TransFAIR study: a European multicentre experimental comparison of EHR2EDC technology to the usual manual method for eCRF data collection

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ABSTRACT

Purpose Regulatory authorities including the Food and Drug Administration and the European Medicines Agency are encouraging to conduct clinical trials using routinely collected data. The aim of the TransFAIR experimental comparison was to evaluate, within real-life conditions, the ability of the Electronic Health Records to Electronic Data Capture (EHR2EDC) module to accurately transfer from EHRs to EDC systems patients’ data of clinical studies in various therapeutic areas.

Methods A prospective study including six clinical trials from three different sponsors running in three hospitals across Europe has been conducted. The same data from the six studies were collected using both traditional manual data entry and the EHR2EDC module. The outcome variable was the percentage of data accurately transferred using the EHR2EDC technology. This percentage was calculated considering all collected data and the data in four domains: demographics (DM), vital signs (VS), laboratories (LB) and concomitant medications (CM).

Results Overall, 6143 data points (39.6% of the data in the scope of the TransFAIR study and 16.9% when considering all data) were accurately transferred using the platform. LB data represented 65.4% of the data transferred; VS data, 30.8%; DM data, 0.7% and CM data, 3.1%.

Conclusions The objective of accurately transferring at least 15% of the manually entered trial datapoints using the EHR2EDC module was achieved. Collaboration and codeign by hospitals, industry, technology company, supported by the Institute of Innovation through Health Data was a success factor in accomplishing these results. Further work should focus on the harmonisation of data standards and improved interoperability to extend the scope of transferable EHR data.

INTRODUCTION

Clinical trials complexity increased over the last decade, leading to a growing amount of data to be collected. Meantime hospitals transitioned from paper records to electronic health records (EHRs), making it possible for reuse in clinical research. Previous studies reported that 13%–75% of the trial data points are redundantly captured in EHR and the electronic data capture (EDC) system and might sometimes be present in a third paper copy. This results in time-consuming redundant data entry, data cleaning and source data verification, leading to an increase burden and costs.

For almost a decade, in addition to regulators, industry forums are recommending the broad implementation of EHRs as eSource in clinical trials. A recent literature review identified attempts to use EHR data as an eSource through direct electronic transfer into EDC systems. Most of the EHR-EDC integration initiatives are usually...
one-time-only, not scalable solutions limited to a single site, single vendor, single pharmaceutical company context, not using standards for data representation.16–18

Several obstacles require to be addressed to enable use of EHR data as source data in multicentric clinical trials. The main obstacles are the lack of integrated workflow between care and clinical research conducted in silos and of intersystem interoperability. Other barriers include resistance to change, and poor quality of EHR data that could influence assessment of outcomes. To improve the transparency and completeness of publications of the results of clinical trials conducted using cohorts or routinely collected data, a reporting guideline, the CONSORT-ROUTINE (extension for the reporting of randomised controlled trials conducted using cohorts and routinely collected data), has been recently developed, including a checklist to facilitate the compliance.19

A widely acceptable and cost-effective approach to interoperability between EHRs and clinical research systems operating under different legal frameworks across Europe1 20 21 was developed by the Innovative Medicines Initiative EHRs for Clinical Research (EHR4CR) project conducted between 2011 and 2016.

The EHR2EDC project, which is a continuation of EHR4CR, is a public–private partnership, funded by the European Institute of Innovation and Technology (EIT) Health involved in improving European healthcare systems. This initiative was led by Sanofi and included three other pharmaceutical companies (AstraZeneca, Janssen, UCB Pharma), a clinical research organisation (ICON), a health data technology company (InSite network platform, Custodix a TriNetX company), four European hospital organisations (Assistance Publique-Hôpitaux de Paris (AP-HP) in Paris, France; Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) in Meldola, Italy; Medizinische Hochschule Hannover (MHH) in Hannover, Germany and Hospital Universitario 12 de Octubre, (12 de Octubre) in Spain) and the European Institute for Innovation through Health Data (a non-for-profit organisation). The aim of this project was to design, develop and evaluate a technology enabling use of EHRs as eSource in clinical trials.22

The objective of the EHR2EDC consortia was to prove that at least 15% of data entered in the EDC can be semiautomatically transferred from its source EHRs. To evaluate this the TransFAIR study was designed, within relevant context of use, by including six different clinical studies across three research sites in Europe. The primary endpoint was the ability to achieve 15% of correct and accurate data transfer from EHRs to study EDC. This percentage was agreed as a consensus, and based on published work on this subject, such as the RE-USE project.1

METHODS

Study design

The TransFAIR study consisted in the experimental comparison of two data collection methods: the EHR2EDC module implementing a semiautomatic transfer of EHR data to an EDC system versus the usual manual data collection (protocol available in online supplemental material). We included real ongoing clinical trials (support CT). Selected trials were conducted according to their protocol and were not affected by the TransFAIR study. FAIR refers to the FAIR principles: Findability, Accessibility, Interoperability and Reuse of data assets guided the design of the EHR2EDC module.23

Data were shared between partners according to the European Union General Data Protection Regulation. The interoperability implementation and data flow were performed within a solution compliant with data privacy and good clinical practice regulations.

Figure 1  General organisation of the TransFAIR study. AP-HP, Assistance Publique-Hôpitaux de Paris; EHR2EDC, Electronic Health Records to Electronic Data Capture; PI, principal investigator ; eCRF, electronic Case Report Form.
EHR2EDC data in scope, module setup, study and patient selection

The data domains of interest were selected based on the frequency of data types collected in a large pool of studies (N=120) and present across multiple therapeutic areas. The results were reviewed by members of the project experts in clinical data standards with extensive experience in designing study eCRFs, including experts from the clinical research organisation (CRO) ICON, for their experience across sponsors and therapeutic areas. The four data domains selected are: demographics (DM), vital signs (VS), laboratory (LB) and concomitant medication (CM), from where a core set of 48 Clinical Data Interchange Standards Consortium (CDISC) data elements was identified and the 20 associated CDISC code lists were mapped to selected terminologies (International Classification of Diseases, 10th Revision (ICD-10), Logical Observation Identifiers Names and Codes (LOINC), Anatomical Therapeutic Chemical (ATC) Classification and Systematised Nomenclature of Medicine Clinical Terms (SNOMED-CT)). CDISC standard is the destination format selected as it is used by pharmaceutical companies or CRO for their eCRF. The semantic mappings developed for this project is accessible at the following site:

It covers four CDISC domains: DM, LB analysis, VS and CM. LOINC is the main reference terminology used on hospital side, however, it has sometimes been necessary to use other terminologies.

Four Fast Healthcare Interoperability Resources (FHIR) profiles associated with a list of standardised value sets were defined to support data extraction specification and guide mappings done by hospitals terminology experts.

The EHR2EDC module, from the InSite platform has been installed successfully in: AP-HP, 12 de Octubre, IRST and MHH.

Six studies from three different Sponsors (AstraZeneca, Janssen and Sanofi) were selected by the consortium according to the following criteria: support CT had to be conducted in a hospital partner with principal investigators agreeing to support the TransFAIR study, it had to include patients during the evaluation period (July to December 2019) and preferably collecting a large number of LB data.

The selected studies were conducted in three hospitals: AP-HP, 12 de Octubre and IRST. MHH only started to map on SNOMED-CT, with weekly data refresh from the clinical live systems, hence was not included.

Data collection and management

For each clinical trial selected for the TransFAIR study, a mirrored EDC database, replicating the study specific EDC database, was set up and connected to the EHR2EDC module of the InSite platform installed at each site. The mirror EDC database represents the ‘experimental’ database while the original database was used as a ‘control’ (figure 1). The data collected in each EDC system of participating clinical trials were captured in the study eCRF (Medidata Classic Rave V.2020.2.0) using traditional manual data entry by a study coordinator or an investigator. In the mirrored database, the same data were collected through the InSite platform (figure 2). Once connected to the InSite platform data, the study coordinator/investigator selects a clinical trial, a subject and a visit (as defined in the protocol). Then he/she must associate the visit to the actual date of the patient’s visit. The
platform provides an interface, with fields prefilled with EHR data (required by study protocol) at the selected date. The study coordinator/investigator can, therefore, review and validate data before their transfer to the mirror EDC.

Several patients were included, and visits completed before the TransFAIR study started. Data were transferred, retrospectively for completed visits and for new visits. Investigators supervised the automated data collection by reviewing, validating and transferring data to the experimental database. Experimental and control databases were then reconciled by the sponsor to identify discrepancies. An absence of difference between data points collected in both databases was classified as OK, while a difference was classified as NOK. Each discrepancy was investigated by the investigator by checking source documents to verify the actual value of the data point for which a discrepancy was identified and to document the reason.

### Study endpoints
The primary endpoints are the percentage of data points accurately processed.

- **Per individual study.**
- **Pooled across studies.**
- **Per data domain pooled across studies.**

### Statistical analysis
Since the TransFAIR was a proof-of-concept study, neither a sample size calculation nor a power consideration was performed. The only hypothesis to be tested was that at least 15% of the datapoints could be semiautomatically and accurately transferred by the EHR2EDC module. Results were analysed individually, for each study and pooled together to be presented across studies.

The percentage of data accurately transferred was calculated as the number of data correctly transferred in the experimental database divided by the total number of data manually entered into the control database.

The hypothesis of transferring at least 15% of the data was tested using a one-sided exact binomial test. An estimate of proportions with their 95% CI was provided. The exact calculation method was used if the approximation of the Normal law was not possible. Subgroup analyses were planned on the following variables: study site and data domain (DM, VS, LB and CM).

The statistical significance level was set at p<0.05 (two sided). The global statistical analysis was carried out with the R software (release V.3.6.3; R Foundation for Statistical Computing, Vienna, Austria), by the Clinical Trial Unit of each site and by ICON.

### RESULTS

#### Presentation of the studies and patient data
The EHR2EDC transfer module of the InSite platform was active from 20 September 2019 to 30 November 2019. The analysis included the data points of five of the six selected studies: AZ D169CC, PCR3001 and TED14856 at 12 de Octubre in Madrid, BCL30003 and D19BC at IRST. The data from the EFC14875 study at AP-HP were excluded from the overall analysis. Most data collected for that study, at that site, were captured using paper as a source.

The data from the five studies databases were pooled and represented a total of 41,424 data points. The subset of data in the scope of the study (ie, DM, VS, LB and CM) represented 19,240 data points, 46.4% of total data collected (figure 3).

#### Primary endpoint: percentage of data accurately transferred (all data)

- **Per individual studies**
  - Studies TED14856 and AZ D19BC had reached higher results than set objective of 15%. They achieved, respectively, 26.5% (one-sided 95% CI 24.0%) and 22.8% (one-sided 95% CI 22.2%) (table 1).
Other studies achieved less than 10.0% of correctly processed data.

- Across studies

The EHR2EDC module was able to transfer accurately 16.9% of data points across studies, (one-sided 95% CI 16.6%) and represents 6143 data points.

Secondary endpoints (data in scope)

- Results per individual study varies between 26.6% and 60.3% (table 1).

The AZ D19BC trials and TED14856 trial both had a majority of VS and LB data (table 2).

- Results pooled across studies: The EHR2EDC module was able to process accurately 39.6% (<0.0001) of data points in scope (N=6143 data points) (table 3).

- Results per data domain pooled across studies: Within each data domain in scope, the percentage of data correctly processed varies. The highest results are observed for VS (40.9%), LB (40.6%) and for DM (34.2%). Data from CM have the lowest percentage: 7.7% (table 4).

DISCUSSION

The concept of mirror study has proven to be an effective method for validation of a novel technology to support data collection, in a relevant context of use: different EHRs, investigation sites, sponsors and studies.

The primary objective of the study was successfully met, with over 15% (16.9%) of the data points entered in the e-CRF correctly processed from EHR source records.

The four domains DM, VS, LB and CM selected by the consortium represent 46.4% of the data collected through the five trials in scope, this results validates the consortium choice.

A per study analysis demonstrates the major contribution of the local LB data followed to a lesser degree by the VS data to achieve an acceptable proportion of transferable data. This suggests that studies in oncology (ex: TED14856 and the AZ D19BC), with high volume of local LB data are best candidates for the early use of this digital data collection technology in the near future.24

The two domains LB and VS covers around 40% of the data in scope and represent more than 96% of accurately transferred data. This reflects the availability and good quality of these data at the hospitals EHRs.

The interoperability challenge has been successfully addressed through the implementation within the EHR2EDC module of a core list of data elements and its associated library of terminology mappings. The

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Percentage of accurately transferred data, overall and by study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital and study</td>
<td>No of data accurately transferred (n)</td>
</tr>
<tr>
<td>12 de Octubre</td>
<td>495</td>
</tr>
<tr>
<td>AZ D169CC (AstraZeneca, NCT03619213)</td>
<td>143</td>
</tr>
<tr>
<td>PCR3001 (Janssen, NCT02257736)</td>
<td>35</td>
</tr>
<tr>
<td>TED14856 (Sanofi, NCT03284957)</td>
<td>317</td>
</tr>
<tr>
<td>IRST</td>
<td>5648</td>
</tr>
<tr>
<td>BCL30003 (Janssen, NCT03390504)</td>
<td>400</td>
</tr>
<tr>
<td>AZ D19BC (AstraZeneca, NCT02516241)</td>
<td>5248</td>
</tr>
<tr>
<td>Total</td>
<td>6143</td>
</tr>
</tbody>
</table>

IRST, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Data transferred per domain and per study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitals and studies</td>
<td>Patients (N)</td>
</tr>
<tr>
<td>12 de Octubre</td>
<td>13</td>
</tr>
<tr>
<td>AZ D169CC (AstraZeneca, NCT03619213)</td>
<td>8</td>
</tr>
<tr>
<td>PCR3001 (Janssen, NCT02257736)</td>
<td>4</td>
</tr>
<tr>
<td>TED14856 (Sanofi, NCT03284957)</td>
<td>1</td>
</tr>
<tr>
<td>IRST</td>
<td>19</td>
</tr>
<tr>
<td>BCL30003 (Janssen, NCT03390504)</td>
<td>2</td>
</tr>
<tr>
<td>AZ D19BC (AstraZeneca, NCT02516241)</td>
<td>17</td>
</tr>
</tbody>
</table>

CM, concomitant medications; DM, demographics; IRST, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori; LB, laboratories; VS, vital signs.
The EHR2EDC module has been efficiently deployed in the four hospitals and the different users trained. The mapping and its implementation were designed to be reusable across studies, with limited (re)verification activities, to provide operational efficiencies, both for the sponsor and for site staff.

The limitations on the results for data in scope highlight a combination of factors affecting the ability to achieve higher performance. Among those factors, we have identified several root causes with possible remediations:

**Regulations**

For DM data (DM domain), legal limitations in collecting ethnicity in Europe produces an artefact as this information is collected during trials. When analysing only legally acceptable DM data, the result was 100%. This suggests that calculation methods and possible automatic quality controls must consider local regulations to be accurate.

**Case report form design**

The primary cause of missing data for the VS and LB domains arises for specific data points collected in study eCRFs to document the execution of the procedure. Most of the empty fields expect a ‘yes’ value for the question ‘Has the test been performed?’/‘Was the blood sample taken?’. This could be resolved by using auto populated fields (updated to a ‘yes’ value if results are present).

**Local investigator’s team practices**

Unlike IRST, other hospitals did not routinely train their staff to fill-in structured forms of the EHRs, and so the proportion of data accurately transferred was adversely affected by the proportion of data collected in EHR as free text or in paper source documents when running a clinical trial.

Special attention should be focused on staff using EHRs to collect patient data associated with a clinical study for preventing free text data entry or paper source. This includes training hospital staff in data quality standards, upgrading quality assurance measures and strengthening data governance activities, to enable EHR data to be trustworthy reused in research.

In the TransFAIR study, the low percentage of CM data correctly transferred reflects that they are more often recorded as free text, for example, in unstructured documents (eg, doctor’s letters) and a large part is prescribed outside of the investigational site and is consequently not captured in the EHR.

**Clinical site maturity/readiness**

Other factors influencing the level of performance include the site maturity in using their EHRs for clinical trials activities. Site organisational capabilities, best practices (EHR data quality assurance, use of EHRs as eSource in clinical trials, just-in-time data flow), skilled staff (data integration, data management) are essential to benefit from this new method of digital data collection.

Guided work effort is needed to augment the proportion of data recorded as eSource in EHRs to be collected using EHR2EDC solutions. Initial focus would expand transferability of structured data in EHRs, and work at rendering unstructured data to be collected. We envision this effort to be made possible through the development of consensus on ‘high-value data sets’, representing the data most commonly collected in clinical trials.

Nevertheless, not all data collected in clinical trials has its correspondence in patients’ EHRs sources. For example, specific forms in eCRFs collect data in relation with the management and evaluation of investigational medicinal products (tracking, patient’s compliance, pharmacokinetic data, etc).

### CONCLUSION

Overall, a 16.9% successful transfer rate was achieved across the five trials included in the TransFAIR study. A
transfer rate of 26.5% of data used as eSource EHRs was achieved in one of the trials.

Clinical investigational sites, CRO staff and sponsor personnel involved in the planning and the execution of trials, as well as those involved in the management of EHR, EDC and EHR2EDC technologies must join forces for success. It is recommended to promote coordination and synchronisation of all actors to align, not only on the European EHR technology standards, but also on addressing the following different dimensions: change management, and new roles, needed to achieve routine use of EHR data as eSource in clinical trials.

A roadmap to transition use EHR2EDC in clinical trials would include the following recommendations: (1) Sponsors should further develop sets of high value data, combining structured and unstructured data to help guide and prioritise the efforts needed for scalability. (2) Clinical sites should initially focus on structured data, such as LB, DM, VS and CM using common data models, for example, HL7 FHIR, increasingly implemented in clinical research, and reference terminologies for example, ICD10, LOINC, ATC, SNOMED, etc. (3) Clinical sites should develop capabilities to leverage data from unstructured format (free text, clinical documents, images), not standardised data, using natural language processing technologies and efforts to enhance both data interoperability and data quality controls. and (4) Collaborative effort at the ecosystem level should be encouraged to create the right incentives to develop and grow the market with technology providers to offer EHR2EDC services to sponsors’ organisations.

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Acknowledgements

Contributors NA contributed to the launch of the consortium and acted as the project director, contributed to the TransFAIR study protocol design, supervised the execution of the study and is guarantor. NG contributed to the data analysis. JD-P wrote the statistical analysis plan, contributed to the study submission, execution, and the data analysis at AP-HP. GC contributed to the protocol design. MT coordinated the study execution. ADGc contributed to the study submission, execution at 12 de Octubre. MTGM contributed to the study submission, execution, the data analysis at 12 de Octubre. ST contributed to the study submission, execution, the data analysis at RST. CS reviewed the protocol. MS contributed to the protocol design. AG reviewed the manuscript. TV performed the statistical analysis. MC contributed to the protocol design, coordinated the study execution, performed the statistical analysis. CD contributed to the protocol design.

Funding Funded by a grant from the EU (ET Health Activity No 18269).

Competing interests The EITHealth funds the EHR2EDC project in which the experimentations described in the article took place. EIT reimburse hospitals for the expenses related to the project. And Sanofi, Janssen and ICON provided partial financial support to hospital consortium partners to attend workshops, covering travel and meal related costs.

Patient consent for publication Consent obtained directly from patient(s)

Ethics approval A TransFAIR study protocol was submitted and received approval from each site's ethics committee (approval numbers: AP-HP: CSE-EDS no 19-16; 12deO: 19/324, IRST 5802/2019). Patients included in the selected support CTs were asked for their oral or written consent to process their data for the TransFAIR study.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available. Data are not available as sharing the data as public access was not part of the inform consent signed by patients.

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REFERENCES
PROTOCOL SUMMARY

SYNOPSIS

Protocol title: Use of Electronic Health Records as eSource; Multicenter European study, comparing manual data collection in an eCRF to data collection using EHR2EDC technology

This is a prospective European comparison of a new computer tool for data collection versus manual entry.

Short title: TransFAIR Study

Protocol Summary: This is a prospective comparison of a new computer tool for data collection versus manual entry.

For this evaluation, several Clinical Trials (CTs) sponsored by EFPIA Partners (Astra Zeneca, Janssen and Sanofi) have been identified as planned or in progress in partner hospitals of the EHR2EDC project. This includes AP-HP (France), 12 Octubre (Spain), IRST (Italy) and MHH (Germany).

These CTs will be conducted in a completely usual way, and will not be affected by the TransFAIR study. The data collected in the CSs will serve as a control. They are named "CONTROL Data".

On a top of each CT, the EHR2EDC autocomplete module will be implemented in a separate mirror study to be used as the experimental arm. It will collect the "TransFAIR Data". The data collected in this way will be compared to the CONTROL Data of its sister CT, to evaluate the new tool.

Figure 1; TransFAIR Study

The TransFAIR study is not a clinical trial, it is a technology evaluation study. The data collected in the TransFAIR study must not be used for any regulatory purpose. Only data collected in the traditional clinical trials (Control) are eligible to support regulatory obligations.
Patients included in the traditional clinical trials, will be informed that their data, collected in the context of the traditional clinical trials (Control) are expected to be collected in the TransFAIR technology study, after receiving their verbal or written consent.

**Figure 2 : Clinical Study vs. TransFAIR study Design**

For the purpose of the study, each protocol in the TransFAIR study will have a specific database setup in mirror of its Clinical Trial sister, this way nullifying the impact on the CT.

**Context**

The Center for Drug Evaluation and Research (CDER) encourages seamless exchange of structured, re-usable information between health care and clinical research systems so that data may be entered once at the point of care and used many times without manual re-entry or manual source data verification. In September 2013, FDA published the *Electronic Source Data in Clinical Investigations* guidance promoting the need for capturing source data in electronic form including data originating from health care systems. Furthermore, the FDA has released a new guidance in July 2018 - *Use of Electronic Health Record Data in Clinical Investigations*. This guidance is intended to assist sponsors, clinical investigators, contract research organizations, institutional review boards (IRBs), and other interested parties on the use of electronic health record data in FDA-regulated clinical investigations.

The value of collecting data directly from EHRs to sponsor EDCs is widely recognized, and offers tremendous promises to streamline medical research, accelerate development of new cure and deliver treatments innovations to patients sooner and cheaper. However, disparate siloed healthcare systems, coupled with complex regulatory framework makes it very difficult today to leverage the data asset in a data privacy and ethically proven way.

The EHR2EDC consortium has established as an objective to address the barriers and challenges to use patient EHRs data as an acceptable eSource and enable seamless data transfer of patient EHRs data to sponsor EDCs system for analysis and generation of evidences. Beside using data for clinical
investigations of new drugs, this will be a key infrastructure component of the health learning system approach aiming at using health data to improve provision of care to patients.

The EHR2EDC consortium has developed a generalizable module allowing semi-automatic transfer (under control of the principal investigator and delegated personnel) of patient data and provenance metadata from Electronic Health Records (EHRs) to Electronic Data Capture systems (EDCs), (i.e. eCRFs). The purpose of this study is to evaluate capability of the EHR2EDC module in real life with real patient data via several clinical protocols in different therapeutic areas, conducted at several investigational sites across Europe.

**Evaluation plan and methods**

This study deals with a technological evaluation, with the objective of semi-automatically* processing a certain number of data usually collected and transcribed manually. The unit of analysis is therefore the data element as entered in an eCRF. The data collected relates to the patients included in the study period transFAIR (or earlier) in one of the trials listed in Table 1 (List of Candidate reference Clinical trials).

The data included in this evaluation are the data for which the EHR2EDC project produced and delivered a mapping catalog to the EHR2EDC pivot model.

The data domains concerned:
- Laboratory examinations
- Demographics
- Vital signs
- Procedures,
- Diagnostic
- Prescriptions (before, during and during hospitalization)
- Present and past medical conditions
- Other (to be further defined, ex:

The control data will firstly be collected and monitored by the sponsor monitors (queries and resolution) in the eCRFs of the reference studies (Control Data). After collection in clinical trial eCRFs. The same data will be collected in the TransFAIR study using the EHR2EDC device.

This evaluation will demonstrate the added value of such technology in clinical trials for hospital site staff in terms of the reduction of time and effort for data collection and entry, and an increase of the data quality of the EDC.

*The term “semi-automatic” is equivalent to “automatically transferred under control of Principal Investigator and delegated personnel”.*
## Objectives and end points

<table>
<thead>
<tr>
<th>Objectives</th>
<th>Endpoints</th>
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</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td>To demonstrate at least 15% of the data usually manually entered into the eCRF can be semi-automatically and accurately transferred into the EDC using EHR2EDC module.</td>
</tr>
<tr>
<td>To assess the percentage of data that can be processed by EHR2EDC</td>
<td><strong>Secondary</strong></td>
</tr>
<tr>
<td>To compare EHR2EDC data collection steps and activities versus the manual data entry process at site level</td>
<td>Measure</td>
</tr>
<tr>
<td>To compare EHR2EDC data collection workload versus the manual entry process at the site level</td>
<td>For each actor the steps and activities will be described and documented for each separate process, to compare the number of steps needed for each process.</td>
</tr>
<tr>
<td>To compare data management activities with or without the EHR2EDC solution the sponsor level</td>
<td>For each actor the workload will be documented through surveys (system/self-reporting) to assess time, effort and usability of each process.</td>
</tr>
<tr>
<td>To compare the data accuracy of the EHR2EDC databases versus CTs databases.</td>
<td>For each study the number of queries (data related enquiries) generated will be compared for each process (feasibility to be confirmed).</td>
</tr>
<tr>
<td><strong>Exploratory</strong></td>
<td>Errorneous data in the two database with the same dataset.</td>
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<tr>
<td>To assess the generalizability of the EHR2EDC module</td>
<td>Description and characterization of:</td>
</tr>
<tr>
<td>To qualify the data quality of each database by comparing the data queries of both databases</td>
<td>- sponsor and site workload between studies from different sponsor</td>
</tr>
<tr>
<td></td>
<td>- data correctly transferred (percentage of the total data transferred and classification of data by domain)</td>
</tr>
<tr>
<td></td>
<td>Characterization, classification and quantification, of the data manager queries and compare the data queries of both databases</td>
</tr>
</tbody>
</table>
Two periods must to be distinguished:

- Retrospective period: will focus on a transfer of data already collected during the RCTs to be semi-automatically transferred into the mirror database.
- Prospective period: data will be collected at least once a week by the PI or delegated personnel.

**TransFAIR study Dates**

- TransFAIR Study Start Date (Planned): 15 July 2019
- TransFAIR Study End Date (Planned): 30 Nov 2019
- Data Base Completed: 07 Dec 2019
- Analysis Completed: 15 Jan 2020
- Report Completed: 30 Jan 2020

**Candidate List of Studies**

The list below, is the studies that meet the eligibility criteria:

- Must be conducted at least one of the EHR2EDC partner hospitals. Preference will be given to studies planned at least two of the partner hospitals.
- Must have more than 4 patient’s visits in the first six months.
- Should collect local laboratory data, demographics, vital signs
Table 1: List of Candidate reference Clinical Trials

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Study No</th>
<th>Phase</th>
<th>Indication</th>
<th>Status (ongoing/planned)</th>
<th>Local lab (high/medium/low)</th>
<th>Vital signs (high/medium/low)</th>
<th>Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>AstraZeneca</td>
<td>AZ D19BC</td>
<td>3</td>
<td>Cancer</td>
<td>Ongoing</td>
<td>medium</td>
<td>high</td>
<td>IRST, Meldola, Italy</td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>AZ D169CC</td>
<td>3b</td>
<td>Cardio</td>
<td>Ongoing</td>
<td></td>
<td></td>
<td>Hospital 12 de Octubre, Madrid, Spain</td>
</tr>
<tr>
<td>Janssen</td>
<td>BLC3003</td>
<td>3</td>
<td>Cancer</td>
<td>ongoing</td>
<td>low</td>
<td>low</td>
<td>IRST, Meldola, Italy</td>
</tr>
<tr>
<td>Janssen</td>
<td>PCR3011</td>
<td>3</td>
<td>Cancer</td>
<td>preparation/planned</td>
<td>low</td>
<td>low</td>
<td>Hospital 12 de Octubre, Madrid, Spain</td>
</tr>
<tr>
<td>Sanofi</td>
<td>TED14856</td>
<td>1b</td>
<td>Cancer</td>
<td>ongoing</td>
<td>high</td>
<td>low</td>
<td>Hospital 12 de Octubre, Madrid, Spain</td>
</tr>
<tr>
<td>Sanofi</td>
<td>EFC15156</td>
<td>3a</td>
<td>Diabetes/cardio</td>
<td>ongoing</td>
<td>high</td>
<td>low</td>
<td>AP-HP - Bichat, Paris, France</td>
</tr>
</tbody>
</table>
Method of evaluation

The analysis will compare the same set of data collected in the Clinical Trial (Control DATA) and entered manually in the sponsor eCRF with the same data collected in the TransFAIR study (TransFAIR DATA) using the EHR2EDC module for each pair of studies. The count of data collected by both methods will be compared to determine the percentage of correct data, achieved by the EHR2EDC transfer.

Each of the data correctly transferred by EHR2EDC, will be qualified by an OK or NOK
- OK: data correctly transferred, which is identical to that collected manually
- NOK: data exposed by the EHR2EDC module, and not validated by the coordinator site

For each study a results file will be produced which will include the following data (not finalized)
- Study
- Site
- Patient participation number
- Visit
- Form
- Fields
- Field value / data point TransFAIR
- Value of the field CONTROL (initial, monito) only if data collected automatically?
- Queries CONTROL possible (I think it will be necessary to define a game of querie relevant to compare because quite a lot of it will not make sense)

Statistical Analysis

Three levels of analysis will be carried out. A multi-protocol analysis will be conducted, combining the different data files, at each hospital level, then across hospitals.

First level: for a pair of study, comparing the control DATA to the TransFAIR DATA.

Second level: at hospital level, the results of the pair study comparison will pooled for all protocols for a given hospital.

Third level: at the project level, the results of hospital level analysis will be pooled across hospitals.

Analysis Plan - General aspects

- Descriptive statistics will be based on means (+/- standard deviation) or medians [minimum-maximum] depending on the distribution of quantitative variables. The qualitative variables will be described in terms of size and percentage.
- Univariate comparisons will use the usual statistical tests after verification of the distribution of the variables (Chi2 or Fisher’s test, t test, anova or their non-parametric equivalents Wilcoxon and Kruskal-Wallis tests).
- The tests and descriptive analyzes will be carried out with a degree of significance of 5%, using the statistical software R and SAS. 95% confidence intervals will be provided for each estimate.
Primary judgment criterion
- An estimate of the proportion with its 95% confidence interval will be provided. The exact calculation method will be used if the approximation of the normal law is not possible

Explanatory analyzes
A subgroup analysis is planned on the following variables:
- Study site
- Type of protocol (trial vs. other type of study)
- Medical specialty concerned by the protocol
- CDISC domain?
- Data type
- Variable (in CDISC terms)
References

Laura Lovett; Pfizer, Ochsner Health team up for clinical trial innovation; https://www.mobihealthnews.com/ February 20, 2019


FDA Guidance for Industry - Use of Electronic Health Record Data in Clinical Investigations - July 2018

https://www.fda.gov/drugs/developmentapprovalprocess/formssubmissionrequirements/electronicssubmissions/ucm464653.htm
