Randomisation mit RANDI2 und OpenClinica

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dkfz.
DEUTSCHES
KREBSFORSCHUNGSZENTRUM
IN DER HELMHOLTZ-GEMEINSCHAFT

RCT

- Randomisierte kontrollierte Studie

Phase II

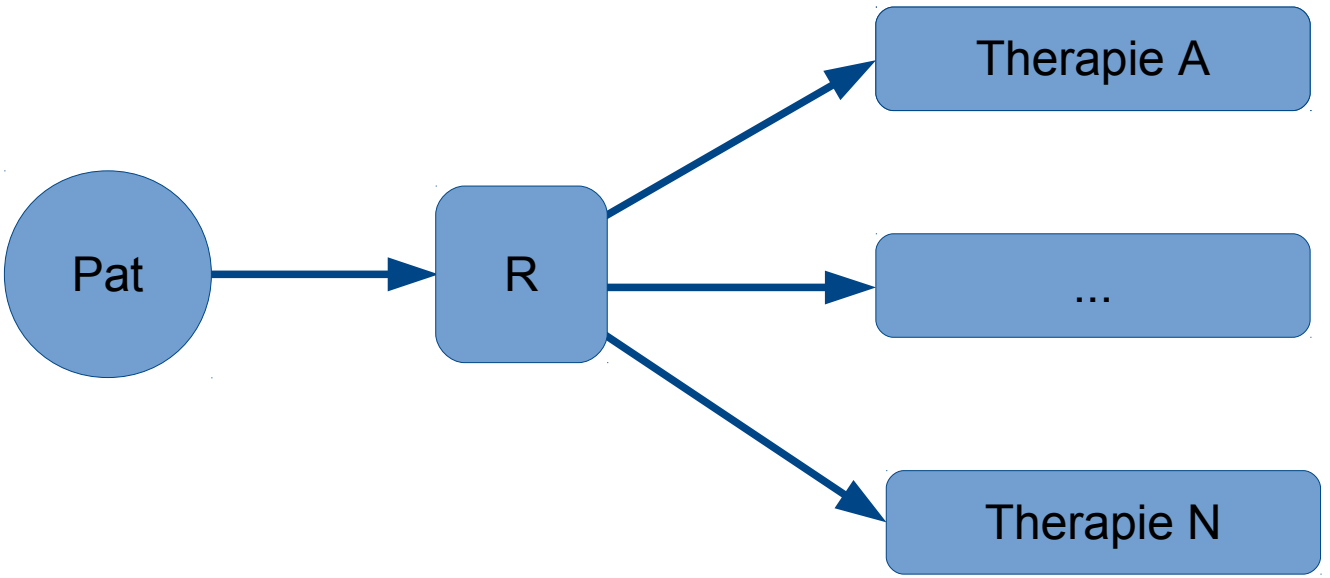
Überprüfung des Therapiekonzeptes; Findung der Therapiedosis

Phase III

Wirksamkeitsnachweis; Marktzulassung

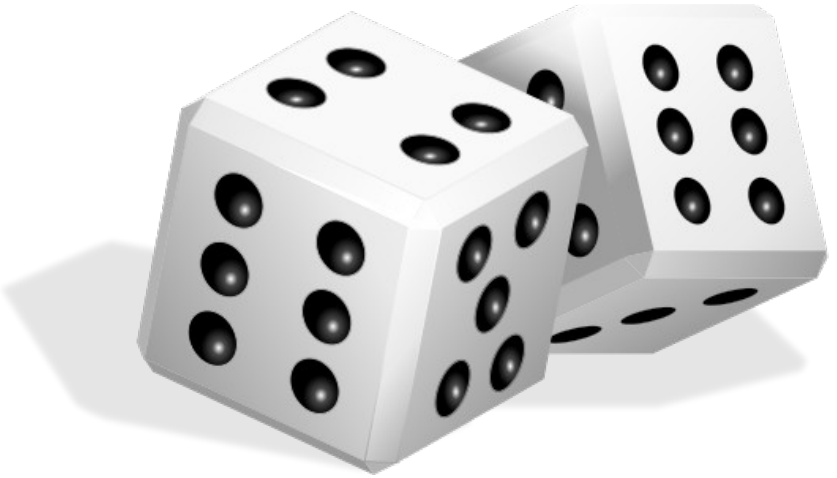
RCT

- Randomisation
  → „Zufällige“ Zuordnung zu den Studienarmen



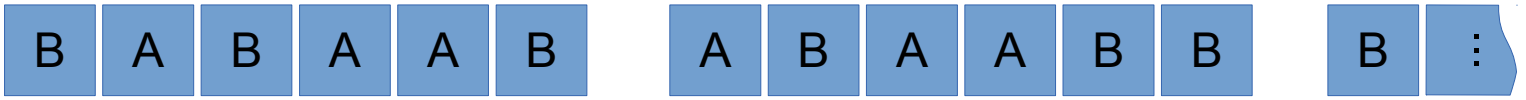
Randomisation

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



Randomisation

- Blockrandomisation
  - Zuordnung Blockweise



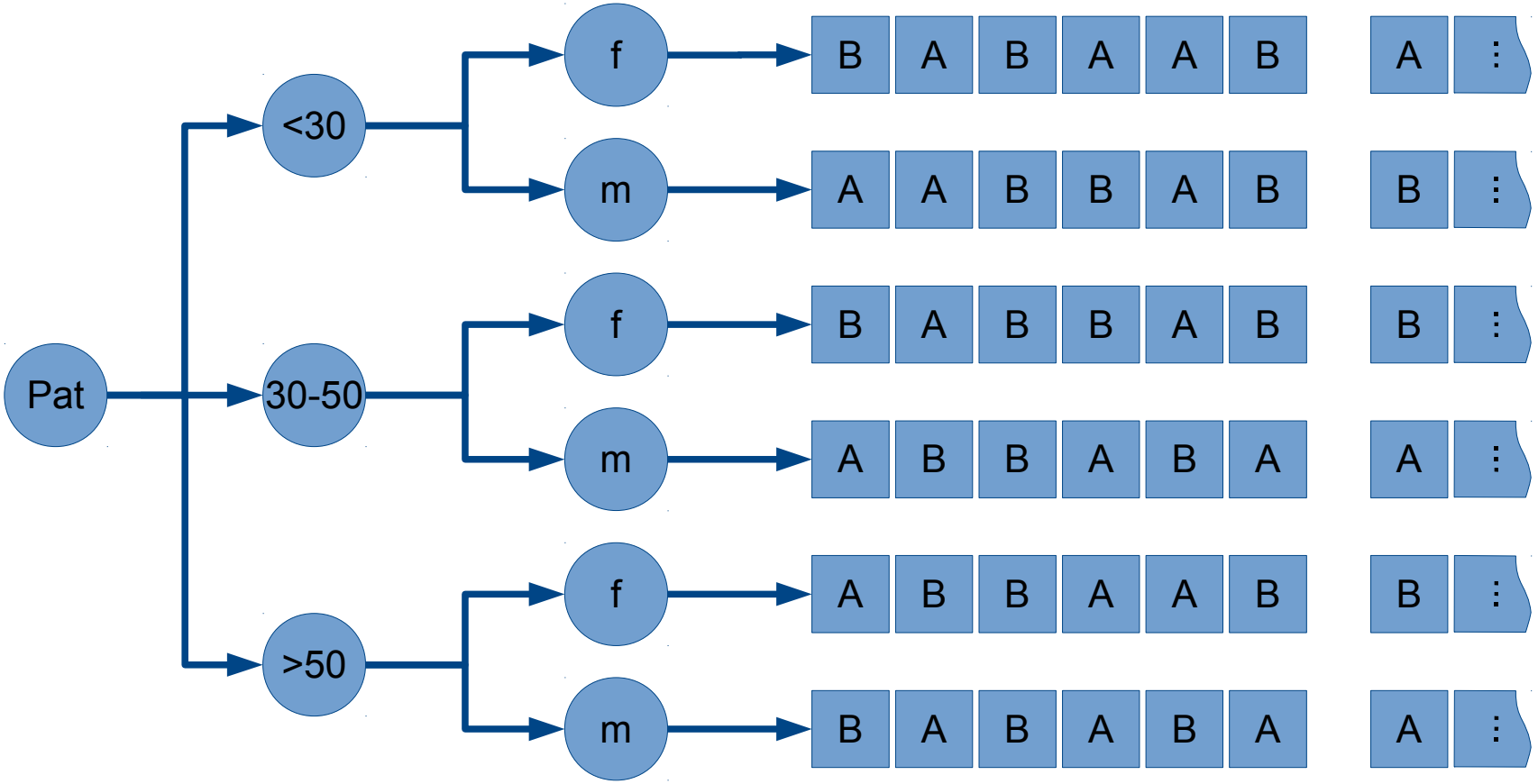
  - Ausgeglichen nach jedem Block
  - Zwischenauswertungen möglich

Stratifikation

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

Stratifikation

- Beispiel Blockrandomisation:



- Alternative Minimierungsalgorithmen

Antwort-adaptive Randomisation

- Idee:

Therapieergebnis für Randomisationen nutzen

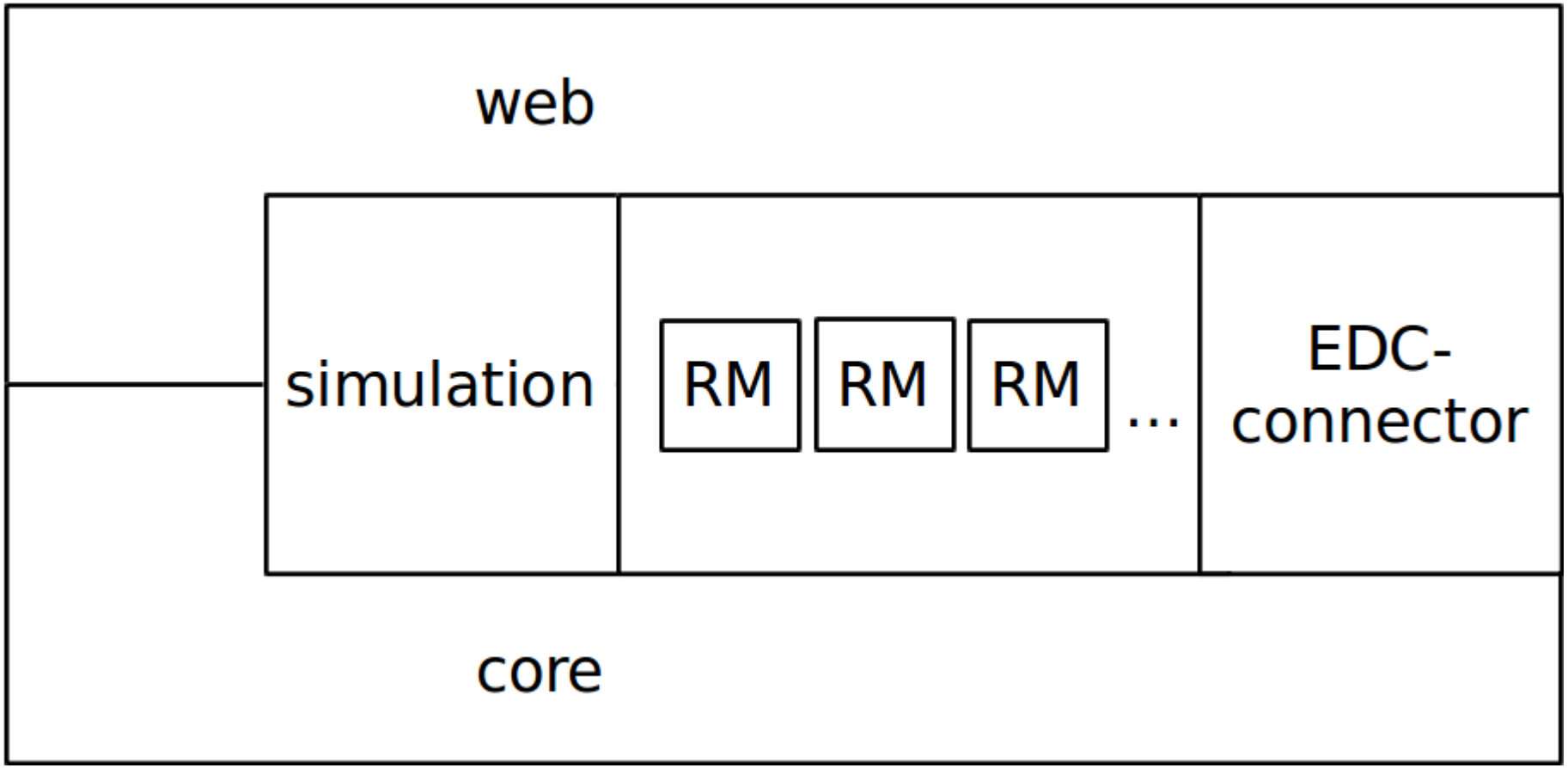
- Einfachste Umsetzung binärer Endpunkt (Erfolg ja/nein)
- **Verlaufs- / Ergebnisdaten erforderlich**
- Stratified and randomized play-the-winner rule (SRPWR)
  - Basiert auf einem Urnenmodell
  - Einfache Realisierbarkeit

RANDI

- Web-Tool zur Randomisation
- Technologie:
  - Scala / Java
  - Liftweb
  - Liquibase
  - Slick
  - ScalaSpec
  - Maven
- Datenbanken: MySQL, Postgres

RANDI2

- Aufbau

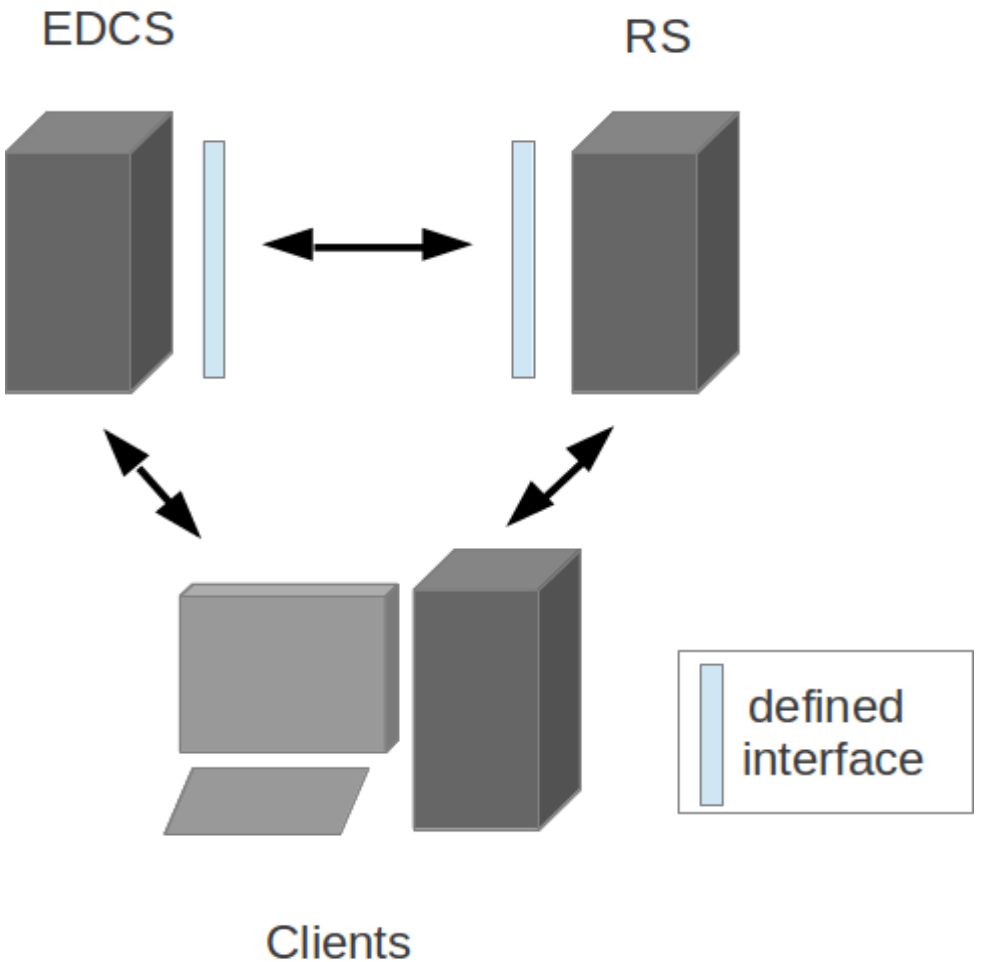


RANDI2

- 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

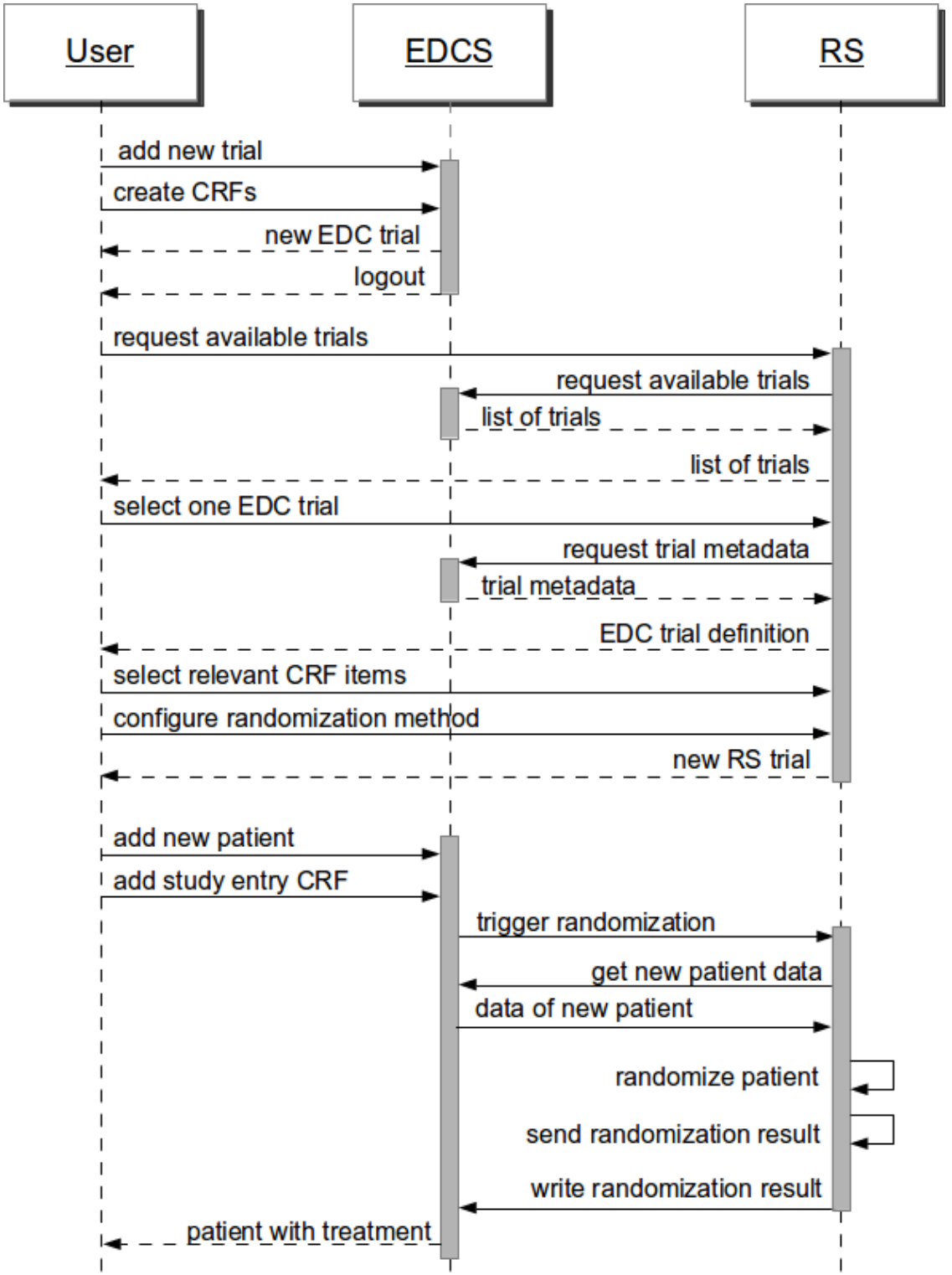
```
<soapenv:Envelope xmlns:soapenv="...">
  <soapenv:Header>...</soapenv:Header>
  <soapenv:Body>
    <v1:getMetadataRequest>
      <v1:studyMetadata>
        <bean:studyRef>
          <bean:identifier>identifier</bean:identifier>
        </bean:studyRef>
      </v1:studyMetadata>
    </v1:getMetadataRequest>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

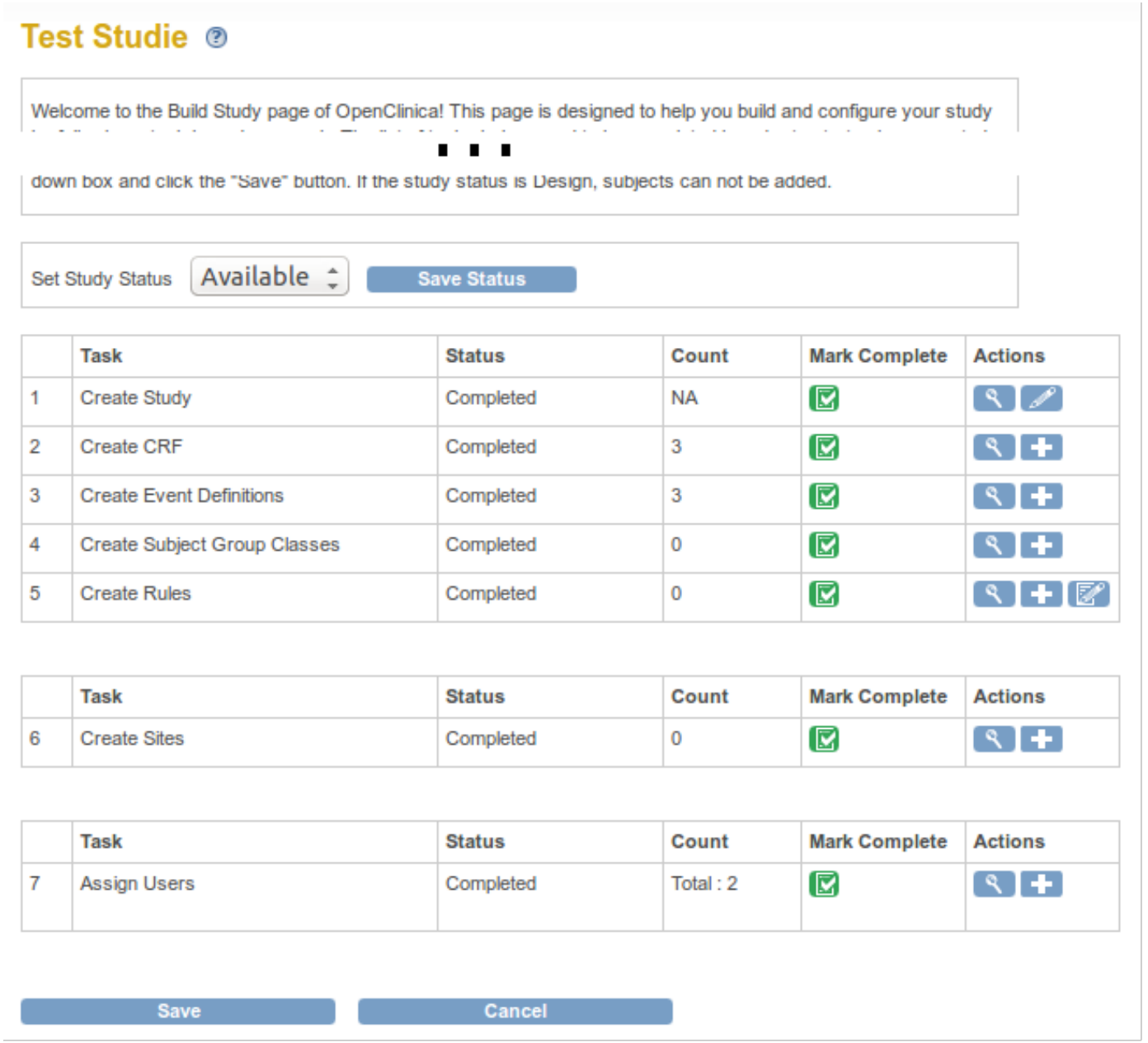
OpenClinica WS

- 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


User
EDCS
RS
add new trial
create CRFs
new EDC trial
logout
request available trials
request available trials
list of trials
list of trials
select one EDC trial
request trial metadata
trial metadata
EDC trial definition
select relevant CRF items
configure randomization method
new RS trial
add new patient
add study entry CRF
trigger randomization
get new patient data
data of new patient
randomize patient
send randomization result
write randomization result
patient with treatment

OpenClinica – Studie anlegen



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:	

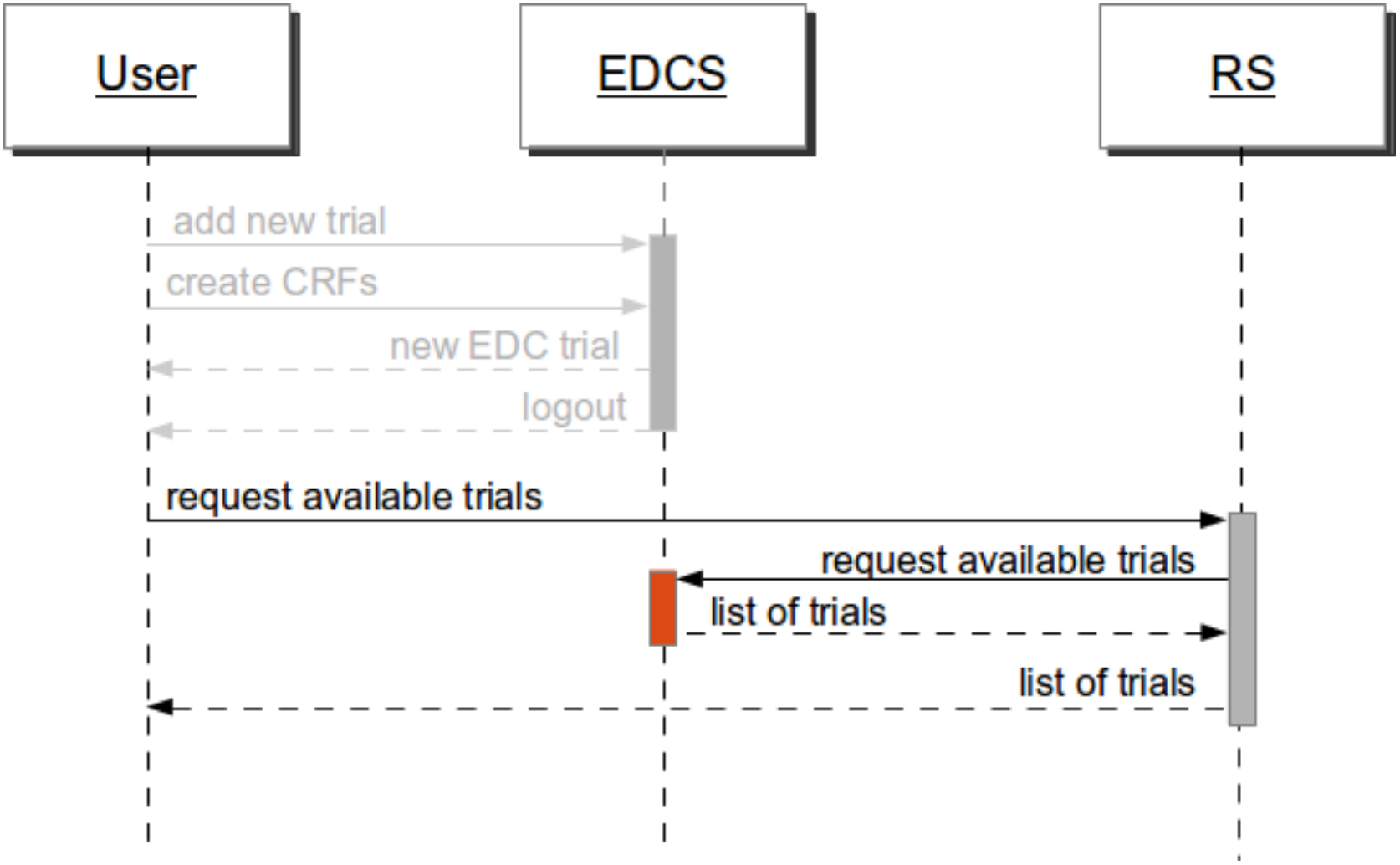
Select All Items | Save and Add More Items | Save and Define Scope | Cancel

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
☑	Geschlecht	Geschlecht des Patienten	0.1	Entry Seite 1	Ungrouped	int		single-select	male, female	No	Yes			1
☐	Alter	Alter des Patienten bei Studieneinschluss	0.1	Entry Seite 1	Ungrouped	int		text	text	No	Yes			1
☐	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


User
EDCS
RS
add new trial
create CRFs
new EDC trial
logout
request available trials
request available trials
list of trials
list of trials

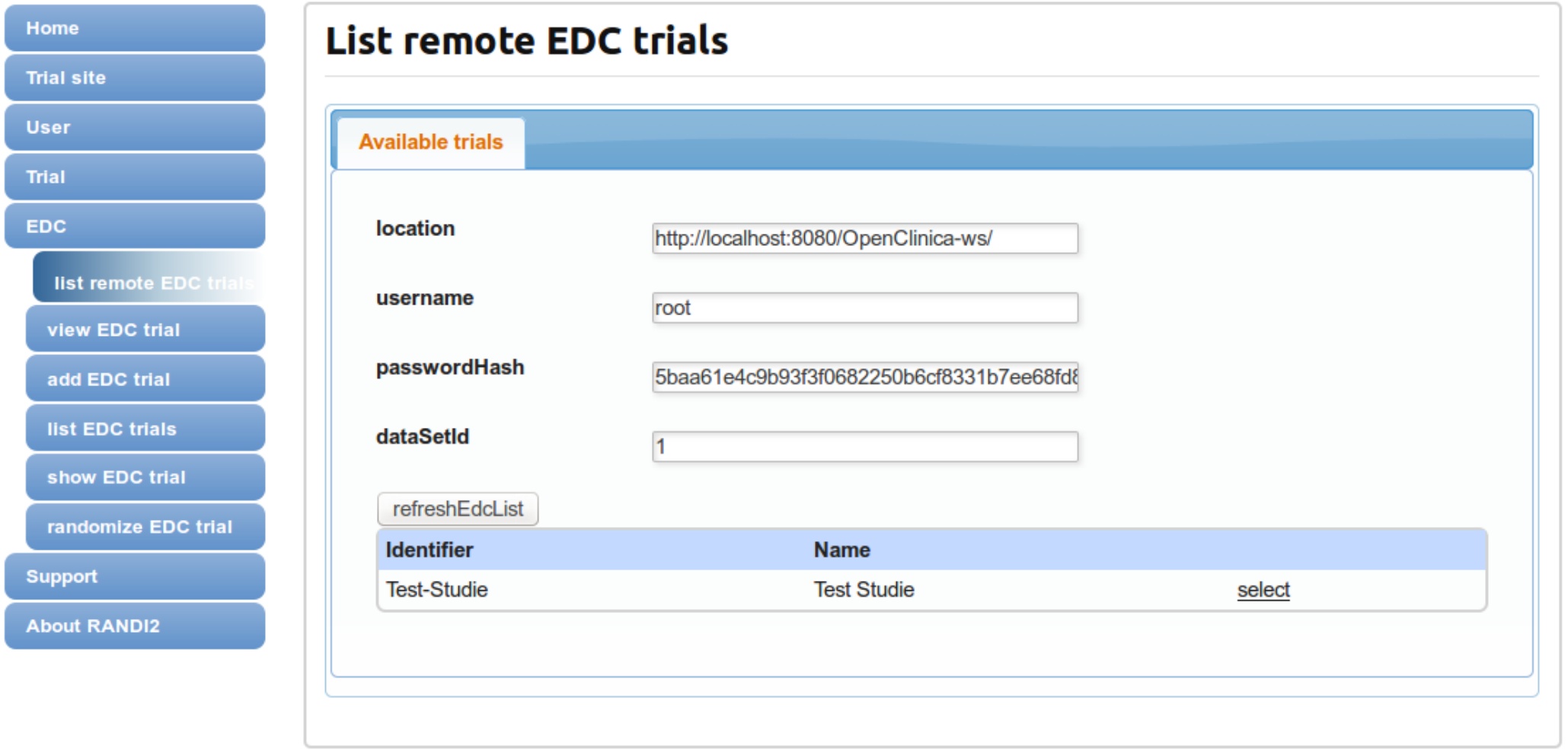
OpenClinica – Study Web Service

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

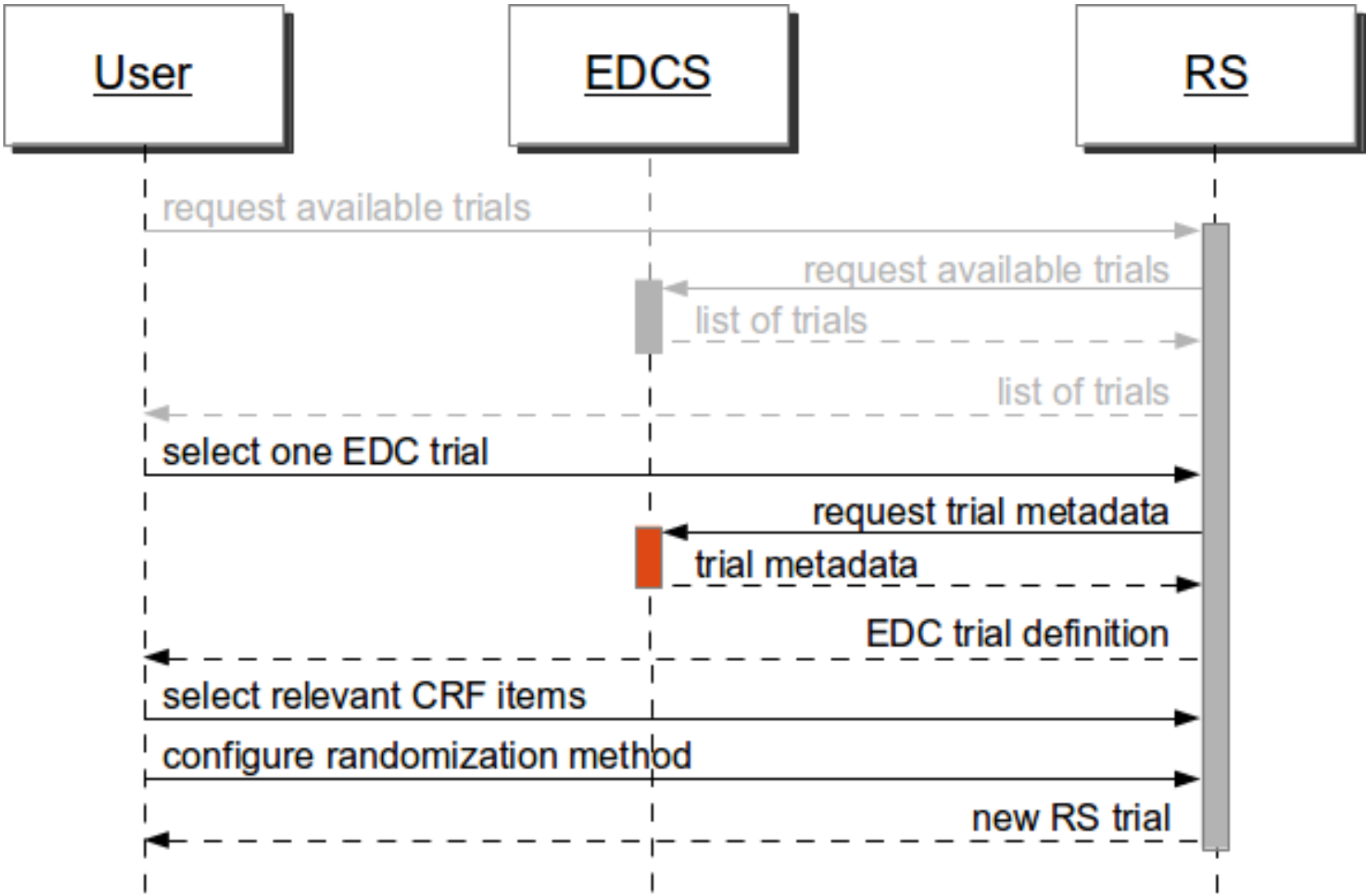
OpenClinica – Study Web Service

```
<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



Ablauf


User
EDCS
RS
request available trials
request available trials
list of trials
list of trials
select one EDC trial
request trial metadata
trial metadata
EDC trial definition
select relevant CRF items
configure randomization method
new RS trial

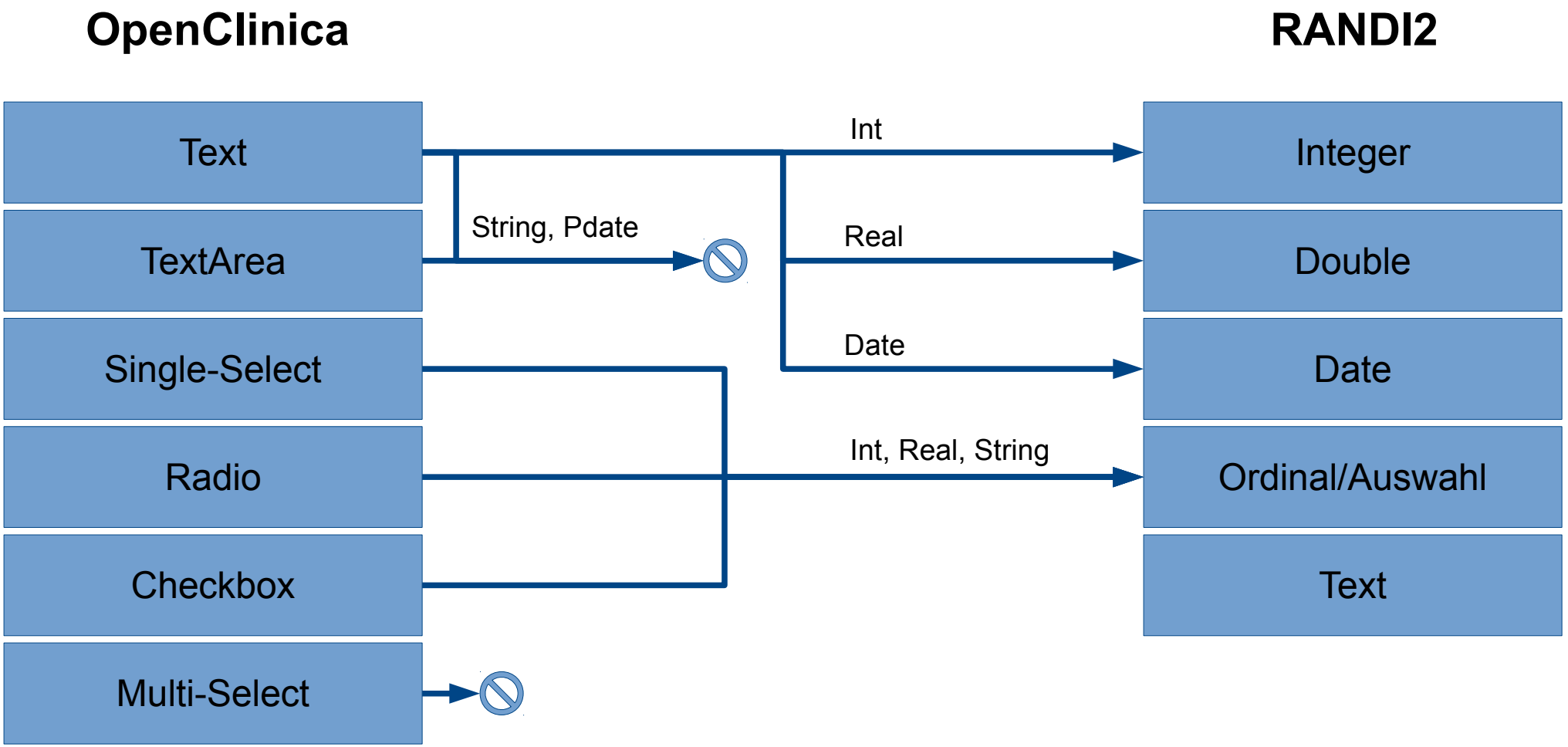
OpenClinica – Study Web Service

```
<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>
```

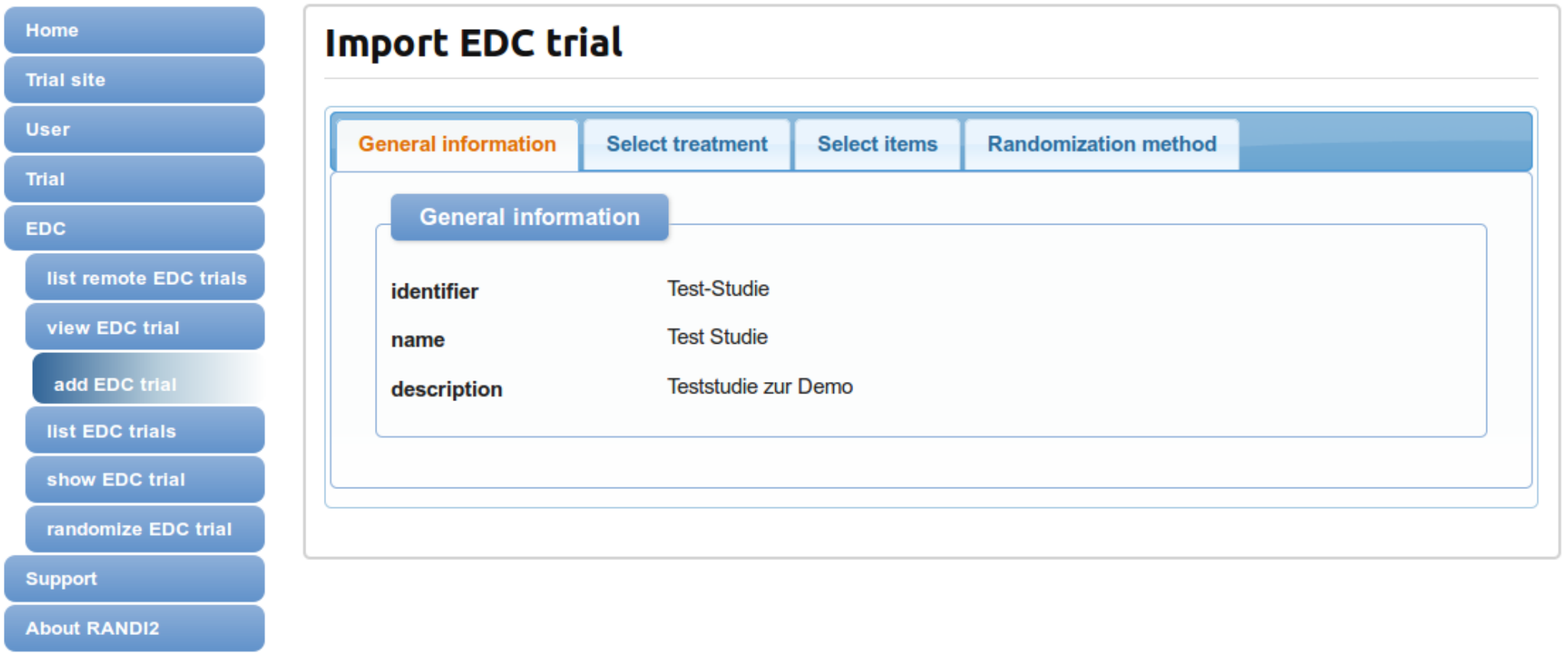
OpenClinica – Study Web Service

```
<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>
```

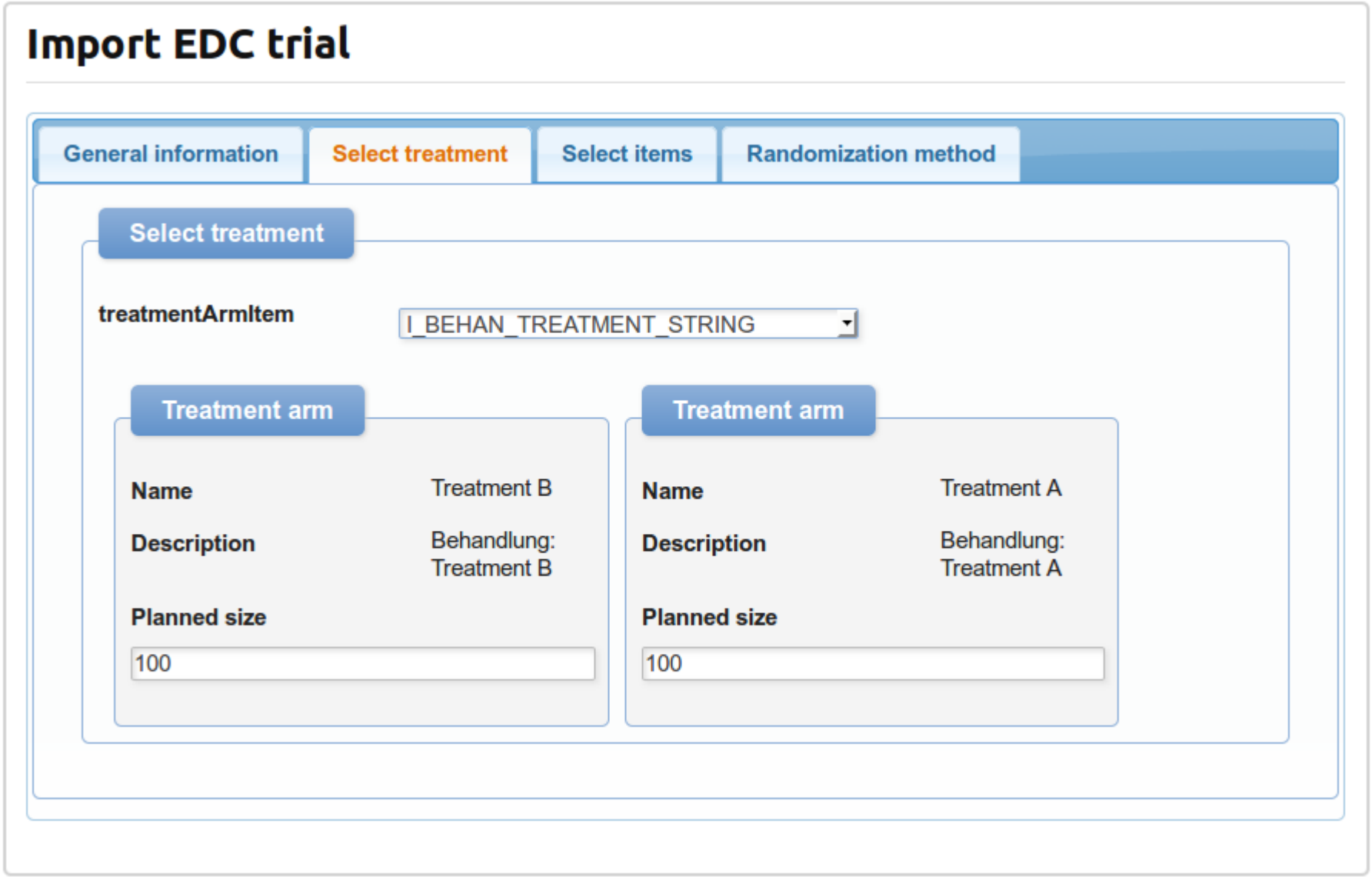
Item-Mapping



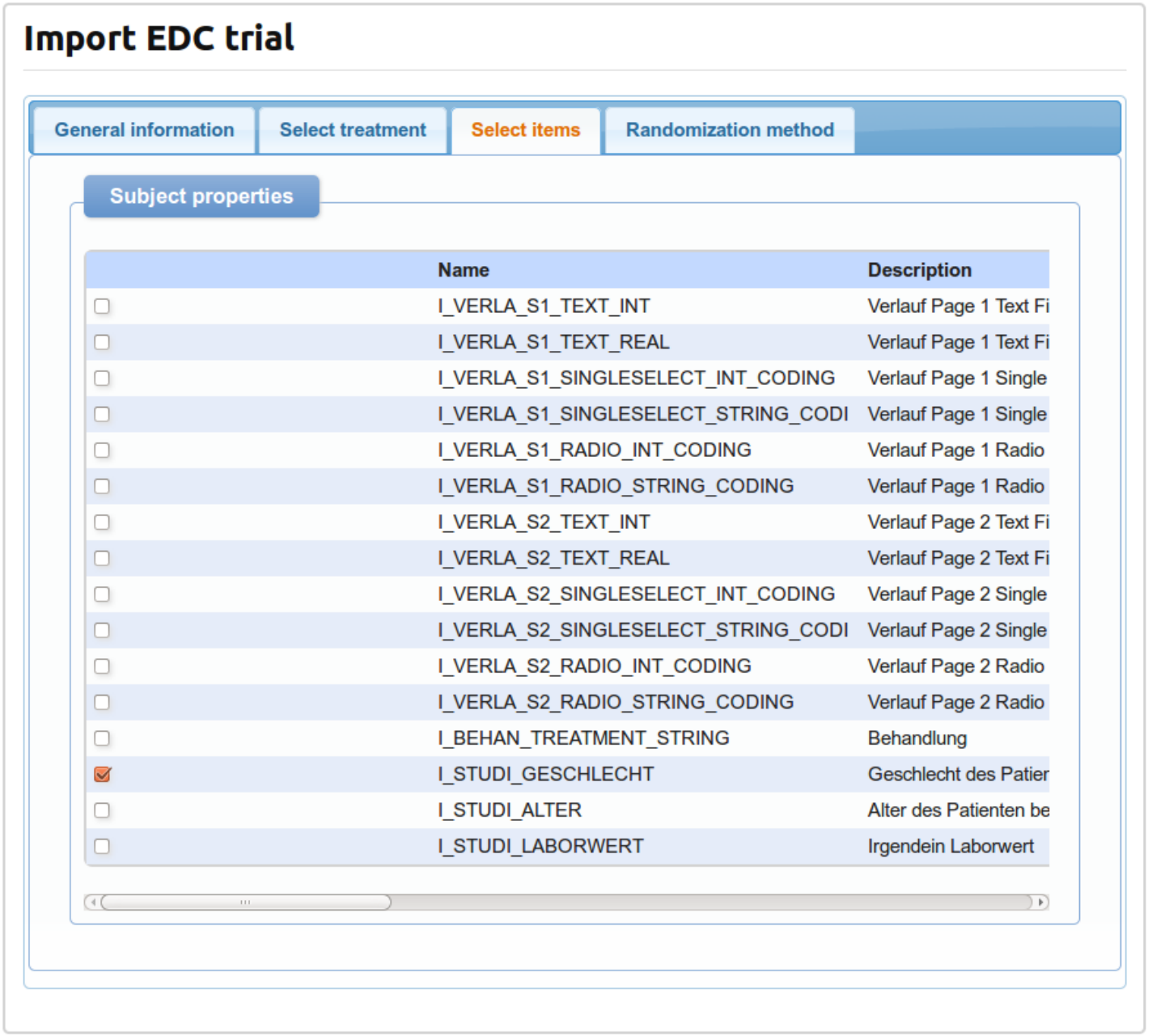
RANDI2 – Studie importieren



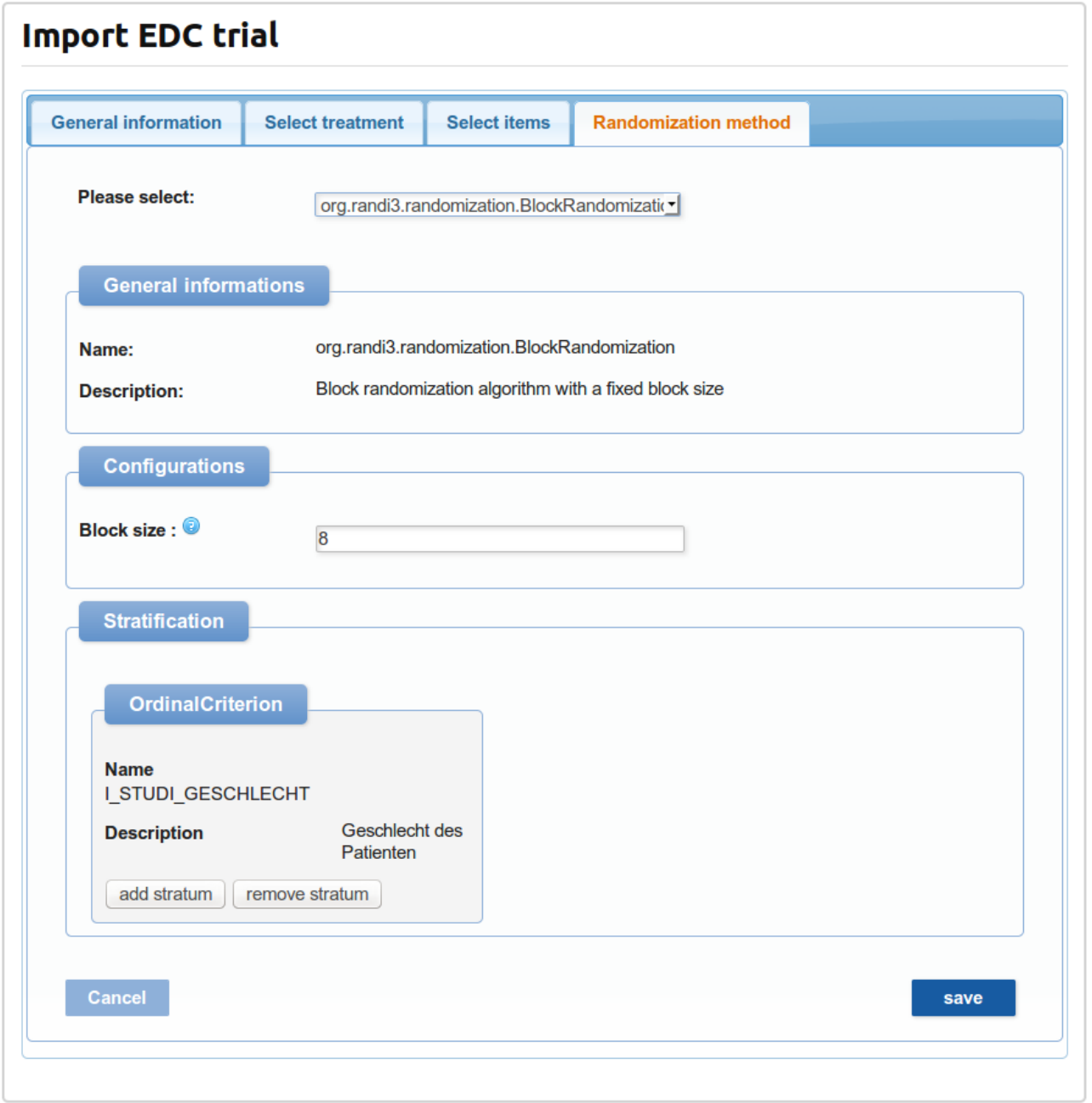
RANDI2 – Studie importieren



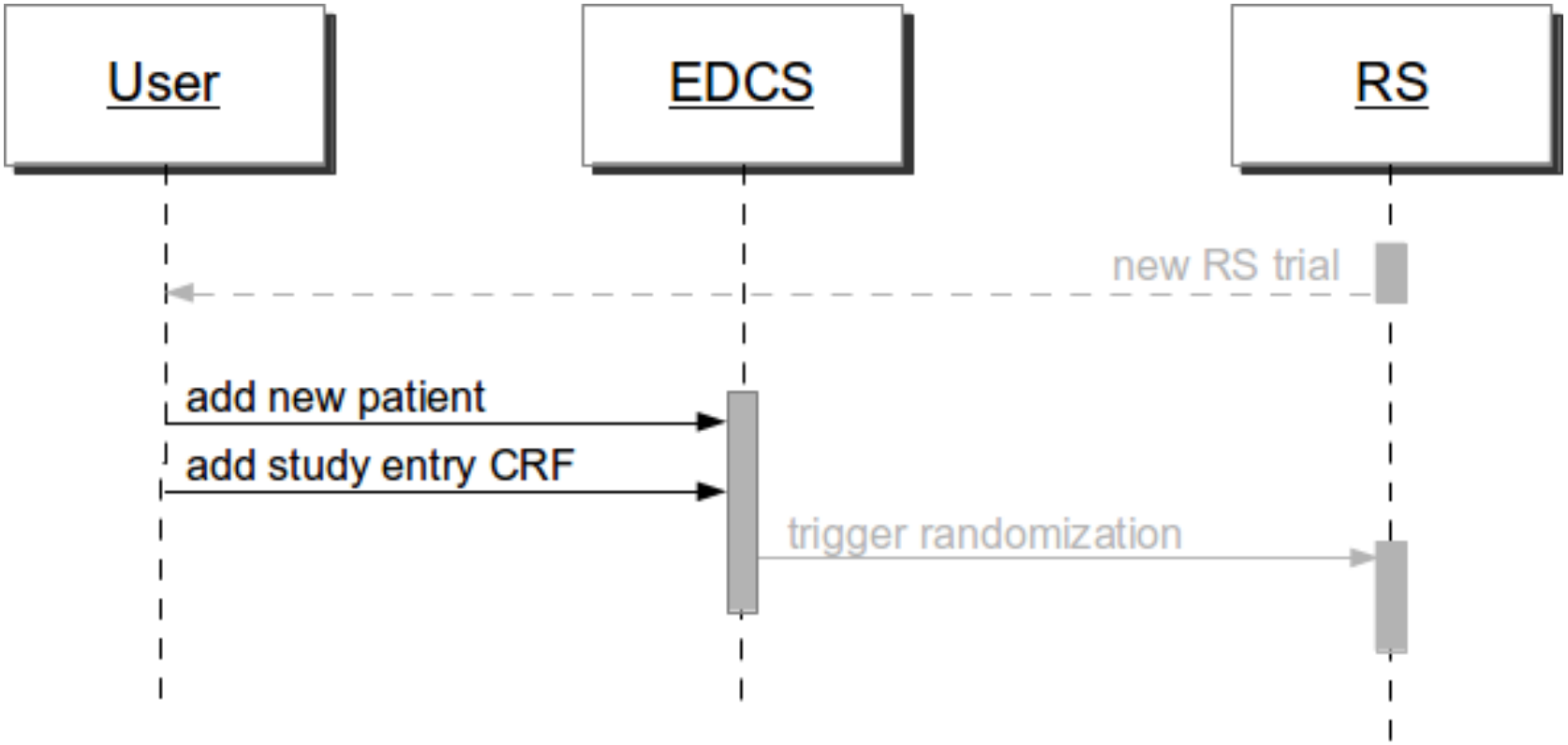
RANDI2 – Studie importieren



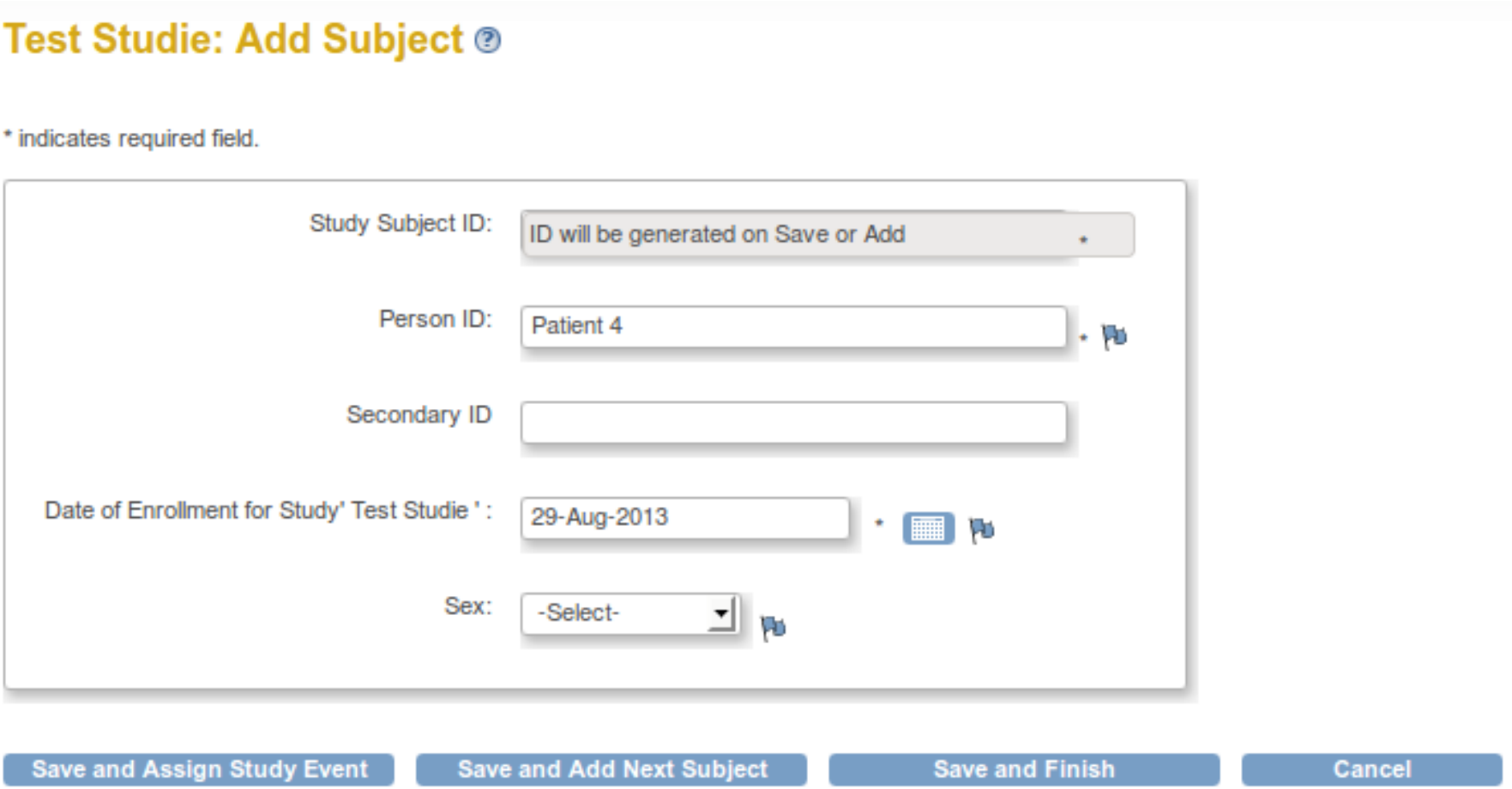
RANDI2 – Studie importieren



Ablauf

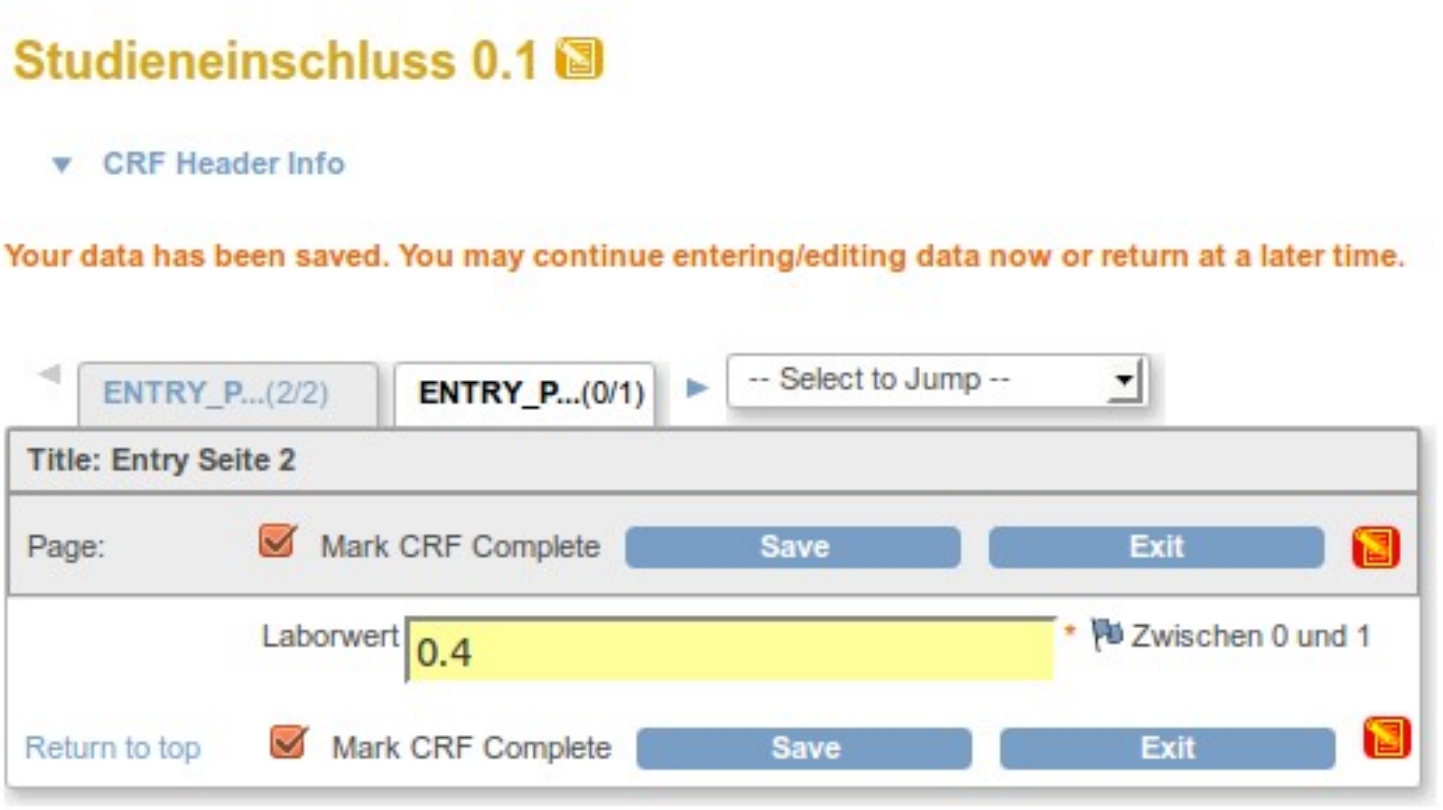

User
EDCS
RS
new RS trial
add new patient
add study entry CRF
trigger randomization

OpenClinica – Patient anlegen

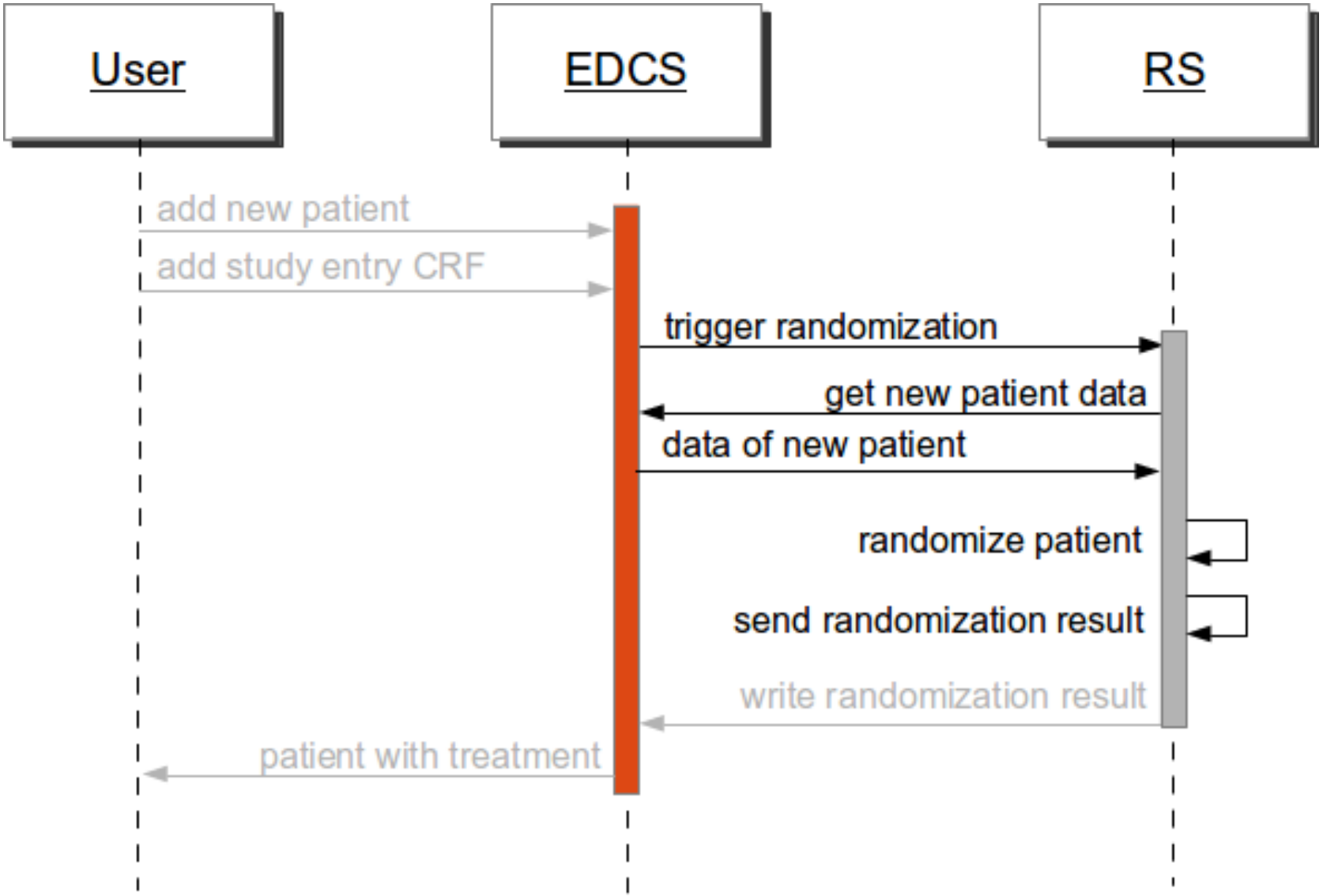


OpenClinica – Patient anlegen

OpenClinica – Patient anlegen



Ablauf


User
EDCS
RS
add new patient
add study entry CRF
trigger randomization
get new patient data
data of new patient
randomize patient
send randomization result
write randomization result
patient with treatment

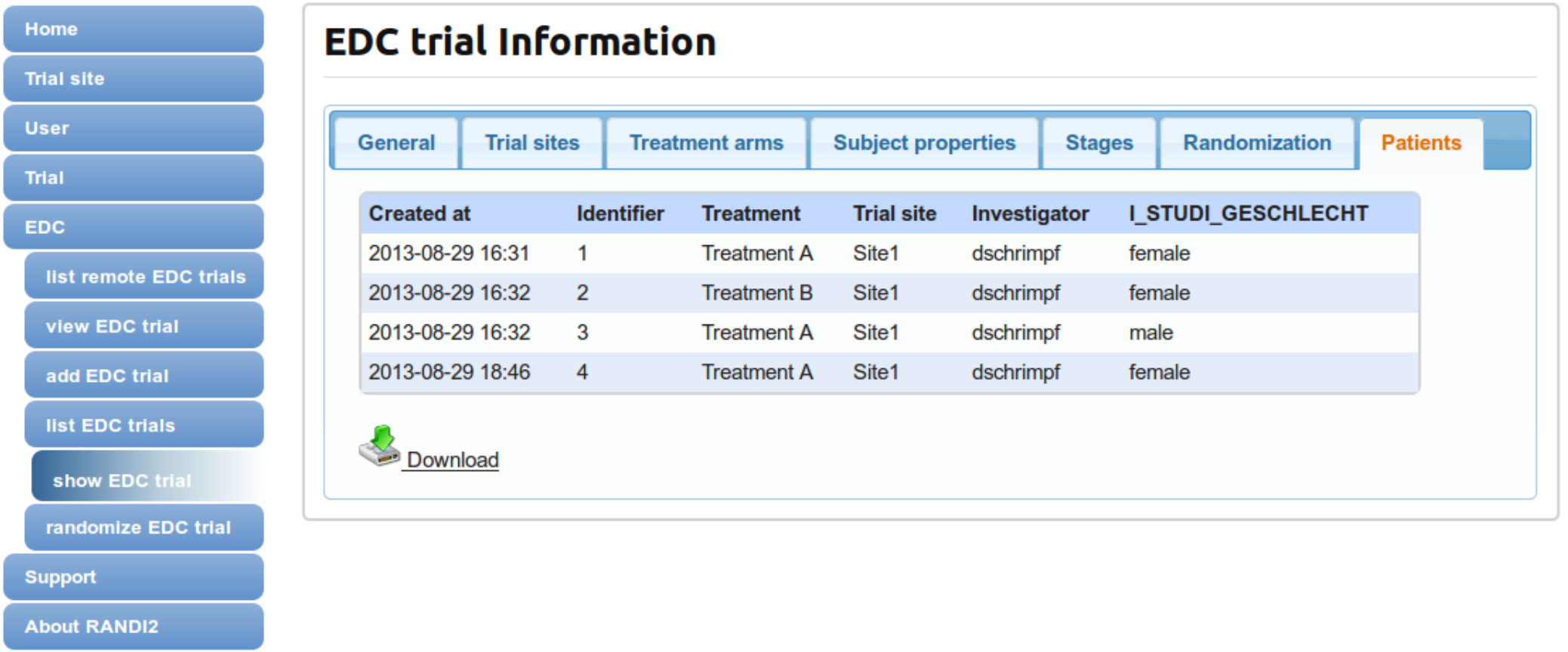
OpenClinica - Study Subject WS

```
<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>
```

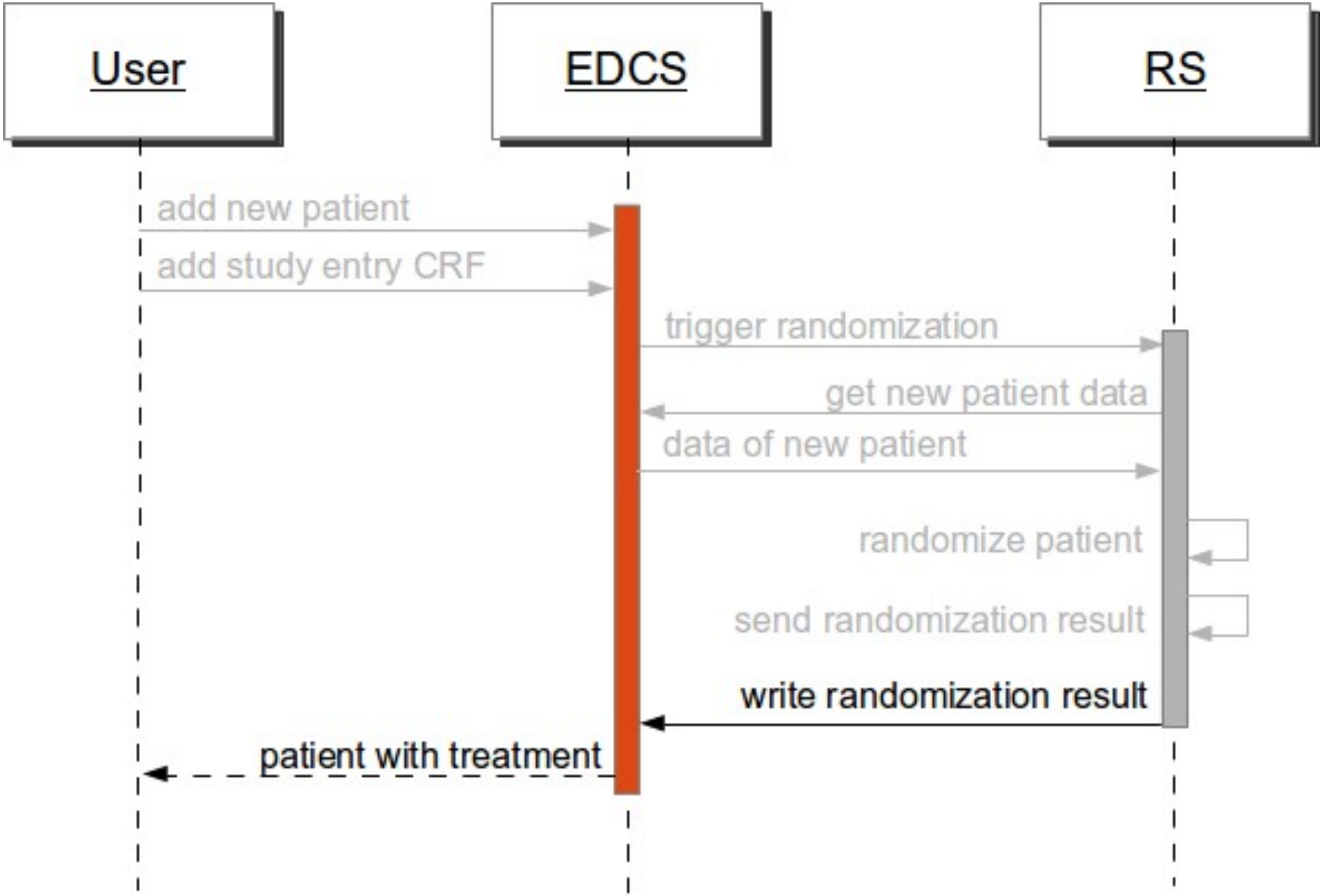
OpenClinica - Study Subject WS

```
<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">
                ...
          </SubjectData>
          <SubjectData SubjectKey="SS_2" OpenClinica:StudySubjectID="2">
              ...
          </SubjectData>
          </ClinicalData>
      </ODM>]]>
      </odm>
    </getStudySubjectResponse>
  </SOAP-ENV:Body>
</SOAP-ENV:Envelope>
```

RANDI2 – Randomisationsliste



Ablauf


User
EDCS
RS
add new patient
add study entry CRF
trigger randomization
get new patient data
data of new patient
randomize patient
send randomization result
write randomization result
patient with treatment

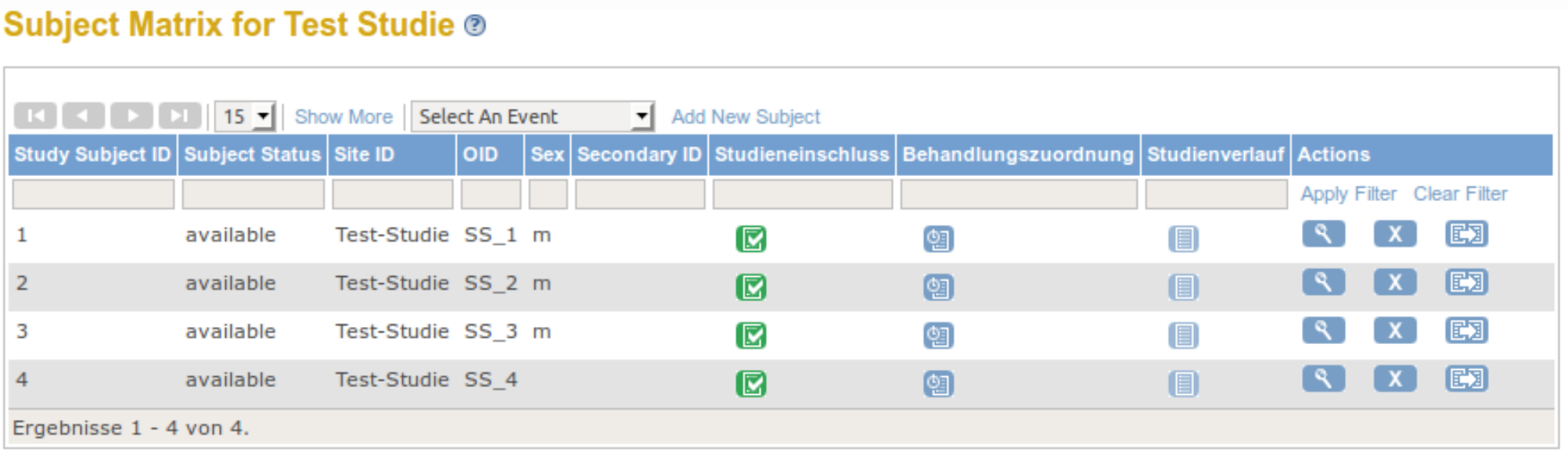
OpenClinica – Event Web Service

```
<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

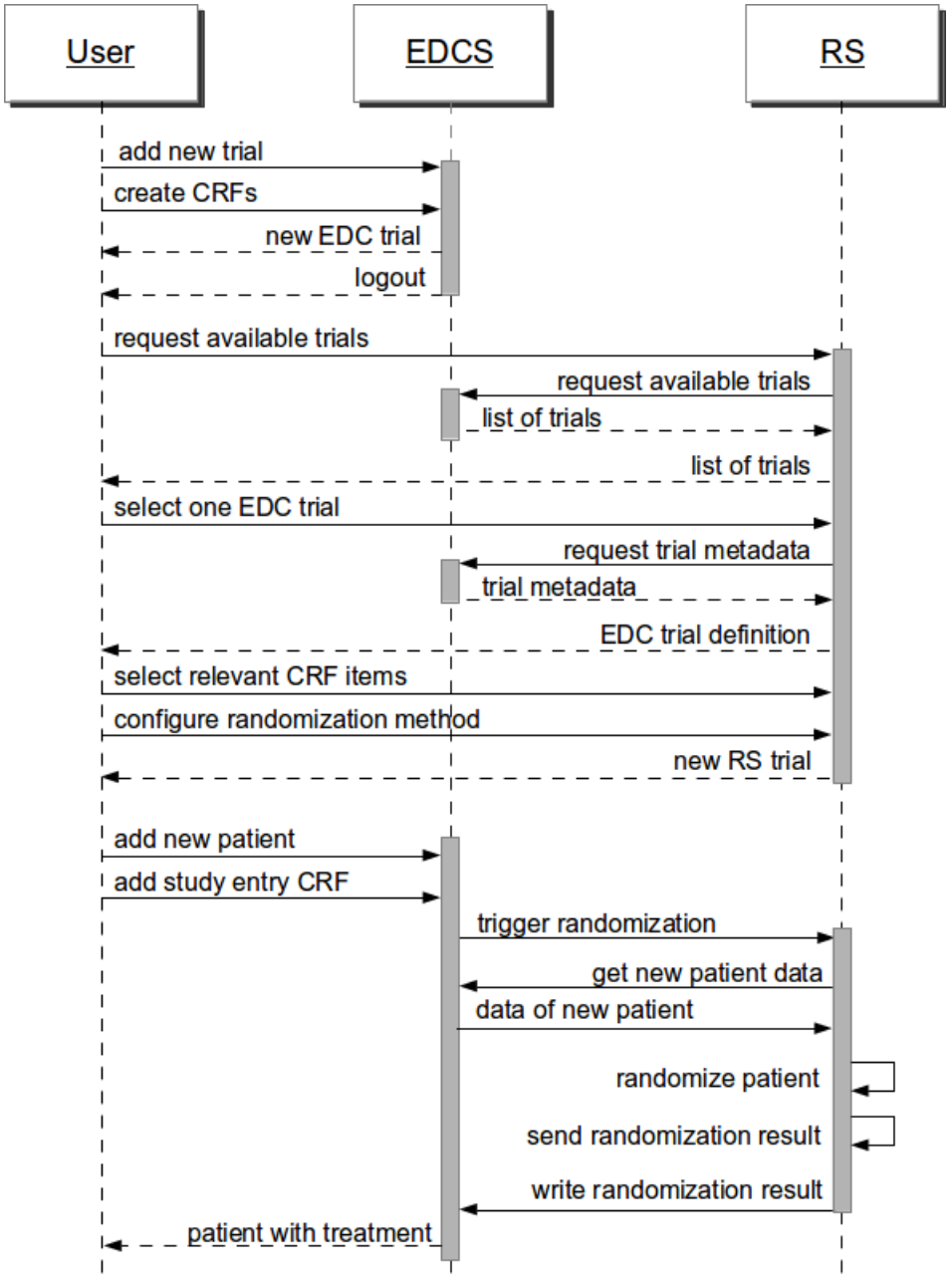
```
<soapenv:Envelope xmlns:bean="...">
  <soapenv:Header>...</soapenv:Header>
  <soapenv:Body>
    <v1:importRequest>
      <odm><![CDATA[
        <ODM ....
             ....
        </ODM>]]>
      </odm>
    </v1:importRequest>
  </soapenv:Body>
</soapenv:Envelope>
```

OpenClinica – Patientenliste



Zusammenfassung

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



Ausblick

- Auf Datenbank von OpenClinica zugreifen:
  - Anmeldedaten 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 ($i = 1, 2, ..., t$), je μ von jeder Sorte
3. Patient gehört zur $k$ten Subgruppe ($k = 1, .2, ..., s$)
   $\rightarrow$ Kugel aus $k$ter Urne mit zurücklegen gezogen
   $\rightarrow$ Patient bekommt Behandlung i
4. Bei Response:
   - Erfolg bei Therapie $i \rightarrow \beta$ Kugeln vom Typ i und α Kugeln der anderen Typen (je $\alpha/(t-1)$)
   - Misserfolg bei Therapie $i \rightarrow \alpha$ 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