CLLdb Export tool Upload template files with new GR01 cases, retrieve data validation and homogenization report. Other features: Contact ピ Links 네 Data analytics platform Documentation Registration center: GR01 » Institute of Applied Biosciences - Center for Research and Technology Hellas User: Eva Minga Username: eva, Role: DM Date: 2022-04-06 EAN CERTH

DATA COLLECTION METHODS

Real-time registration systems



Retrospective data registration

Data registration tools

- Massive import of patient retrospective data
- Transform and upload data exports from other sources
- Data homogenization and integration
- ✓ Available for edit online

Integration and validation mechanisms

elimination of data inconsistency and redundancy enhanced data management and organization

DATA COLLECTION METHODS

Real-time registration systems

A. Online web forms for prospective data registration

CLLdb			EVN
GR01 Data collection, manag Institute of Applied Biosciences - Center for			version 2.0 2020-03-27
Home page Retrospective data re	gistration 👻 Data retrieval 👻 Documen	tation • Contact	
Register new GR01 ca	ase		
Basic patient data Patient		gnosis Comorbidit	ties at diagnosis Lab data at diagnosis
Registration data Patient ld	Referral hospital information		Referral physician
PO	Hospital		Physician
Gender Year of birth M F YYYY Diagnosis data Diagnosis	Age Date of diagnosis	Country Age at diagnosis	Ethnic origin
~	dd/mm/yyyy		Diagnosis comment
Treatment status	Start date of treatment	Date of last follow-up	
Current status Survival status Alive Dead	Date of last known alive		
Cancel registration		Save p	patient data
			- Institute of Applied Blockences (INAB), CERTH

- Organize data in order to facilitate data registration and improve data management
 - separate categories
 - multiple timepoints
- Create different types of forms for controlled access to data management according to user roles and access privileges
- Design dynamically adjusted forms based on selected criteria

DATA COLLECTION METHODS

Real-time registration systems

A. Online web forms for prospective data registration

Data that are requested only under specific conditions:

Treatment status		
Treatment status	Treated	O Untreated
Treatment status		
Treatment status	O Treated	Untreated
Start date of treatment *		Front-line treatment type
dd/mm/yyyy 🗖		~

DATA COLLECTION METHODS

Real-time registration systems

B. Retrospective data registration tools



X	specifically	designed	template	registration	files	according	to requirements	

ER			European Res	earch Initiativ	e on Chr	onic Ly	mphocytic Leu	ıkemia		Strictly Conf	idential		
				ERICLL D	ΔΤΔΕ	RAS	F						
european resea	european research initiative on CLL						NOTE:	Please consider	that this databas	e is not intended,	and therefore it i	s not designed, to	
Patient Lab id	Conden	Manage of high	Diamaria	Date of	Rai sta	ige at	Binet stage at	Comorbidities	CIRS score	Date of last	Current status	Date of death	Treatment
Patient Lab Id	ient Lab id Gender	Year of birth	Diagnosis	diagnosis diagnosis diagnosis		at diagnosis	at diagnosis	contact	Current status	Date of death	status		
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					- 111	-							
					IV	-							
					n/a	-							

* adjusted to local necessities and project-specific data collection

- Protected sheets, including data validation
 - warnings, notes, validation rules and drop down lists



Data upload, validation and import tool

integrate multi originated data from different sources into a central repository

DATA COLLECTION METHODS

Data Validation and Integration

- translation of terms / conversion of data
- validation of data formats
- detection of data redundancy
- additional constraints and rules for the comparison of related fields

DATA COLLECTION METHODS

Data Validation and Integration

Examples of reported errors

Data format errors

- del11q date: '2014., 2017.04.12.', error in date NOTE: date must be in 'DD/MM/YYYY' format
- Hg: 'Low' is invalid for numeric field Hg.
- b2-microglobulin:'130', value violates numeric limits (0.1-100)

Data redundancy errors

- Patient id: X2 already exists
- Date of blood test: 2016-04-03', There is another blood test for this patient with the same date.

Predefined values

- Type of first treatment: 'FC', value is not included in the list of predefined values.
- Response to first treatment: 'CR, MRD negative', value is not included in the list of predefined values.

DATA COLLECTION METHODS

Data Validation and Integration

Required Data

- Missing patient data: Start date of treatment is a required field for treated patients.
- Date of diagnosis of non-hematological neoplasm: Information is required when Other non-hematological malignant neoplasms=YES

Data inconsistency

- Rai stage at diagnosis: 'II' is not a valid value for Diagnosis 'SLL'
- Description of hematological adverse events at 1st-line treatment is not applied when depended information is missing: Adverse events at 1st-line treatment is empty

Date compare

- Date of diagnosis: '30/04/2015' cannot be more than 15 days greater than Date of first treatment: '05/02/2015'
- Start date of 3rd-line treatment: '10/01/2016' cannot be earlier than Start date of treatment – 2nd line of treatment: '11/02/2016'
- Date of death:'19/02/1997' cannot be less than del17p date: '13/11/2002'

DATA COLLECTION METHODS

Data Validation and Integration

Examples of reported warnings

Warnings on missing data

Further treatment at relapse / progression is essential for analysis (missing data)

Warnings on missing data for depended fields

Missing ULN for b2-microglobulin is required for b2-microglobulin='3.49'

Warnings on data transformation

- Date of best response to treatment='27/04/20' has been auto-converted into '2020', please correct file if necessary and upload again (required format: 'DD/MM/YYYY')
- Tissue type: BM has been replaced with 'Bone Marrow'

DATA COLLECTION METHODS

Data Validation and Integration

- translation of terms / conversion of data
- validation of data formats
- detection of data redundancy
- additional constraints and rules for the **comparison of related fields**

Prospective data registration — Data rules and constraints are implemented in the forms

- Form cannot be saved if required fields are empty \checkmark
- Form input fields are restricted to the defined data format. \checkmark
- Multiple choice or single choice options and drop down lists ensure data consistency \checkmark - restricting input to the list of allowed values -
- Fields are dynamically displayed in order to avoid data inconsistency \checkmark - only if applicable based on user's input -
- Required Fields are dynamically added based on user's input \checkmark
- Duplicate records cannot be saved \checkmark

DATA COLLECTION METHODS

Data Validation and Integration

- translation of terms / conversion of data
- validation of data formats
- detection of data redundancy
- additional constraints and rules for the comparison of related fields

Retrospective data registration

Data validation procedure

Data validation reports

Data validation report

Upload of Amsterdam dataset

O Amsterdam data have been successfully uploaded!

File: ERIC_CLLdb_TretSeqAmsterdam Ø Verified sheet: Main data Ø Verified sheet: Subsequent lines of treatment

Dataset status

Center code: Amsterdam

Number of uploaded cases: 43 Number of validated cases: $11\,/$ 43 (Number of cases with errors: 32)

Error [Data curation is required] Total number of errors: 56

Data validation report

 Main data (43 rows)

 15 / 43 processed rows with data have been validated.

 A Number of rows with errors in sheet:

 28

 A There are warnings (40) to review in this sheet

Subsequent lines of treatment (8 rows) 3 / 8 processed rows with data have been validated. A Number of rows with errors in sheet: 5 A There are warnings (3) to review in this sheet

O Reference exists in this sheet for 6 / 43 (13.95%) cases

Lownload data validation report in a tab-delimited text file.

DATA COLLECTION METHODS

Data Validation and Integration



- validation of data formats
- detection of data redundancy
- additional constraints and rules for the comparison of related fields

Retrospective data registration



Reference exists in this sheet for 6 / 43 (13.95%) cases
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DATA COLLECTION METHODS

Data Validation and Integration



L Download data validation report in a tab-delimited text file

DATA COLLECTION METHODS

Example of retrospective data registration system for the INAB CLL database:

Upload of new dataset

- Upload template file
- Wait for the system to process excel data:
 - Organize information
 - Validate data types
 - Check rules and constraints
- Retrieve data validation report
 - Errors in dataset
 - Review warnings

CLLdb version 2.0 | 2020-03-27 GR01 Data collection, management and analysis system Institute of Applied Biosciences - Center for Research and Technology Hellas Home page Retrospective data registration Data retrieval Documentation Contact INAB CLL database is a data registration and management system for the collection and analysis of clinicobiological data of patients with Chronic Lymphocytic Leukemia, developed and hosted in Institute of Applied Biosciences (INAB), Center for research and Technology Hellas (CERTH). Select template: CLL database Description: CLL database (CLLdb.xlsx): Template file for retrospective data collection - Institute of Applied Biosciences (INAB), CERTH

DATA COLLECTION METHODS

Example of retrospective data registration system for the INAB CLL database:

Upload of new dataset

- Upload template file
- Wait for the system to process excel data:
 - Organize information
 - Validate data types
 - Check rules and constraints
- Retrieve data validation report
 - Errors in dataset
 - Review warnings

Data curation process

- Update data in the template file according to the report
- Upload the updated version

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DATA RETRIEVAL AND ANALYSIS

Tools for data retrieval and analysis, based on user access privileges

Query tools

- allowing for dynamic definition of selection filters in order to retrieve data

Export modules

- report generation (patient summary)
- selected data download (authorized anonymized)
- retrieve anonymized data

Statistic and Visualization tools

- statistical analysis
- visualization (diagrams)



Download data

options

DATA RETRIEVAL AND ANALYSIS

- 1. data selection
 - Query / Search tools

2. data retrieval

Preview results for selected set of cases - Including data visualization modules





DATA RETRIEVAL AND ANALYSIS

Data Retrieval

Data filtering

Query tool supporting dynamic definition of selection filters.

Query tool
Demographic Data
Treatment Status
Survival Status
1st Line Treatment
Submit Query



DATA RETRIEVAL AND ANALYSIS

A web-based application for online statistical analysis

 \checkmark Project-based configuration



DATA RETRIEVAL AND ANALYSIS

A web-based application for online statistical analysis

Data descriptive statistics and correlations

- 1. Dynamic preview and edit in real-time
- 2. Correlations between variables
- 3. Comparisons in different sub-groups and datasets
- 4. Advanced statistical analysis based on personalized prediction model



Descriptive Summary	Plot							Demographic
Decryptive Surveyary P	rai stage at diagnosis correlated to binet stage at diagnosis	Table						Gender
Descriptive Statistics								OFOM
Correlations	63.39 % data available	rai_stage_at_diagnosis	0	1		-	IV	Year of birth
Comparisons		binet_stage_at_diagnosis						1910 - 2021 Date of diagnosis
Statistical Analysis	29 60	A	73.33	21.48	4.13	1.06	0.00	2000 - 2021
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NOARD AND ADVANCED		c	0.00	0.00	0.00	36.25	63.75	0 - 100
Propared Scientifics >								Current status
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POF Reports *	, ,, ,, ,, ,, ,, ,,							Status at diagnosis
•								Treatment status
	Choose a type of diagram:							
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Prepared scenarios for statistical analysis Automatically generated **pdf report**

