FeatureCloud

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 826078.

Privacy preserving federated machine learning and blockchaining for reduced cyber risks in a world of distributed healthcare

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Deliverable D8.1
"Report on performance benchmarks"

Work Package 8
"Testing and evaluation in clinical translation"

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Document information

Grant Agreement Number 826078			**Acronym FeatureCloud**	
Full title	Privacy preserving federated machine learning and blockchaining for reduced cyber risks in a world of distributed healthcare			
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This project has received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement No 826078.

Acronyms and definitions

ADR	adverse drug reaction
API	application programming interface
BfArM	Federal Institute for Drugs and Medical Devices (Germany)
CAPI	Computer-Assisted Personal Interview
CASTOR	CApture and STORe clinical trial management software
concentris	concentris research management GmbH
CSV	Computer System Validation
CTCM	Clinical Trial Centre Maastricht
DNA	Deoxyribonucleic acid
eCOA	electronic Clinical Outcome Assessment
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EGCUT	Estonian Genome Center at the University of Tartu
ePRO	electronic Patient-Reported Outcomes
eTMF	electronic Trial Master File
EU	European Union
GCP	Good Clinical Practice
GND	Gnome Design SRL
GP	General Practitioner
IARC	International Agency for Research on Cancer
ICD-10/11	International Classification of Diseases version 10 or 11, resp.
ICH	International Council for Harmonisation of Technical Requirements of Pharmaceuticals for Human Use
MACRO	Multicenter Academic Clinical Research Organization
MCTQ	Munich Chronotype Questionnaire
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines & Healthcare products Regulatory Agency (UK)
MINI	Mini-International Neuropsychiatric Interview
MUG	Medizinische Universitaet Graz
NEO-PI-R	Neuroticism-Extraversion-Openness Personality Inventory Revised
NMR	Nuclear magnetic resonance
Patients	In this deliverable, we use the term “patients” for all research subjects. In FeatureCloud, we will focus on patients, as this is already the most vulnerable case scenario and this is where most primary data is available to us. Admittedly, some research subjects participate in clinical trials but not as patients but as healthy individuals, usually on a voluntary basis and are therefore not dependent on the physicians who care for them. Thus to increase readability, we simply refer to them as “patients”.
PI	Principal Investigator
RI	Research Institute AG & Co. KG
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SBA	SBA Research Gemeinnützige GmbH
SDU	Syddansk Universitet
SLA	service-level agreement
SNP	single-nucleotide polymorphism
SPSS	Statistical Package for Social Sciences
SSP	Swedish universities Scales of Personality
STATA	STAtistics and daTA software
TUM	Technische Universität München

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UM	Universiteit Maastricht
UMR	Philipps Universität Marburg
WHO	World Health Organisation

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1 Objectives of the deliverables based on the Description of Action

The objective was to ensure that software programmers are made aware by clinical scientists, biostatisticians and monitors of all features necessary for usability and to fulfil nationally required reporting features, e.g., serious adverse event (SAE), for a phase II/III type clinical study based on MACRO or similar interfaces. This entailed many more and longer interdisciplinary consultations than initially anticipated, both from a technological and a bioinformatics perspective and explains why this deliverable was massively delayed. However, it was essential to provide performance benchmarks, i.e. a full feature and usability list to clinical study recording based on MACRO and several other user interfaces, including close to a market analysis and user interviews, plus keeping nationally required reporting features in mind, e.g. for serious adverse events (Objective 1, Task 1). The goal is to provide a basis for decision making regarding which essential features of commonly used clinical trial software would FeatureCloud need to either reimplement (e.g. as apps) or how FeatureCloud apps can ensure compatibility with existing software, like MACRO, when they provide localized results.

2 Executive Summary / Abstract

In addition to MACRO (https://www.elsevier.com/solutions/macro), CASTOR emerged as a second, possibly preferable trial management system. Moreover OpenClinica, emerged as a high quality, open-access trial management system, which is not used by CTCM, but may gain widespread use amongst academic and commercial trialists and compatibility with as many features as possible would be recommended. However, in the course of clinical trial planning, all teams decided to focus on MACRO. CASTOR will thus serve as an alternative analysis. As it is recommended to confirm usability with other leading trial software (**Fig. 1**). The essential question to be asked now, following this benchmark analysis, is whether FeatureCloud should provide apps that provide the essential (and as many as possible recommended) MACRO features in a federated fashion, or whether FeatureCloud should aim for apps that allow for importing MACRO and/or CASTOR export file formats (after local pre-processing at each local site), which will then subsequently processed by federated machine learning and statistics apps. This decision will be finalized during the next funding period in the light of the results of this report, and after discussing the advantages and disadvantages of both options, also from a clinical trialist/user perspective.

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Product	Deployment	21 CFR Part 11 Compliance	Document Management	Electronic Data Capture	HIPAA Compliant	Monitoring	Patient Database	Recruiting Management
Castor EDC (99 reviews)	☁	✓	✓	✓	✓	✓	✓	✓
Clinical Conductor CTMS (28 reviews)	☁	✓	✓	✓	✓	✓	✓	✓
OpenClinica (12 reviews)	☁	✓	✓	✓	✓	✓	✓	✓
Medrio (48 reviews)	📱 ☁	✓	✓	✓	✓	✓	✓	✓
eAdjudication (2 reviews)	☁	✓	✓	✓	✓	✓	✓	✓
ClinicSoftware.com (11 reviews)	🖥 📱 ☁	✓	✓	✓	✓	✓	✓	✓
Research Manager (40 reviews)	☁	✓	✓	✓	✓	✓	✓	✓
Smartsheet (1442 reviews)	📱 ☁	✓	✓	✓	✓	✓	✓	✓

Fig. 1: *Features and ratings of the 10 leading Clinical Trial Management Software packages (www.capterra.com)*

3 Introduction (Challenge)

From a regulatory perspective, in addition to primary and secondary trial outcome analysis the management of adverse events is of utmost patient importance, but currently includes cloud based data transfer and reporting. The decision whether an event is related to the trial intervention is made by the PI and the Safety Board. Thus, privacy relevant events are currently entered into the cloud that are not necessarily related to the trial or its intervention(s). Nevertheless, FeatureCloud will have to comply with EU, national and (e.g. in Germany) regional law. At an EU level (ICH guidelines: CPMP/ICH/377/95, June 1995 from the European Medicines Agency), SAE reporting needs to be performed by the investigator within 24 hours of awareness. The sponsor will be notified automatically by the system. In case the investigator has not all information available, she/he can still adjust and complete the notification afterwards. It is then the task of the sponsor to notify the authorities (if applicable). Once the sponsor and the investigator have agreed about the nature of the event, the investigator can sign the SAE form. By signing the SAE form, the investigator states that the information is complete and correct according to her/his knowledge. It is then the task of the sponsor to notify the authorities (if applicable and dependent on the causality of the SAE): Fatal or life-threatening unexpected adverse drug reactions (ADRs): Regulatory agencies should be notified as soon as possible but no later than 7 calendar days after first knowledge by the sponsor that a case qualifies, followed by a report as complete as possible within 8 additional calendar days. This report must include an assessment of the importance and implication of the findings, including relevant previous experience with the same or similar medicinal products. All other serious ADRs are unexpected reactions that are not fatal or life-threatening and must be filed as soon as possible but no later than 15 calendar days after first knowledge by the sponsor that the case meets the minimum criteria for expedited reporting. The SAEs need to be reported to the competent authorities

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of all participating countries (e.g. BfArM in Germany), the applicable ethics commission and the participating investigators immediately but not later than 15 days of awareness (GCP-V, §12 and §13). The data needs to be pseudonymised. This communication and reporting needs to be enabled independent of the main data transfer and analysis. One alternative option may be to leave SAE reporting separate from main outcome parameter analysis. In addition to clinical trial software, access to deeply phenotyped longitudinal human biobanks and databases are becoming increasingly relevant for clinical research and to prepare clinical trials, e.g. to estimate pre-trial screening effort. Regarding this challenge, it had therefore been recommended to liaise additionally with the Estonian Biobank to enquire about their options and requirements for FeatureCloud access.

4 Methodology

Features necessary for usability and to fulfil nationally required reporting features, e.g., serious adverse events, for a phase II/III type clinical study based on MACRO or similar interfaces (Task 1), include from a clinical scientist, monitor and biostatistician’s view the following full feature and usability list and performance benchmarks, including nationally required reporting features, e.g. serious adverse events, currently for the Netherlands, Germany, and Estonia.

Use cases

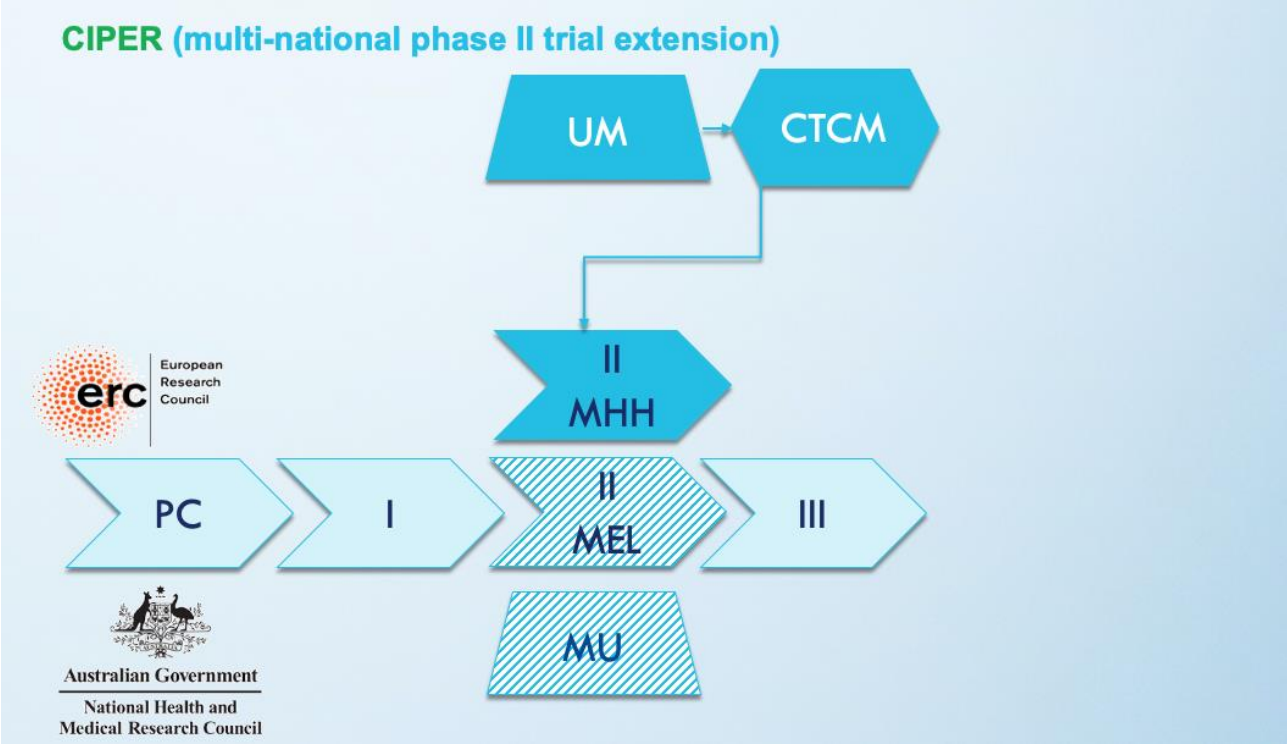

Fig. 2: CIPER. *A multinational phase II trial extension from Australia in Germany coordinated from Maastricht, NL. Data acquisition within MACRO is completed, analysis ongoing. Data has been transferred for multi-site analysis simulation by FeatureCloud.*

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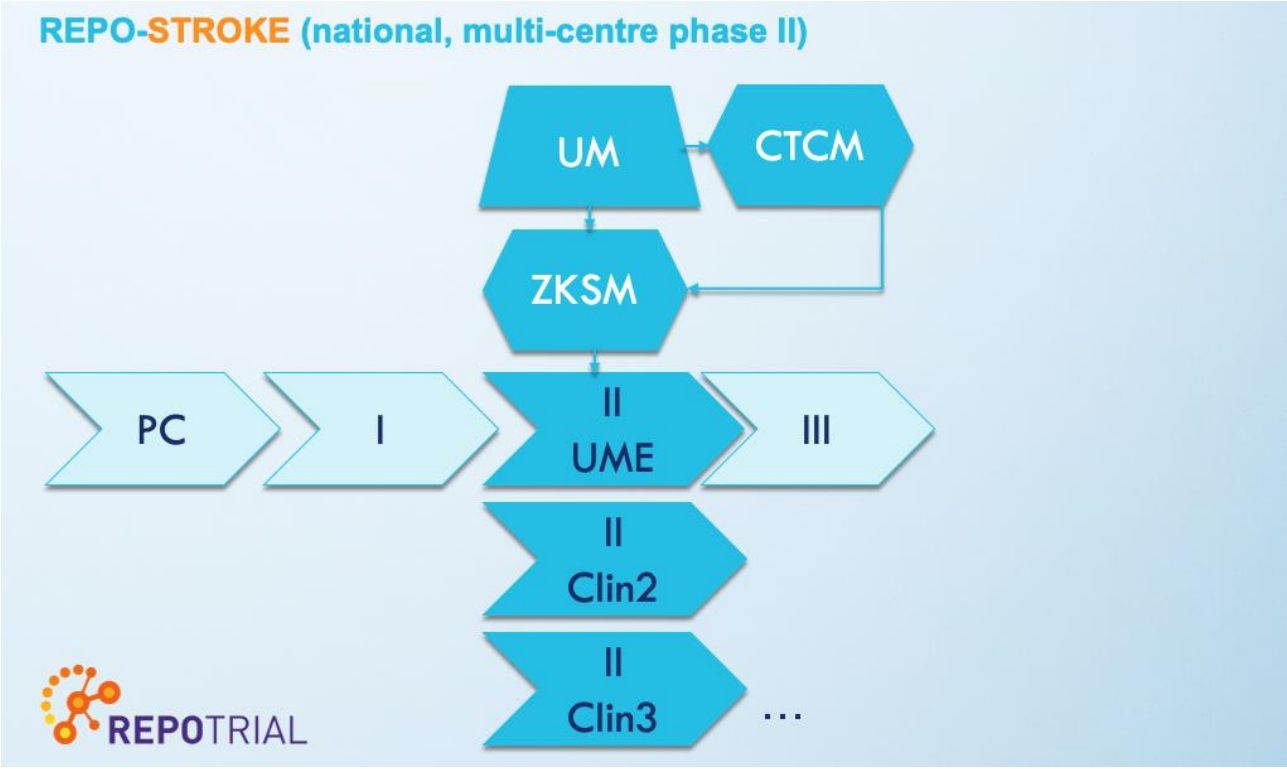

Fig. 3: REPO-STROKE. *A national, multicentre phase II trial in Germany for the indication ischemic stroke, coordinated from Maastricht, NL. Data acquisition within CASTOR and first patient in will commence approximately in June 2021. Data for multi-site analysis either by FeatureCloud or simulated afterwards. Patient stratification pre-tested in different biobanks.*

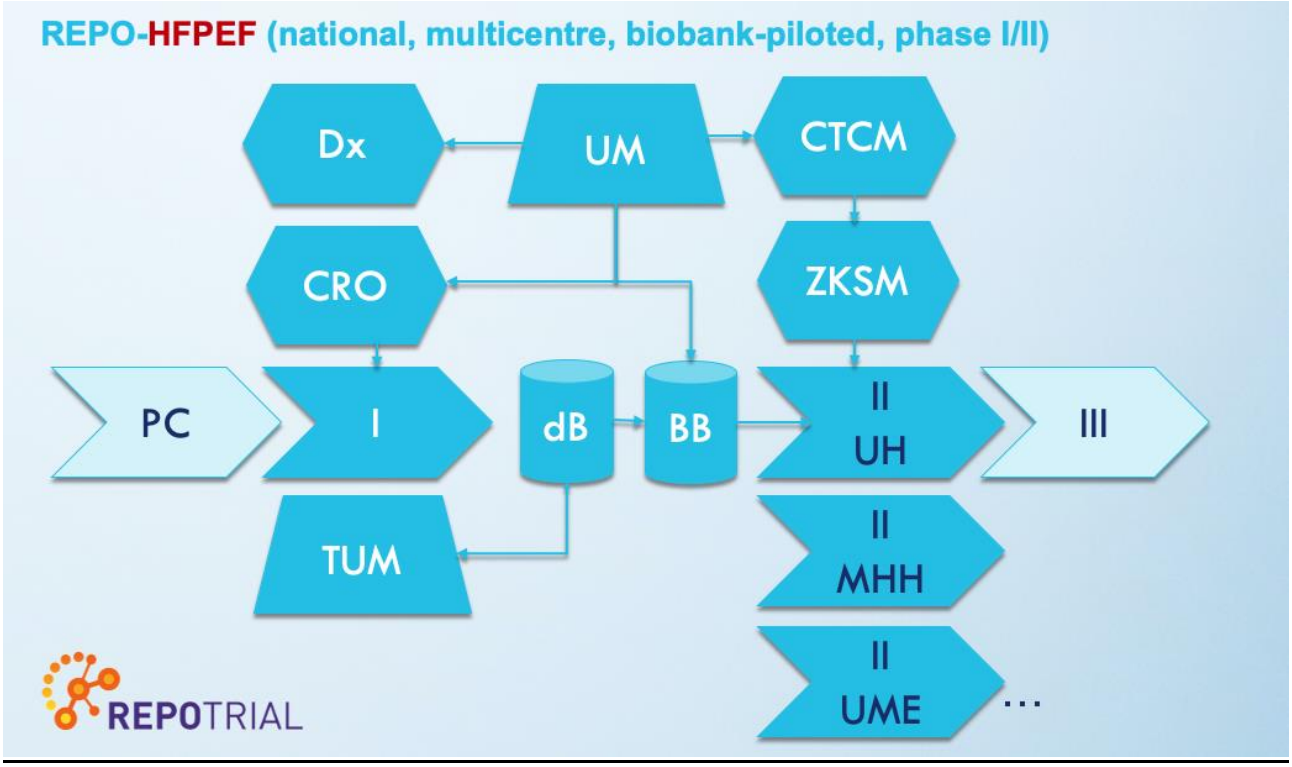

Fig. 4: REPO-HFPEF. *A national, multicentre phase II trial in Germany for the indication heart failure with preserved ejection fraction, coordinated from Maastricht, NL. Data acquisition within CASTOR and first patient in will commence approximately in January 2022. Data for multi-site analysis either by FeatureCloud or simulated afterwards. Patient stratification pre-tested in different biobanks including Estonia.*

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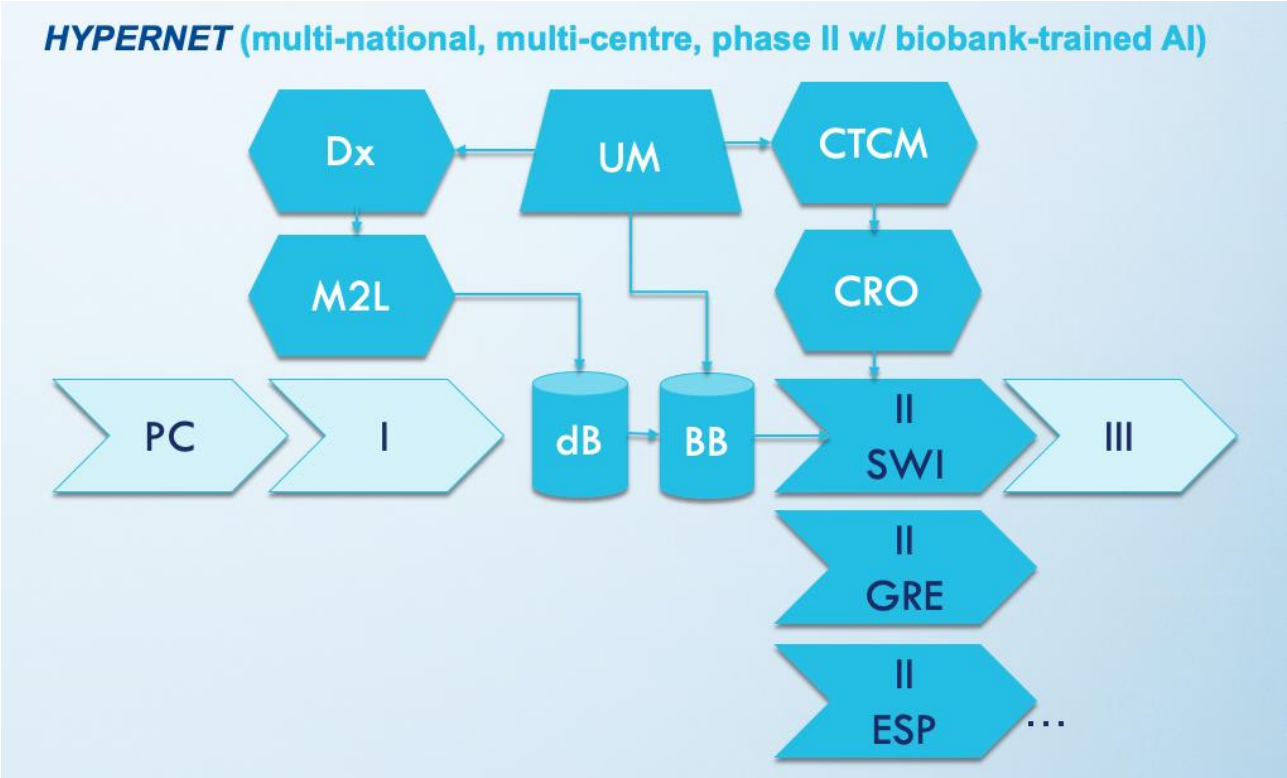

Fig. 5: HYPERNET. *A multinational, multicentre phase II trial in five European countries for the indication resistant hypertension, coordinated from Maastricht, NL. Data acquisition within and open system and first patient in will commence approximately in January 2022. Data for multi-site analysis either by FeatureCloud or simulated afterwards. Patient stratification pre-tested in different biobanks including Estonia. Currently in round 2 evaluation by Horizon Europe.*

5 Results

MACRO is a common Academic trial resource with fully open architecture (**Fig. 6**), where staff and software are audited according to Good Clinical Practice (GCP), conforming to internationally recognised ethical and scientific quality requirements for designing, conducting, recording and reporting clinical trials involving human subjects. MACRO users need to be assured that the rights, safety and well-being of trial subjects are protected, and that the results of the clinical trials are credible and accurate. Compliance and Audit features include, auditable by MHRA, compliant with ICH Good Clinical Practice, compliant with EU Clinical Trial Directive, and Medicines for Human Use (Clinical Trials) Regulations, ISO27001 certified data centre, FDA 21 CFR Part 11 compliant, providing an audit log and audit trail, double time stamp. User/customer support requires a four-hour SLA response, email and phone support, extensive help files, demo videos for new features, face-to-face training, online user forum for sharing best practice, annual user group web meeting. Data Entry needs to be possible online and offline. During data entry, values need to be immediately validated and re-evaluated on saving. Derived values need to be automatically calculated. eSignatures and approvals need to be possible as well as alerts, prompts and reminders and a visual status overview. Clinical coding should be with Medical Dictionary for Regulatory Activities (MedDra, meddra.org) integration. Remote data entry should be possible. With respect to data management, predefined and custom reporting and multiple export formats including SPSS, SAS, STATA and CSV are necessary together with integrated data clarification and source data verification processes, flexible database lock features, data import, a fully compliant data archive, event-driven email alerts. To design the study within the tool, drag and drop form design is desirable, full control of page layout, building of a user-designed library for easy re-use, conditional activation of visits, forms and

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questions, advanced calculations and derivations, flexible and edit checks, test and training environments, supports for all trial formats from Phase I to IV, scaling from a single site to large multinational trials, allowing for all standard question types plus laboratory normal ranges, inclusion of attachments, clinical coding of responses, and repeating question groups (tables). With respect to system management and security, the tool should allow to create, register and administer databases, define user roles comprising sets of permissions, assign user roles per study and/or per site, specify password properties and assign/change passwords, monitor system activity, set minimum and maximum password length, and password expiry period, implement a timeout period before repeat log-in is required, build-in browser technology for protecting or blocking data during transfer from study site (if applicable), including secure socket layer encryption and digital signatures.

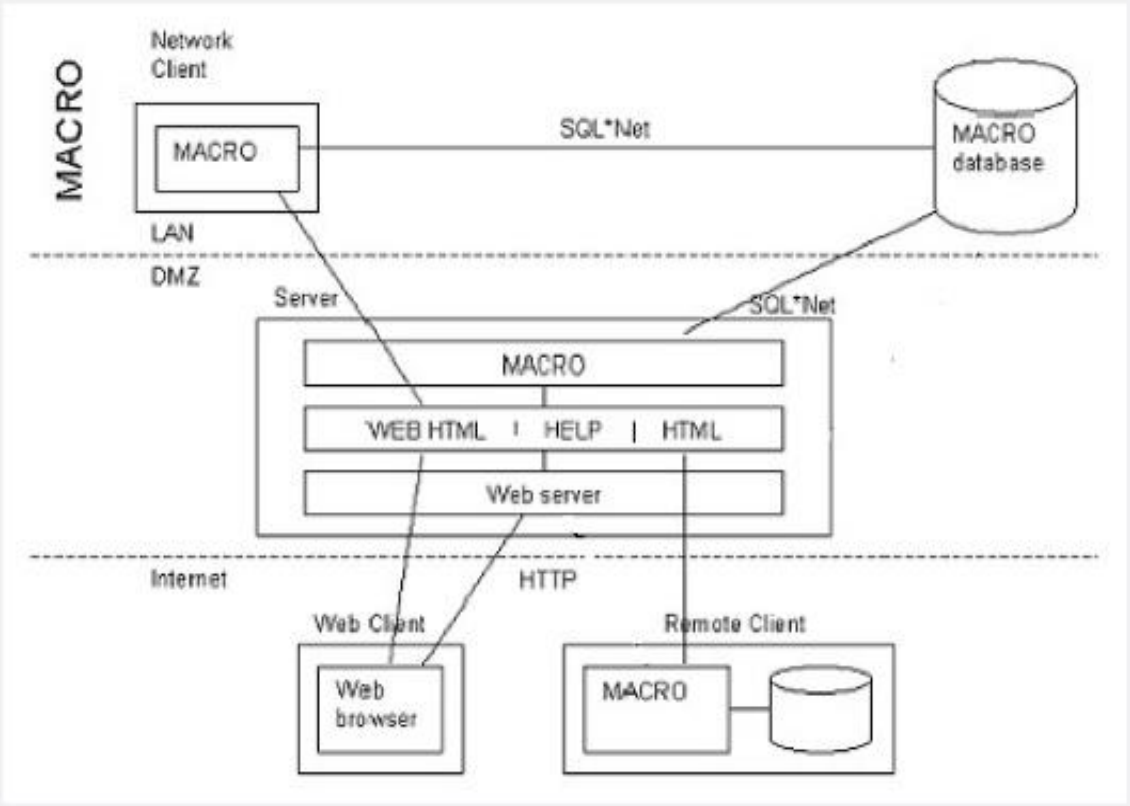

Fig. 6 *MACRO Architecture*

CASTOR (castoredc.com) is a cloud-based data solution, enabling researchers to capture and integrate data from any source. Features include Castor EDC (Electronic Data Capture), electronic Case Report Form (eCRF), electronic Patient Reported Outcomes (ePRO), electronic Clinical Outcome Assessment (eCOA), and electronic Trial Master File (eTMF). The advanced form builder allows for advanced calculations within and across forms, e.g. complex real-time edit checks and limiting field visibility based on multiple conditions being met, is end user-friendly, imports pre-built forms, has up to 21 different field types (**Fig. 7**), allows for repeated measurements, e.g. forms for repeating and unscheduled data such as SAE forms and clinical observations (e.g. blood pressure).

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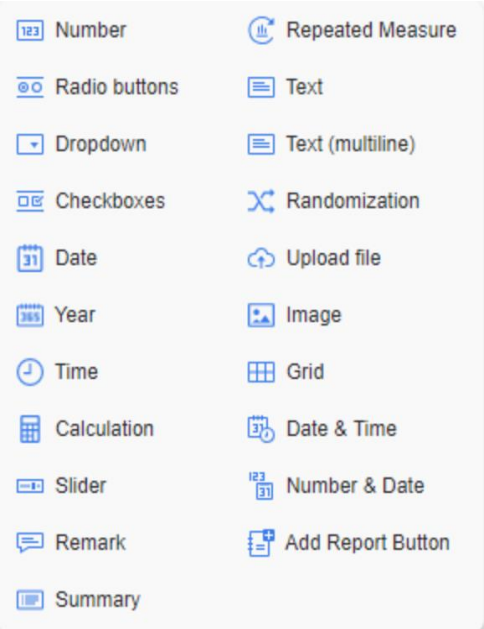

Fig. 7: *Field types in CASTOR*

The **Estonian Biobank** cohort is a volunteer-based sample of the Estonian resident adult population (aged ≥18 years). The current number of participants—close to 52000-—represents a large proportion, 5%, of the Estonian adult population, making it ideally suited to population-based studies. General practitioners (GPs) and medical personnel in the special recruitment offices have recruited participants throughout the country. At baseline, the GPs performed a standardized health examination of the participants, who also donated blood samples for DNA, white blood cells and plasma tests and filled out a 16-module questionnaire on health-related topics such as lifestyle, diet and clinical diagnoses described in WHO ICD-10. A significant part of the cohort has whole genome sequencing (100), genome-wide single nucleotide polymorphism (SNP) array data (20 000) and/or NMR metabolome data (11 000) available (http://www.geenivaramu.ee/for-scientists/data-release/). The data are continuously updated through periodical linking to national electronic databases and registries. A part of the cohort has been and can be re-contacted for follow-up purposes and resampling, and targeted invitations are possible for specific purposes, for example people with a specific diagnosis and interventional trials. For the recruitment of participants and for the collection of samples and health data, a unique network of data collectors was set up consisting of GPs and other medical personnel in private practices and hospitals or in the recruitment offices of the EGCUT. Geographically, all 15 Estonian counties participated and a total of 454 GPs, representing around 56% of all registered GPs,9 and 186 nurses were involved. The questionnaire was initially developed in 2001 in collaboration with the World Health Organization’s International Agency for Research on Cancer (IARC). The list of data items and samples collected has grown in the past 12 years (**Tab. 1**).

6 Open issues

Ethics applications need to be complemented or amended with FeatureCloud requirements. Moreover, from all desired features, the programmers of FeatureCloud will choose which to prioritise and whether to link them into existing softwares or if they design their own clinical trial software.

The main problem to be solved by FeatureCloud is using existing distributed data in a privacy-preserving manner for machine learning. Therefore, we intend to use existing solutions for collecting, storing and curating medical data by providing on-the-fly importers for as many of the software

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solutions mentioned above as possible. The biggest challenge is to consider patient consent and allow patients to specify their level of consent in a convenient and legally safe way through the FeatureCloud user interface. For that, FeatureCloud needs to be able to retrieve the consent of the owner of a piece of data to be imported from external sources. We will investigate if this is possible with anonymous identifiers attached to the data stored in medical software that is locally stored in the hospital. In case this proves to be unfeasible, FeatureCloud needs to handle medical data management by itself. What this implies for the individual components is briefly discussed in **Tab. 2**.

7 Conclusion

Currently four test cases, see section methodology, are possible for FeatureCloud with clear features necessary for usability and to fulfil nationally required reporting. In the next step, the consortium will decide how the necessary features will be covered by FeatureCloud implementations, having two obvious main options: (1) Reimplementing essential features directly into apps, or (2) making FeatureCloud compatible for processing localized MACRO export files - or a hybrid solution.

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8 Tables and other supporting documents

Table 1: Data items collected by the EGCUT for the Estonian Biobank:

Year	Measurements and samples
2002–10	Baseline questionnaire and measurements: • Computer-assisted genetic epidemiological questionnaire is filled. Information available in the electronic medical records is added to self-reported health information while the source of the information is recorded • Anthropometric measurements taken: weight, height, waist and hip circumferences, hair and eye colour, dominant hand • Blood pressure and resting heart rate are measured • Venous blood sample (30–50 ml) is drawn for DNA, WBCs and plasma
2003	Extra modules were added to the baseline questionnaire for participants with hypertension
2004	Extra modules were added to the baseline questionnaire for participants with type 2 diabetes.
2007	• Sleep module (MCTQ) and psychiatric module (MINI and SSP) were added to the questionnaire (for participants with specific diagnoses only) • Personality test (NEO-PI-R) added to the questionnaire with a separate informed consent form
2011–12	Food neophobia module[10] added to the baseline questionnaire
	Additional samples taken as part of a follow-up project: • Buccal swabs • Venous blood sample for RNA and serum for clinical biochemical analysis
2012	Dynamometrics, electrocardiogram, and spirometry were added to the measurements taken by the recruiter as part of a follow-up project. All equipment was standardized and the standard operating procedures were harmonized with the German National Cohort[11]

MCTQ, Munich Chronotype Questionnaire;[12] MINI, Mini-International Neuropsychiatric Interview;[13] SSP, Swedish universities Scales of Personality;[14] NEO-PI-R, Neuroticism-Extraversion-Openness Personality Inventory Revised.[15]

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Table 2: Feature and parameter list to be considered from a clinical point of view for implementation in FeatureCloud

#	Feature/Parameter	Clinical perspective	IT perspective
1	Auditable by MHRA	Desirable if UK study site is involved	Affects the environment for the controller and global backend. Requires it to be secure and protected from outside access (see D2.2 for more security measures). Adds requirements to the consent management in FeatureCloud, ensuring their rights are upheld (e.g., allowing to revoke consent). Also affects design of the non-configurable parts of the frontend (for configurable parts, see 27 ff.) to include all necessary information to ensure patients safety.
2	Compliant with ICH Good Clinical Practice	Essential	
3	Compliant with EU Clinical Trial Directive	Essential	
4	Compliant with Medicines for Human Use (Clinical Trials) Regulations	Essential	
5	ISO27001 certified data centre	Essential	
6	FDA 21 CFR Part 11 compliant	Desirable if USA study site is involved	
7	Audit log and audit trail	Essential	Patient and medical doctor frontend needs to include this information. *Component: Frontend, Global Backend, Controller*
8	Double time stamp.	Desirable	Consider time zone for all electronic signatures in the data model. *Component: Frontend, Global Backend*
9	User/customer support by a four-hour SLA response, email and phone support	Optional	*Not relevant*
10	Extensive help files, demo videos for (new) FeatureCloud features	Desirable	Provide a manual for the frontend, establish a process to keep documentation up-to-date with the newest version *Components: Frontend*
11	Face-to-face training	Optional	*Not relevant*
12	Online user forum for sharing best practice	Optional	Integrate a forum or other means of communication between users in the

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#	Feature/Parameter	Clinical perspective	IT perspective
			FeatureCloud platform *Components: Frontend, Global Backend*
13	Annual user group web meeting	Optional	Provide the technical framework for such online meetings, advertise it on the FeatureCloud platform or notify users appropriately *Components: Frontend, Global Backend*
14	Data Entry online and offline	Desirable	Allow for accessing the controller from the internet, potentially requiring additional security measures *Components: Controller*
15	During data entry, values need to be immediately validated and re-evaluated on saving	Essential	Implement validation mechanisms triggered upon data entry *Components: Frontend, Controller*
16	Derived values to be automatically calculated	Desirable	Implement logic calculating derived values in a flexible and extensible way (e.g., by allowing for entering dynamically evaluated expressions) *Components: Frontend, Controller*
17	eSignatures and approvals	Essential	Extend the patient frontend accordingly *Components: Frontend, Global Backend*
18	Alerts, prompts and reminders and a visual status overview	Desirable	Extend the frontend for patients accordingly *Components: Frontend, Global Backend*
19	Clinical coding with Medical Dictionary for Regulatory Activities (MedDra, meddra.org) integration	Essential	Add according fields and verify them automatically using an API *Components: Frontend, Controller*
20	Remote data entry	Desirable	*See 14*
21	Data management with predefined and custom reporting and multiple export formats including SPSS, SAS, STATA and CSV	Essential	Implement export functionality *Components: Frontend, Controller*
22	Integrated data clarification and	Essential	Extend the frontend with information about data fields, allow for linking data entries with original

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#	Feature/Parameter	Clinical perspective	IT perspective
	source data verification		source *Components: Frontend, Controller*
23	Flexible database lock features	Optional	Allow for blocking write access to data entries when being edited *Components: Controller*
24	Data import	Desirable	Implement import functionality *Components: Frontend, Controller*
25	Data archive, fully compliant	Desirable	Can be solved using a compliant export feature as an extension to *21*
26	Event-driven email alerts	Essential	Send emails upon changes made to patient entries. Allow for configuring this behaviour in the frontend *Components: Frontend, Controller*
27	Drag and drop form design	Optional	This requires the frontend to be highly configurable. Furthermore, the designed forms need to be shared with other participating parties to ensure homogeneous data structure. It requires a form builder, together with rudimentary database modelling functionality. *Components: Frontend, Global Backend*
28	Control of page layout	Desirable	
29	User-designed library for easy re-use	Desirable	
30	Conditional activation of visits, forms and questions	Essential	
31	Advanced calculations and derivations	Desirable	
32	Flexible and edit checks	Essential	
33	Test and training environments	Desirable	Can be added as part of the frontend, requires isolated environments for test purposes. *Components: Frontend, Global Backend, Controller*
34	Supports for all trial formats from Phase I to IV	Essential	Affects the data model and features 14, 20-24, 26
35	Scaling from a single site to large multinational trials	Essential	This has been considered from the start and is extensively covered in WP7. *Components: Frontend, Global Backend,*

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#	Feature/Parameter	Clinical perspective	IT perspective
			Controller
36	All standard question types	Essential	Affects the data model and import/export functionality, see *14, 20, 24, 26*
37	Laboratory normal ranges	Essential	
38	Inclusion of attachments	Desirable	
39	Clinical coding of responses	Desirable	
40	Repeating question groups (tables)	Optional	Extension to features *27-32*
41	Create, register and administer databases	Desirable	Extension to data modeller, requires by features *27-32*
42	Define user roles comprising sets of permissions	Essential	Affects user management already considered in the user and session model of the global backend. Requires additional forms in the frontend for permission management. *Components: Frontend, Global Backend, Controller*
43	Assign user roles per study and/or per site	Essential	
44	Specify password properties and assign/change passwords	Essential	
45	Monitor system activity	Desirable	
46	Set minimum and maximum password length, and password expiry period	Desirable	
47	Implement a timeout period before repeat log-in is required	Essential	
48	Build-in browser technology for protecting or blocking data during transfer from study	Essential	All data traffic over the internet is encrypted using SSL. See also D2.2, KPI 4 *Components: Frontend, Global Backend, Controller*

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#	Feature/Parameter	Clinical perspective	IT perspective
	site (if applicable)		
49	Secure socket layer encryption and digital signatures	Essential	
50	EDC (Electronic Data Capture)	Essential	Affects the data model and import/export functionality, see *14, 20, 24, 26*
51	electronic Case Report Form (eCRF)	Essential	
52	electronic Patient Reported Outcomes (ePRO)	Desirable	
53	electronic Clinical Outcome Assessment (eCOA)	Desirable	
54	electronic Trial Master File (eTMF)	Desirable	
55	Advanced calculations within and across forms, e.g. complex real-time edit checks and limiting field visibility based on multiple conditions being met	optional	Links features *15, 16* with form builder features *27-32.* Requires an extension of the form builder.
56	Import pre-built forms	Desirable	Extension to form builder, see features *27-32*
57	Repeated measurements, e.g. forms for repeating and unscheduled data such as SAE forms and clinical observations (e.g. blood pressure).	Essential	

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