

Randomisation mit RANDI2 und OpenClinica

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RCT

- Randomisierte kontrollierte Studie

Phase II

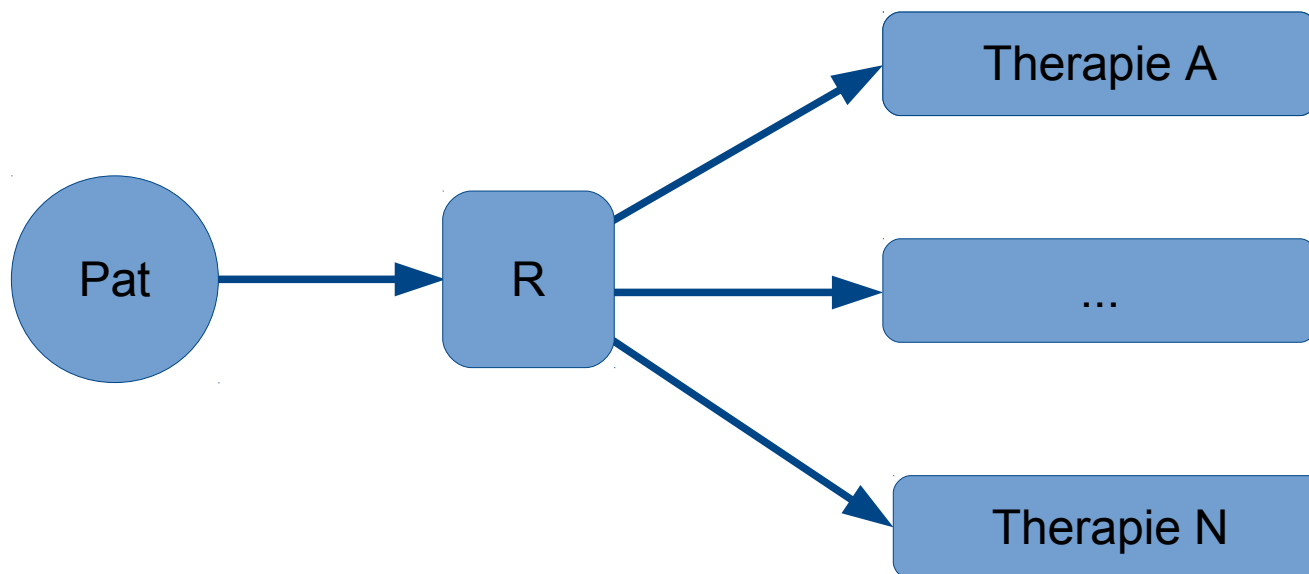
Überprüfung des Therapiekonzeptes; Findung der Therapiedosis

Phase III

Wirksamkeitsnachweis; Marktzulassung

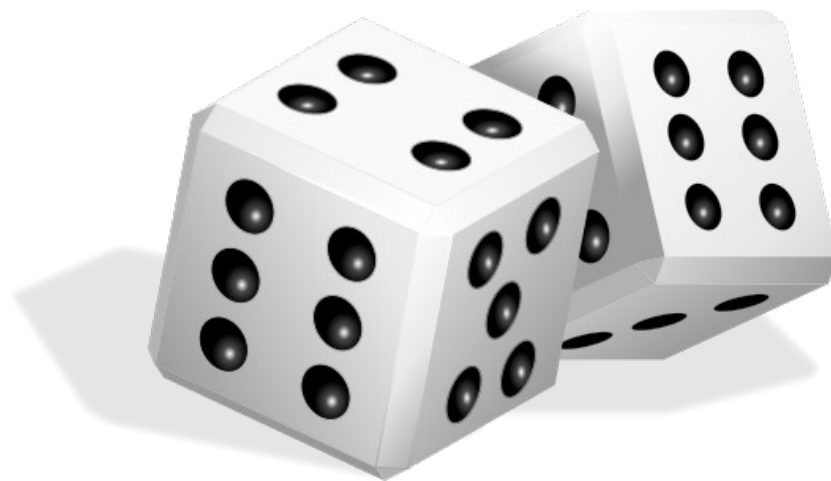
RCT

- Randomisation
→ „Zufällige“ Zuordnung zu den Studienarmen



Randomisation

- Vollständige Randomisation
 - Keine Auswahlverzerrung (selection bias)
 - Risiko der Unausgeglichenheit der Behandlungen



Randomisation

- Blockrandomisation
 - Zuordnung Blockweise



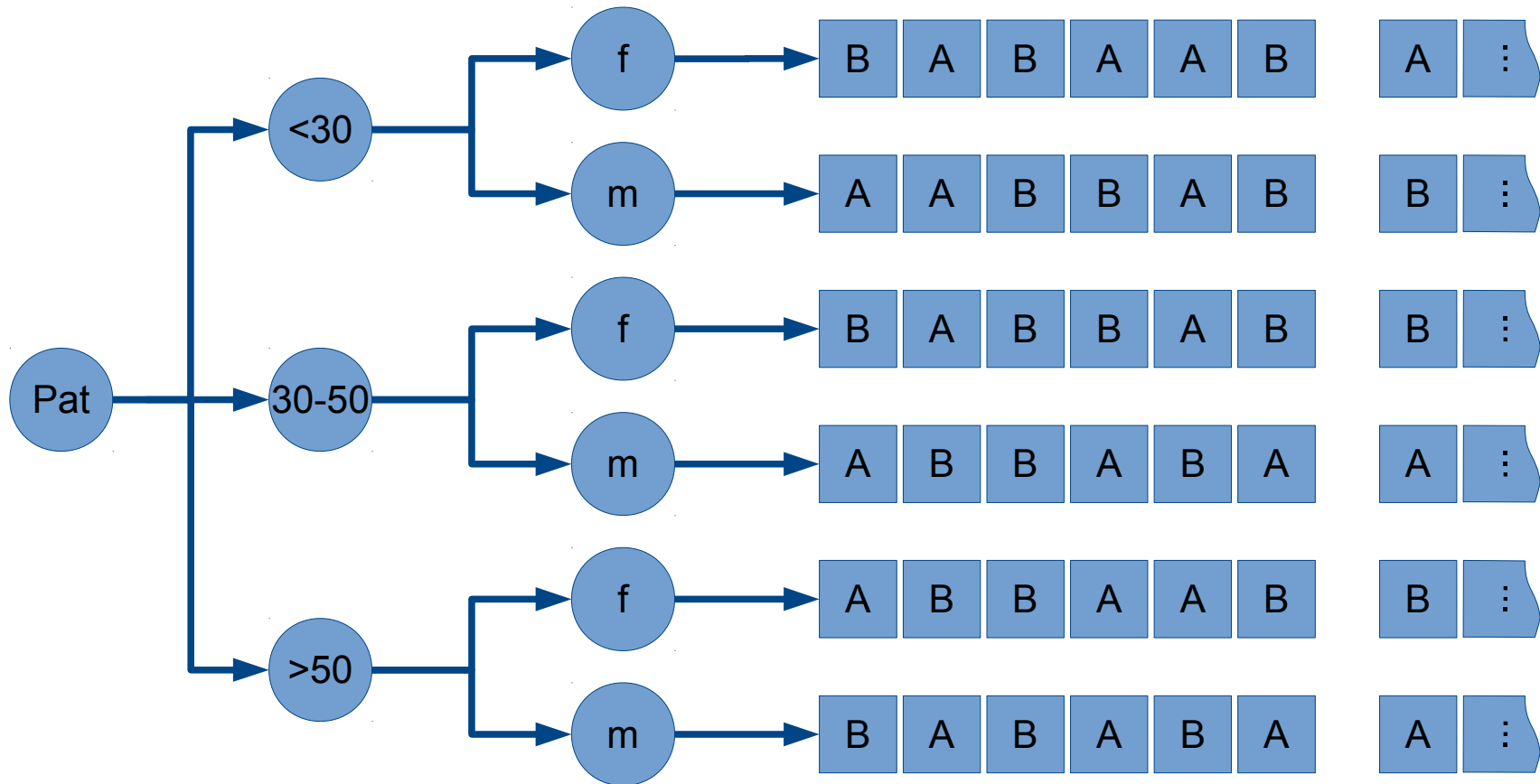
- Ausgeglichen nach jedem Block
- Zwischenauswertungen möglich

Stratifikation

- Ausgeglichenheit bekannter Einflussfaktoren
 - Geschlecht
 - Altersgruppen
 - ...
- **Patientendaten erforderlich**

Stratifikation

- Beispiel Blockrandomisation:



- Alternative Minimierungsalgorithmen

Antwort-adaptive Randomisation

- Idee:

Therapieergebnis für Randomisationen nutzen

- Einfachste Umsetzung binärer Endpunkt (Erfolg ja/nein)
- **Verlaufs- / Ergebnisdaten erforderlich**
- Stratified and randomized play-the-winner rule (SRPWR)
 - Basiert auf einem Urnenmodell
 - Einfache Realisierbarkeit

RANDI

- Web-Tool zur Randomisation

- Technologie:

- Scala / Java

- Liftweb

- Liquibase

- Slick

- ScalaSpec

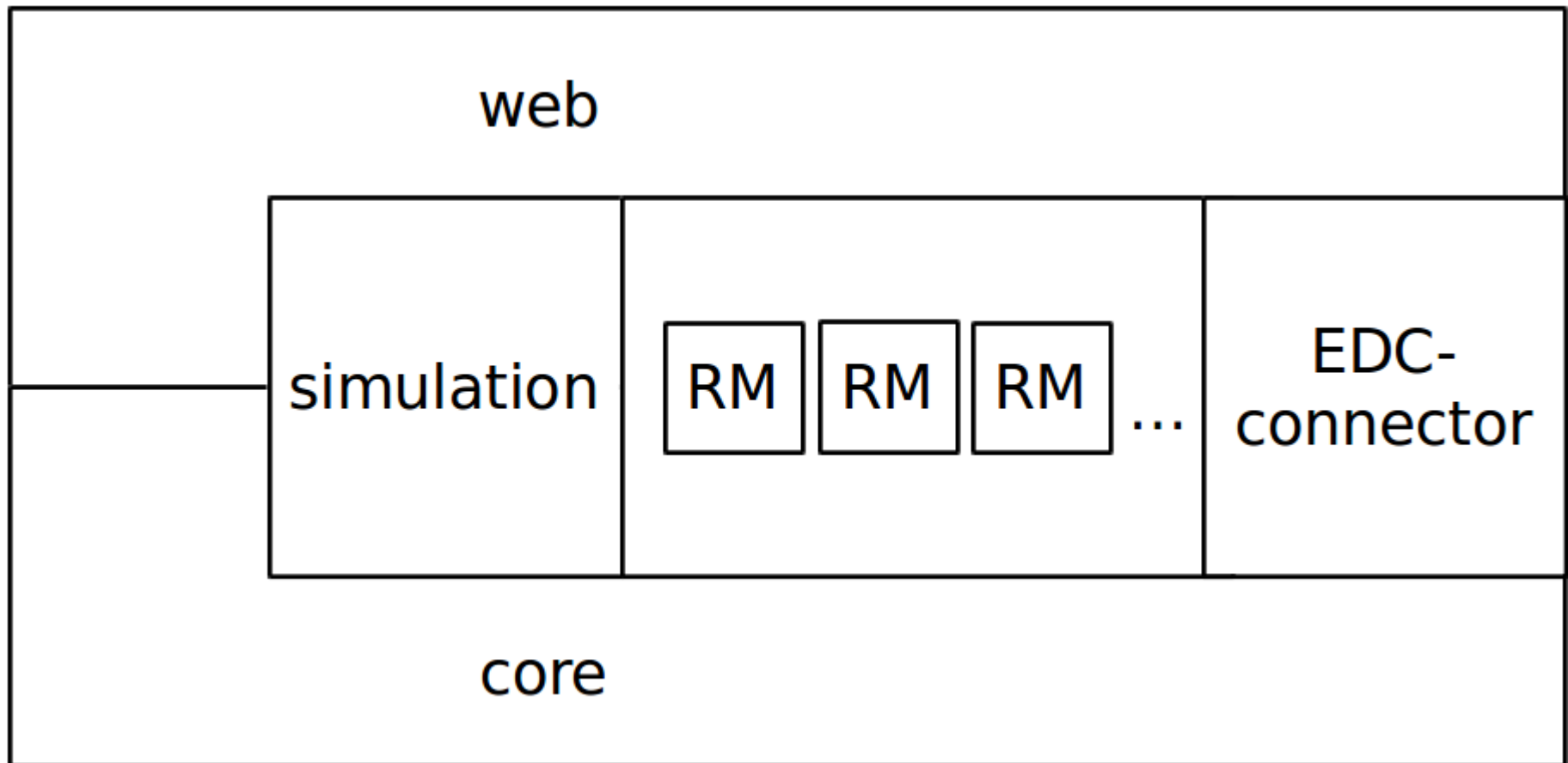
- Maven

- Datenbanken: MySQL, Postgres



RANDI2

- Aufbau

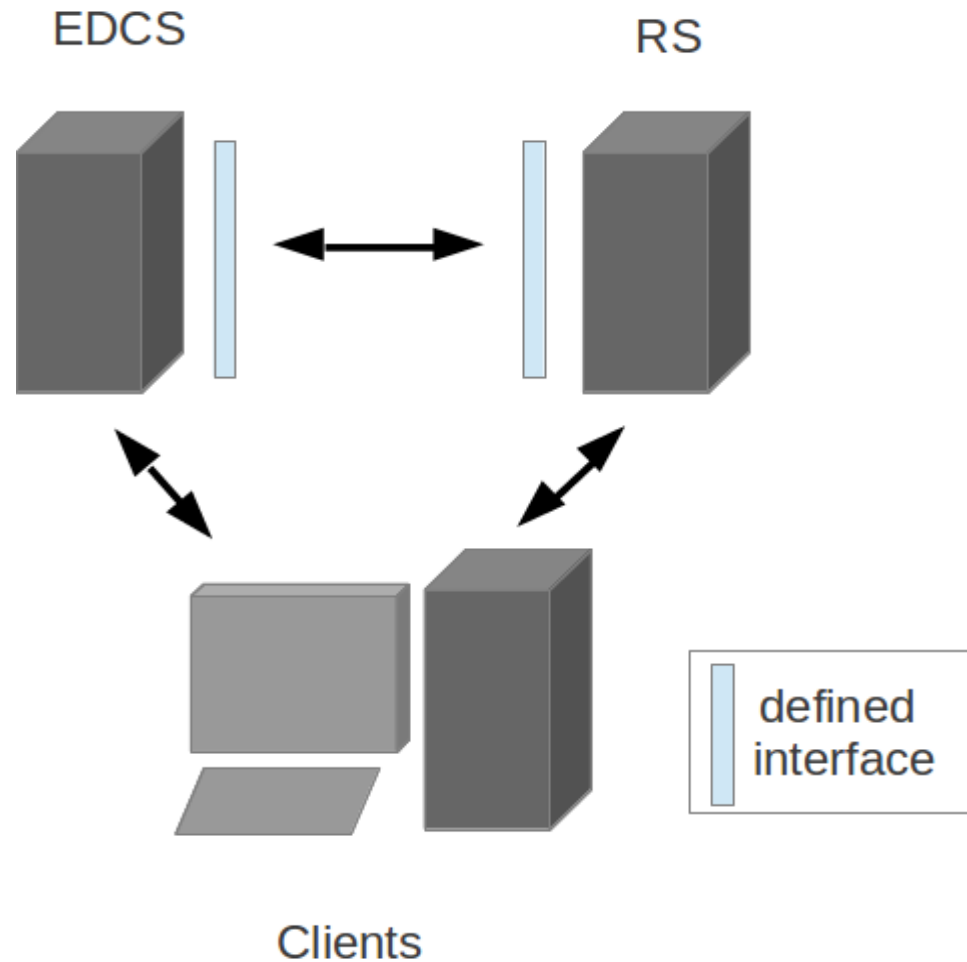


RANDI2

- Randomisationsmethoden:
 - Vollständige Randomisation
 - Trunkierte Randomisation
 - Blockrandomisation
 - Urnenmodell nach Wei
 - Minimierungsalgorithms
 - SRPWR
 - ...

Ziel

Gespeicherten Daten von OpenClinica für die Randomisation nutzen



Ablauf

- Studie in OpenClinica anlegen
 - Mithilfe der Metadaten in RANDI2 konfigurieren
-
- Prüfarzt fügt Patient in OpenClinica hinzu
 - Randomisation mit Daten aus OpenClinica
 - Ergebnis zurück in OpenClinica schreiben

Was wird benötigt?

- Liste der Studien
- Metadaten der Studien
- Patientendaten
- Import der Randomisationsergebnisse

OpenClinica WS

- SOAP und CDISC ODM

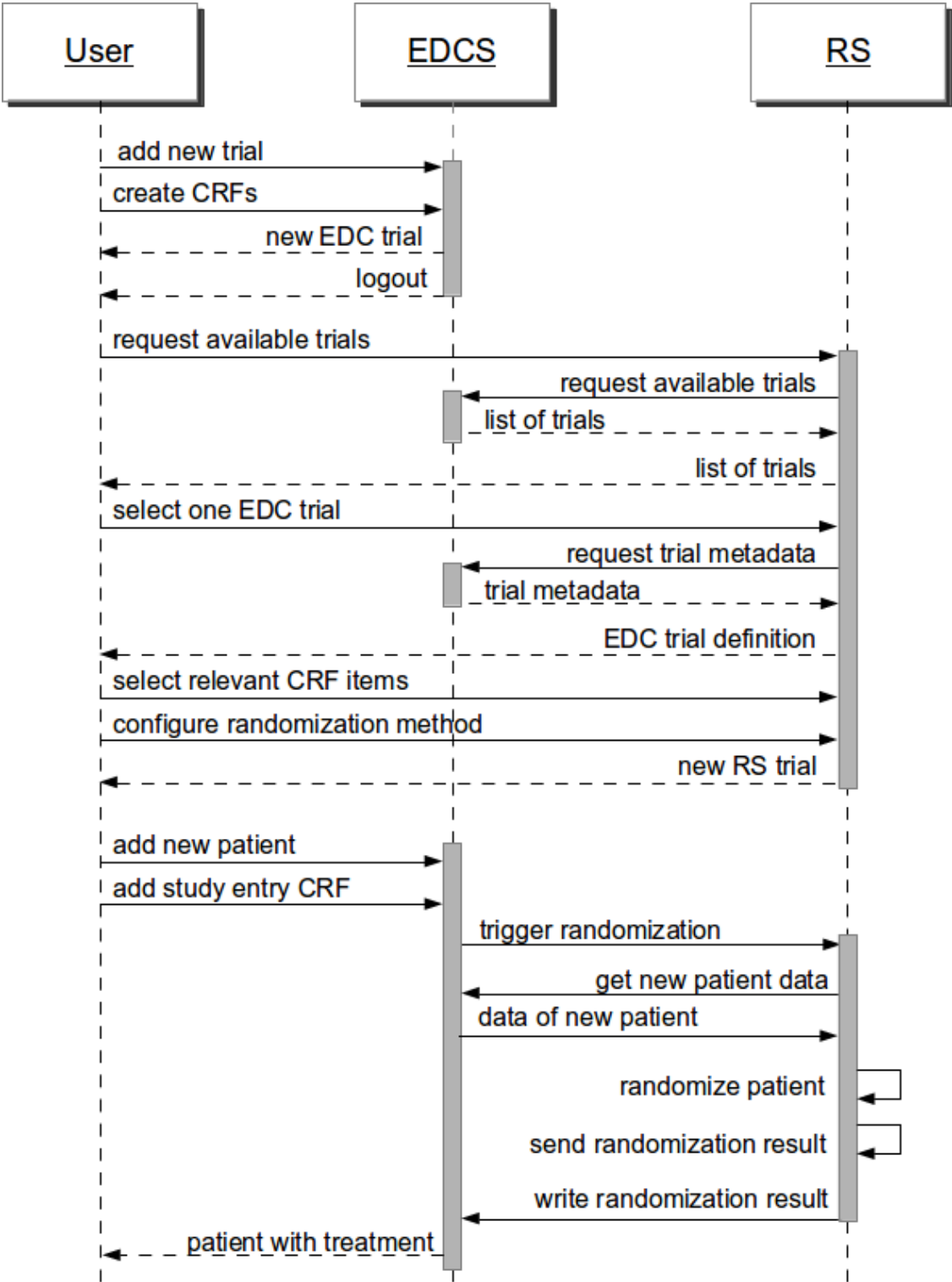
```
<soapenv:Envelope xmlns:soapenv="...">
  <soapenv:Header>...</soapenv:Header>
  <soapenv:Body>
    <v1:getMetadataRequest>
      <v1:studyMetadata>
        <bean:studyRef>
          <bean:identifier>identifrier</bean:identifier>
        </bean:studyRef>
      </v1:studyMetadata>
    </v1:getMetadataRequest>
  </soapenv:Body>
</soapenv:Envelope>

<SOAP-ENV:Envelope xmlns:SOAP-ENV="...">
  <SOAP-ENV:Header/>
  <SOAP-ENV:Body>
    <createResponse xmlns="http://openclinica.org/ws/study/v1">
      <result>Success</result>
      <odm><![CDATA[<Study OID="S_DEFAULTS1">
        <GlobalVariables>
          <StudyName>Default Study</StudyName>
          <StudyDescription> </StudyDescription>
          <ProtocolName>default-study</ProtocolName>
        </GlobalVariables>
        <MetaDataVersion>
          <Protocol>
          </Protocol>
        </MetaDataVersion>
      </Study>]]>
    </odm>
  </createResponse>
</SOAP-ENV:Body>
</SOAP-ENV:Envelope>
```

OpenClinica WS

- Study Web Service (listAll, getMetadata)
- Study Subject Web Service (listAllByStudy, create, isStudySubject)
- Event Web Service (schedule)
- Data Web Service (import)

- Service zum Datenexport fehlt
 - Hinzugefügt in Study Subject Web Service
 - Nutzt Datasets zum Export von Daten



OpenClinica – Studie anlegen


Test Studie

Welcome to the Build Study page of OpenClinica! This page is designed to help you build and configure your study






















down box and click the "Save" button. If the study status is Design, subjects can not be added.




Set Study Status

Available 

Save Status

	Task	Status	Count	Mark Complete	Actions
1	Create Study	Completed	NA		 
2	Create CRF	Completed	3		 
3	Create Event Definitions	Completed	3		 
4	Create Subject Group Classes	Completed	0		 
5	Create Rules	Completed	0		  

	Task	Status	Count	Mark Complete	Actions
6	Create Sites	Completed	0		 

	Task	Status	Count	Mark Complete	Actions
7	Assign Users	Completed	Total : 2		 

Save

Cancel

OpenClinica – DataSet anlegen

Create Dataset: Select Items

Please select one CRF from the **left side info panel**, then select one or more items in a CRF that you would like to include to this dataset. You may select all items in the study by going to the "View Selected Items" (hyperlink) page and clicking "Select All".

You may also click Event Attributes/Subject Attributes to specify which event/subject attribute will be shown in the dataset.



Use task pane on the left side to select CRFs

Event Name:	Studieneinschluss
CRF Name:	Studieneinschluss
Description:	

Select All Items

Save and Add More Items

Save and Define Scope

Cancel

Show the following items in this dataset:

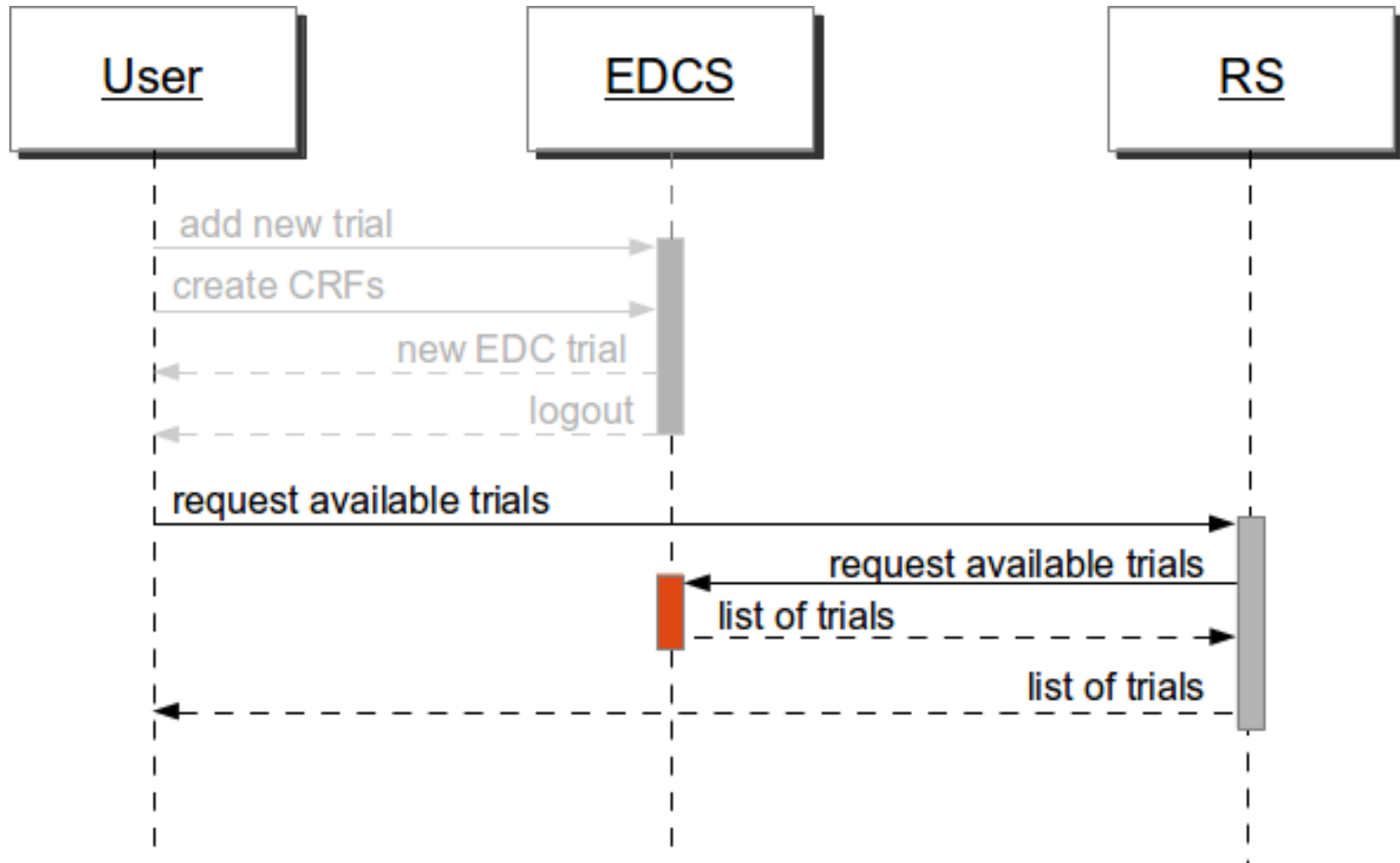
	Name	Description	Version(s)	Section(s)	Group(s)	Data Type	Units	Response Type	Response Label	PHI	Required?	Double Data Entry	Default Value	Max Repeats
<input checked="" type="checkbox"/>	Geschlecht	Geschlecht des Patienten	0.1	Entry Seite 1	Ungrouped	int		single-select	male, female	No	Yes			1
<input type="checkbox"/>	Alter	Alter des Patienten bei Studieneinschluss	0.1	Entry Seite 1	Ungrouped	int		text	text	No	Yes			1
<input type="checkbox"/>	Laborwert	Irgendein Laborwert	0.1	Entry Seite 2	Ungrouped	real		text	text	No	Yes			1

Save and Add More Items

Save and Define Scope

Cancel

Ablauf



OpenClinica – Study Web Service

```
<soapenv:Envelope xmlns:soapenv="..." xmlns:v1="...">  
  <soapenv:Header> ... </soapenv:Header>  
  <soapenv:Body>  
    <v1:listAllRequest/>  
  </soapenv:Body>  
</soapenv:Envelope>
```

OpenClinica – Study Web Service

```
<SOAP-ENV:Envelope xmlns:SOAP-ENV="...">
  <SOAP-ENV:Header/>
  <SOAP-ENV:Body>
    <listAllResponse xmlns="http://openclinica.org/ws/study/v1">
      <result>Success</result>
      <studies>
        <study>
          <identifier>default-study</identifier>
          <oid>S_DEFAULTS1</oid>
          <name>Default Study</name>
        </study>
        <study> ... </study>
      </studies>
    </listAllResponse>
  </SOAP-ENV:Body>
</SOAP-ENV:Envelope>
```

RANDI2 – Studien anzeigen

Home

Trial site

User

Trial

EDC

list remote EDC trials

view EDC trial

add EDC trial

list EDC trials

show EDC trial

randomize EDC trial

Support

About RANDI2

List remote EDC trials

Available trials

location

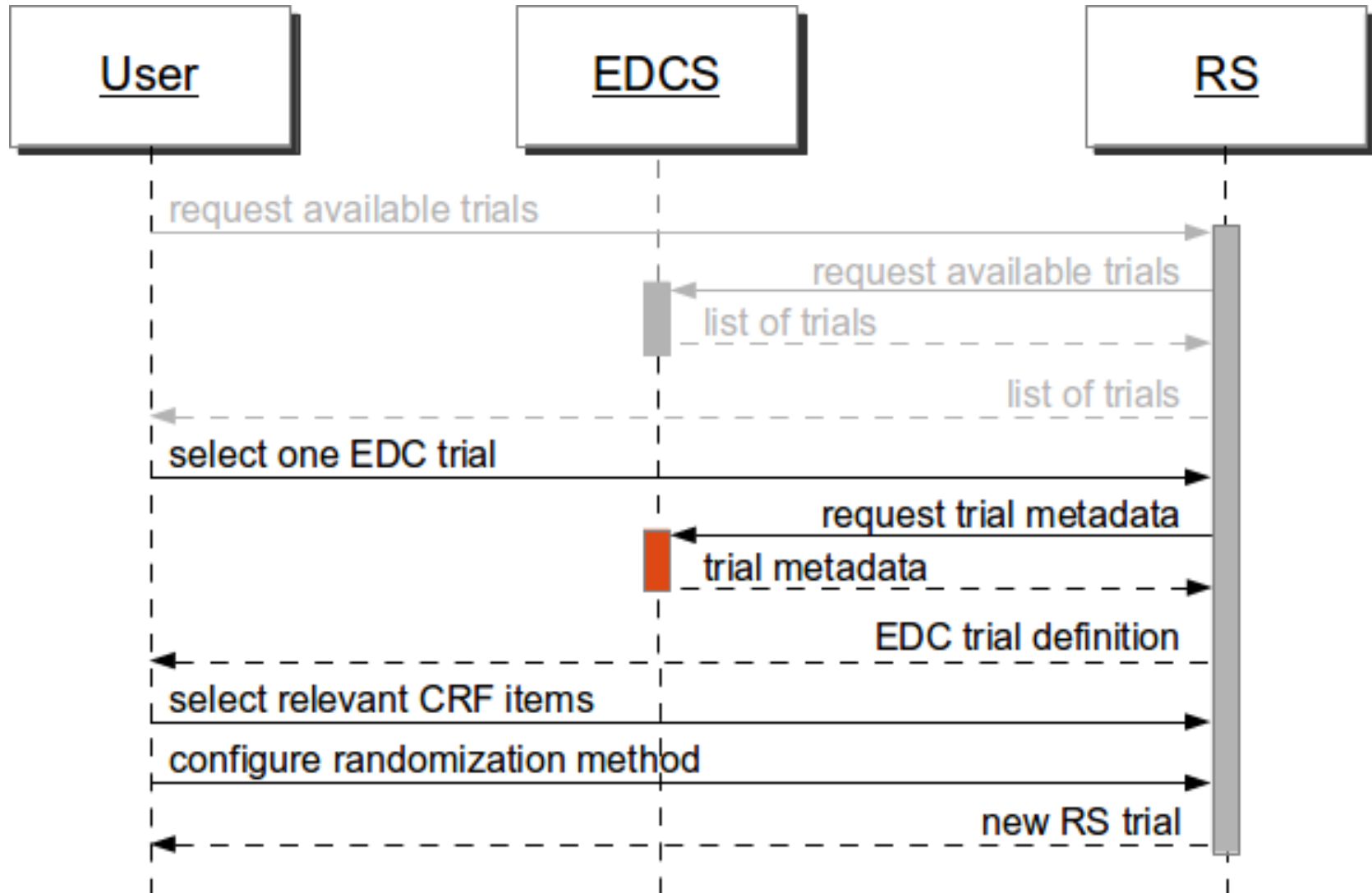
username

passwordHash

dataSetId

Identifier	Name	
Test-Studie	Test Studie	select

Ablauf



OpenClinica – Study Web Service

```
<soapenv:Envelope xmlns:soapenv="...">
  <soapenv:Header>...</soapenv:Header>
  <soapenv:Body>
    <v1:getMetadataRequest>
      <v1:studyMetadata>
        <bean:studyRef>
          <bean:identifier>identifier</bean:identifier>
        </bean:studyRef>
      </v1:studyMetadata>
    </v1:getMetadataRequest>
  </soapenv:Body>
</soapenv:Envelope>
```

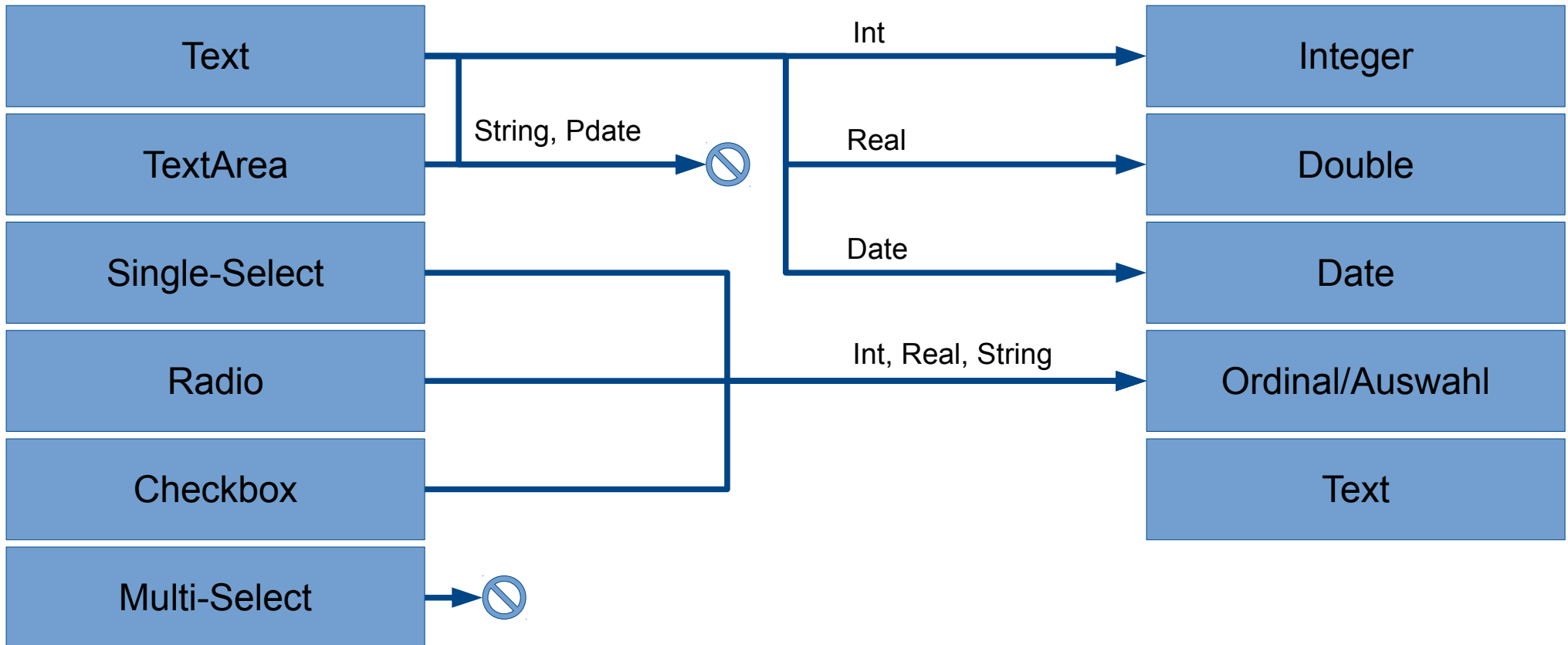
OpenClinica – Study Web Service

```
<SOAP-ENV:Envelope xmlns:SOAP-ENV="...">
  <SOAP-ENV:Header/>
  <SOAP-ENV:Body>
    <createResponse xmlns="http://openclinica.org/ws/study/v1">
      <result>Success</result>
      <odm><![CDATA[<Study OID="S_DEFAULTS1">
        <GlobalVariables>
          <StudyName>Default Study</StudyName>
          <StudyDescription> </StudyDescription>
          <ProtocolName>default-study</ProtocolName>
        </GlobalVariables>
        <MetaDataVersion>
          <Protocol>
          </Protocol>
        </MetaDataVersion>
      </Study>]]>
    </odm>
  </createResponse>
</SOAP-ENV:Body>
</SOAP-ENV:Envelope>
```

Item-Mapping

OpenClinica

RANDI2



RANDI2 – Studie importieren

Home

Trial site

User

Trial

EDC

list remote EDC trials

view EDC trial

add EDC trial

list EDC trials

show EDC trial

randomize EDC trial

Support

About RANDI2

Import EDC trial

General information

Select treatment

Select items

Randomization method

General information

identifier	Test-Studie
name	Test Studie
description	Teststudie zur Demo

RANDI2 – Studie importieren

Import EDC trial

General information **Select treatment** Select items Randomization method

Select treatment

treatmentArmItem

Treatment arm		Treatment arm	
Name	Treatment B	Name	Treatment A
Description	Behandlung: Treatment B	Description	Behandlung: Treatment A
Planned size	<input type="text" value="100"/>	Planned size	<input type="text" value="100"/>

RANDI2 – Studie importieren

Import EDC trial

General information Select treatment **Select items** Randomization method

Subject properties

	Name	Description
<input type="checkbox"/>	I_VERLA_S1_TEXT_INT	Verlauf Page 1 Text Fi
<input type="checkbox"/>	I_VERLA_S1_TEXT_REAL	Verlauf Page 1 Text Fi
<input type="checkbox"/>	I_VERLA_S1_SINGLESELECT_INT_CODING	Verlauf Page 1 Single
<input type="checkbox"/>	I_VERLA_S1_SINGLESELECT_STRING_CODI	Verlauf Page 1 Single
<input type="checkbox"/>	I_VERLA_S1_RADIO_INT_CODING	Verlauf Page 1 Radio
<input type="checkbox"/>	I_VERLA_S1_RADIO_STRING_CODING	Verlauf Page 1 Radio
<input type="checkbox"/>	I_VERLA_S2_TEXT_INT	Verlauf Page 2 Text Fi
<input type="checkbox"/>	I_VERLA_S2_TEXT_REAL	Verlauf Page 2 Text Fi
<input type="checkbox"/>	I_VERLA_S2_SINGLESELECT_INT_CODING	Verlauf Page 2 Single
<input type="checkbox"/>	I_VERLA_S2_SINGLESELECT_STRING_CODI	Verlauf Page 2 Single
<input type="checkbox"/>	I_VERLA_S2_RADIO_INT_CODING	Verlauf Page 2 Radio
<input type="checkbox"/>	I_VERLA_S2_RADIO_STRING_CODING	Verlauf Page 2 Radio
<input type="checkbox"/>	I_BEHAN_TREATMENT_STRING	Behandlung
<input checked="" type="checkbox"/>	I_STUDI_GESCHLECHT	Geschlecht des Patier
<input type="checkbox"/>	I_STUDI_ALTER	Alter des Patienten be
<input type="checkbox"/>	I_STUDI_LABORWERT	Irgendein Laborwert

RANDI2 – Studie importieren

Import EDC trial

- General information
- Select treatment
- Select items
- Randomization method**

Please select:

General informations

Name: org.randi3.randomization.BlockRandomization
Description: Block randomization algorithm with a fixed block size

Configurations

Block size :

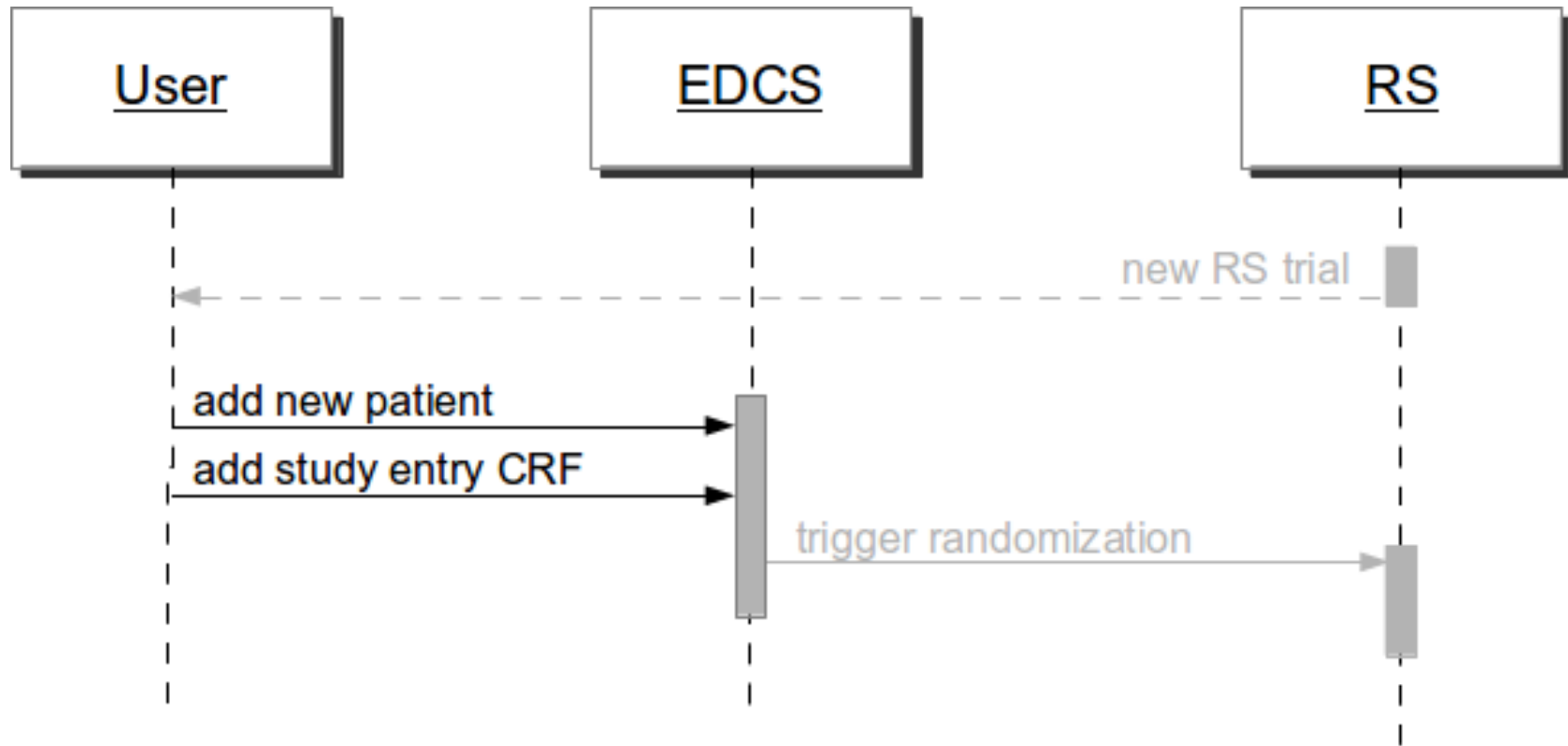
Stratification

OrdinalCriterion

Name
I_STUDI_GESCHLECHT

Description Geschlecht des Patienten





Ablauf



OpenClinica – Patient anlegen

Test Studie: Add Subject

* indicates required field.

Study Subject ID:	<input type="text" value="ID will be generated on Save or Add"/>	*
Person ID:	<input type="text" value="Patient 4"/>	* 
Secondary ID	<input type="text"/>	
Date of Enrollment for Study ' Test Studie ' :	<input type="text" value="29-Aug-2013"/>	*  
Sex:	<input type="text" value="-Select-"/>	* 

Save and Assign Study Event

Save and Add Next Subject

Save and Finish

Cancel


OpenClinica – Patient anlegen


Studieneinschluss 0.1


▼ CRF Header Info


◀ ENTRY_P...(0/2) ENTRY_P...(0/1) ▶ -- Select to Jump --

Title: Entry Seite 1

Page: 

Geschlecht * 

Alter *  Zwischen 18 und 60

[Return to top](#) 

OpenClinica – Patient anlegen


Studieneinschluss 0.1


▼ CRF Header Info


Your data has been saved. You may continue entering/editing data now or return at a later time.

◀ ENTRY_P...(2/2) ENTRY_P...(0/1) ▶ -- Select to Jump -- ▼

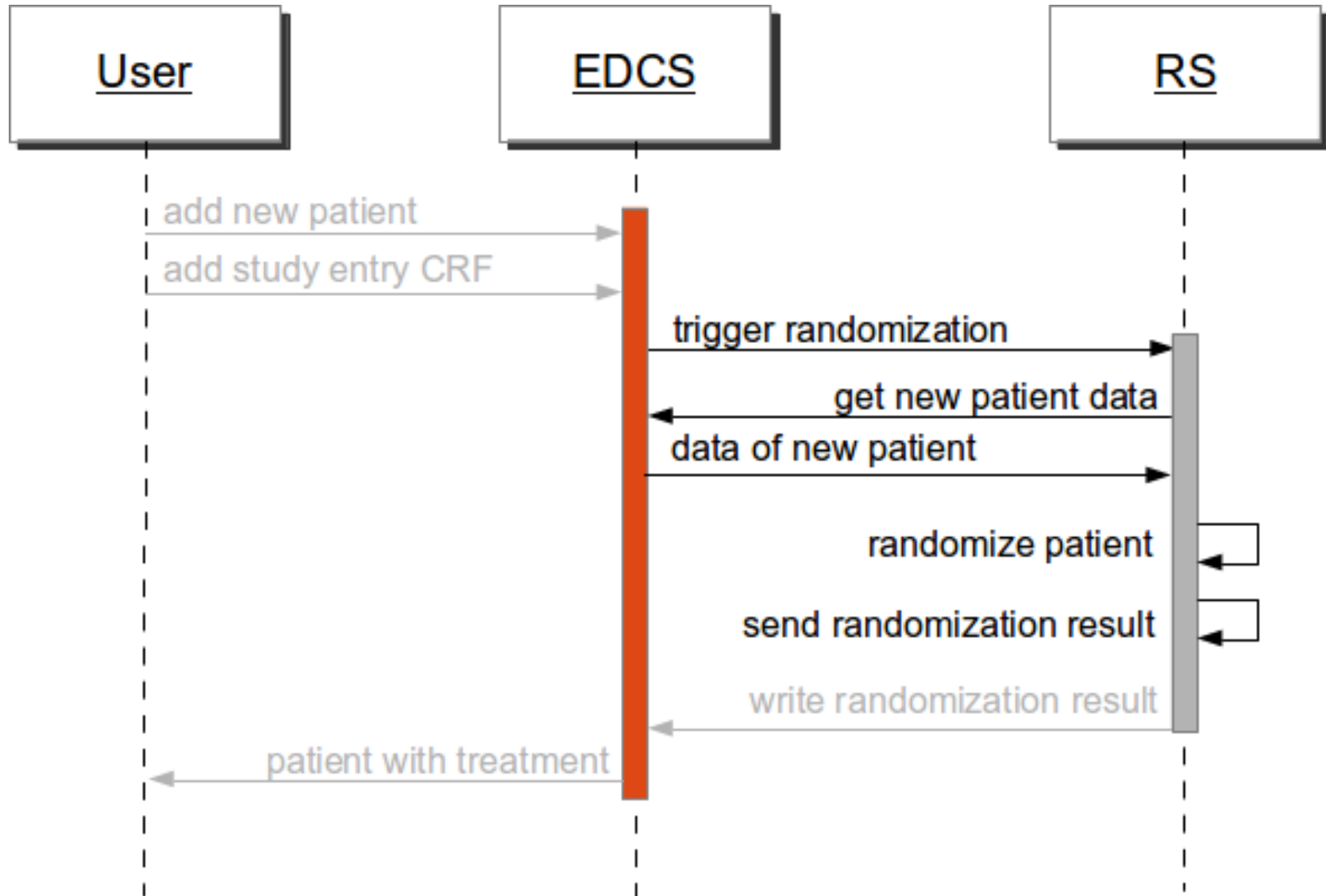
Title: Entry Seite 2

Page: Mark CRF Complete 

Laborwert *  Zwischen 0 und 1

Return to top Mark CRF Complete 

Ablauf



OpenClinica - Study Subject WS

```
<soapenv:Envelope xmlns:bean="...">
  <soapenv:Header>...</soapenv:Header>
  <soapenv:Body>
    <v1:getStudySubjectRequest>
      <v1:studyRef>
        <bean:identifier>Test-Studie</bean:identifier>
      </v1:studyRef>
      <v1:dataSetIdentifier>1</v1:dataSetIdentifier>
    </v1:getStudySubjectRequest>
  </soapenv:Body>
</soapenv:Envelope>
```

OpenClinica - Study Subject WS

```
<SOAP-ENV:Envelope xmlns:SOAP-ENV="">
  <SOAP-ENV:Header/>
  <SOAP-ENV:Body>
    <getStudySubjectResponse xmlns="http://openclinica.org/ws/studySubject/v1">
      <odm><![CDATA[<?xml version="1.0" encoding="UTF-8"?>
        <ODM FileOID="RandomizationDataSet" Description="...">
          <ClinicalData StudyOID="S_DEFAULTS1" MetaDataVersionOID="v1.0.0">
            <SubjectData SubjectKey="SS_1" OpenClinica:StudySubjectID="1">
              <StudyEventData StudyEventOID="SE_STUDIENEINSCHLUSS">
                ...
              </StudyEventData>
            </SubjectData>
            <SubjectData SubjectKey="SS_2" OpenClinica:StudySubjectID="2">
              ...
            </SubjectData>
          </ClinicalData>
        </ODM>]]>
      </odm>
    </getStudySubjectResponse>
  </SOAP-ENV:Body>
</SOAP-ENV:Envelope>
```

RANDI2 – Randomisationsliste

EDC trial Information

General

Trial sites

Treatment arms

Subject properties

Stages

Randomization

Patients

Created at	Identifier	Treatment	Trial site	Investigator	I_STUDI_GESCHLECHT
2013-08-29 16:31	1	Treatment A	Site1	dschrimpf	female
2013-08-29 16:32	2	Treatment B	Site1	dschrimpf	female
2013-08-29 16:32	3	Treatment A	Site1	dschrimpf	male
2013-08-29 18:46	4	Treatment A	Site1	dschrimpf	female



[Download](#)

Home

Trial site

User

Trial

EDC

list remote EDC trials

view EDC trial

add EDC trial

list EDC trials

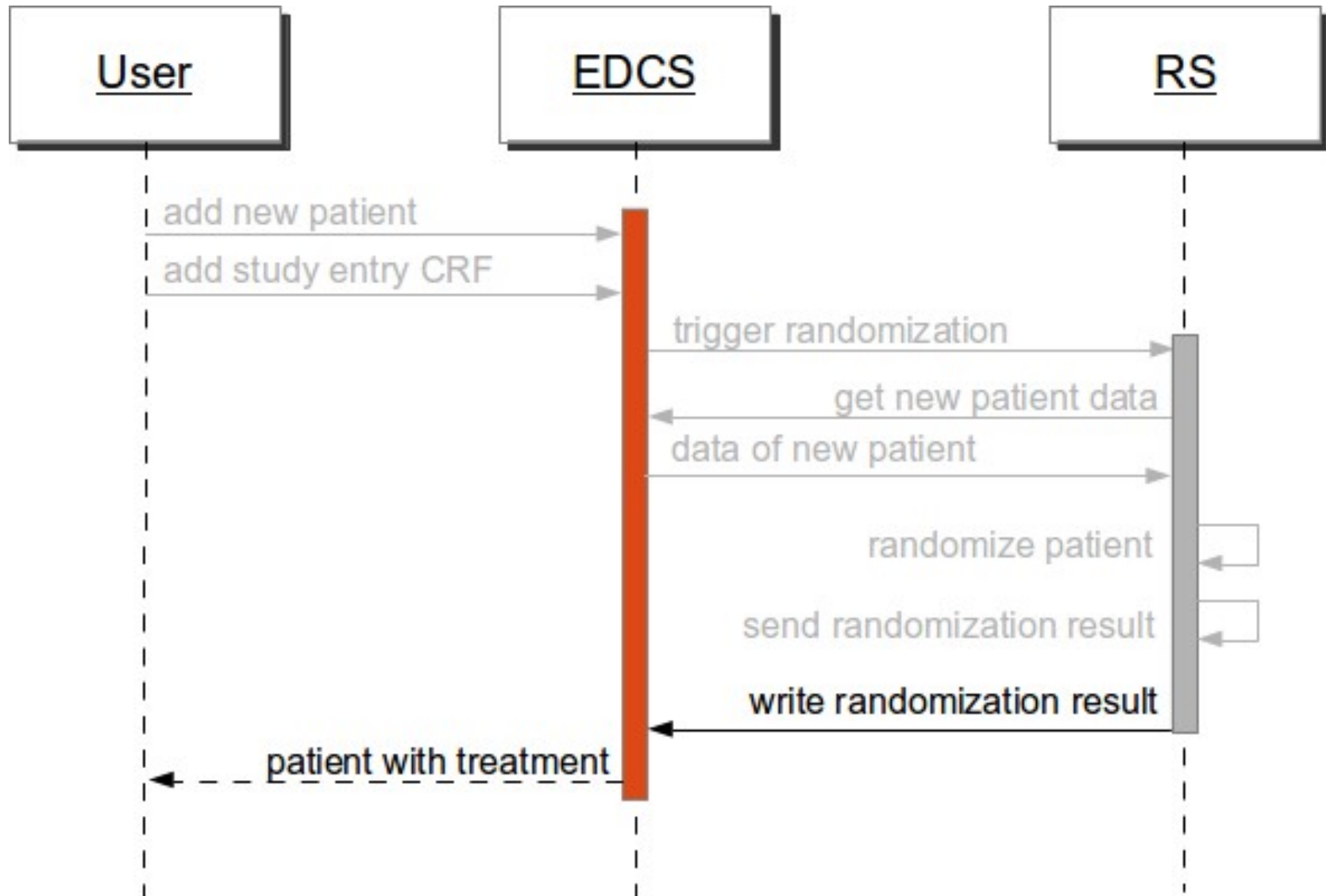
show EDC trial

randomize EDC trial

Support

About RANDI2

Ablauf



OpenClinica – Event Web Service

```
<soapenv:Envelope xmlns:bean="...">
  <soapenv:Header>...</soapenv:Header>
  <soapenv:Body>
    <v1:scheduleRequest>
      <v1:event>
        <bean:studySubjectRef>
          <bean:label>Patient1</bean:label>
        </bean:studySubjectRef>
        <bean:studyRef>
          <bean:identifier>default-study</bean:identifier>
        </bean:studyRef>
        <bean:eventDefinitionOID>SE_TREATMENT_8829</bean:eventDefinitionOID>
        <bean:location>RANDI2</bean:location>
        <bean:startDate>2013-08-26</bean:startDate>
      </v1:event>
    </v1:scheduleRequest>
  </soapenv:Body>
</soapenv:Envelope>
```

OpenClinica – Data Web Service

```
<soapenv:Envelope xmlns:bean="...">
  <soapenv:Header>...</soapenv:Header>
  <soapenv:Body>
    <v1:importRequest>
      <odm><![CDATA[
        <ODM .....
          .....
        </ODM>]]>
      </odm>
    </v1:importRequest>
  </soapenv:Body>
</soapenv:Envelope>
```

OpenClinica – Patientenliste

Subject Matrix for Test Studie ?

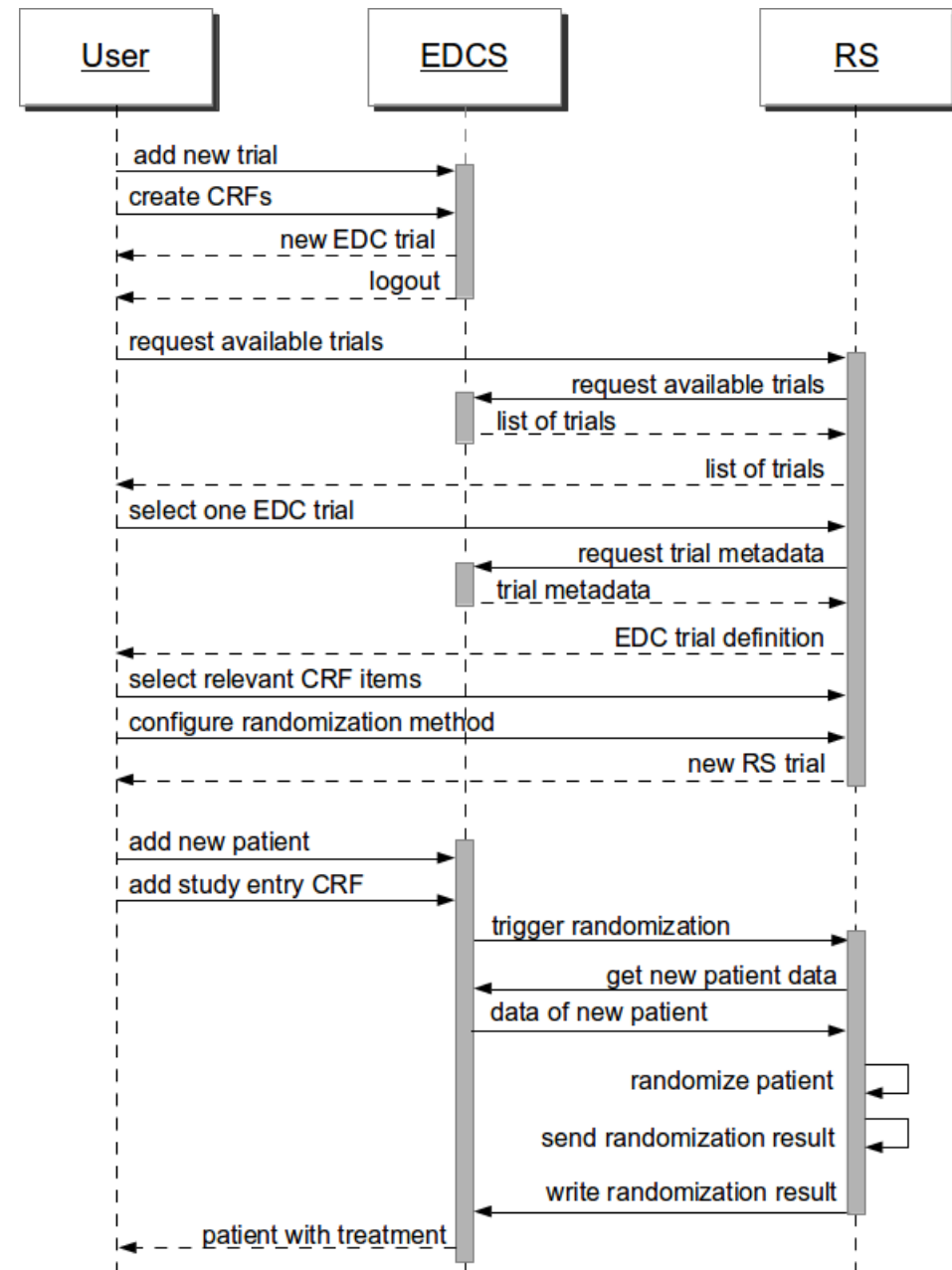
Navigation: ⏪ ⏩ 15 Show More Select An Event Add New Subject

Study Subject ID	Subject Status	Site ID	OID	Sex	Secondary ID	Studieneinschluss	Behandlungszuordnung	Studienverlauf	Actions
									Apply Filter Clear Filter
1	available	Test-Studie	SS_1	m		<input checked="" type="checkbox"/>			
2	available	Test-Studie	SS_2	m		<input checked="" type="checkbox"/>			
3	available	Test-Studie	SS_3	m		<input checked="" type="checkbox"/>			
4	available	Test-Studie	SS_4			<input checked="" type="checkbox"/>			

Ergebnisse 1 - 4 von 4.

Zusammenfassung

- Datenaustausch zwischen beiden Systeme
- Prüfarzt Daten nur in ein System
- Komplexe Randomisationsmethoden durchführbar



Ausblick

- Auf Datenbank von OpenClinica zugreifen:
 - Anmeldeinformationen zur Auswahl stellen
 - DataSet Identifier auslesen
 - Trigger für die Randomisation erstellen
- Oberfläche für Item-Auswahl verbessern
 - Anzeige nach Events und Forms
 - Einschluss- / Ausschlusskriterien hinzufügen
- Studienzentren
- OpenClinica WS – Projekt erweitern

Fragen?

SRPWR

- SRPWR(μ , α , β , t , s)
 - t - Behandlungen
 - s - Strata
 - μ , α , β Definieren die W' für die nächste Zuordnung
 - $\mu > 0$
 - α , β sind ein Vielfaches von $(t - 1)$
 - $0 \leq \alpha(t - 1) \leq \beta$

SRPWR

- ① Definiere s Strata; t Behandlungen;
- ② s Urnen mit je t verschiedenen Kugeln markiert mit i ($i = 1, 2, \dots, t$), je μ von jeder Sorte
- ③ Patient gehört zur k ten Subgruppe ($k = 1, 2, \dots, s$)
→ Kugel aus k ter Urne mit zurücklegen gezogen
→ Patient bekommt Behandlung i
- ④ Bei Response:
 - Erfolg bei Therapie i → β Kugeln vom Typ i und α Kugeln der anderen Typen (je $\alpha/(t - 1)$)
 - Misserfolg bei Therapie i → α Kugeln vom Typ i und β Kugeln der anderen Typen (je $\beta/(t - 1)$)
- ⑤ Schritt 3 und 4 werden wiederholt bis alle Patienten zugeordnet wurden