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Assessing the Financial Impact of Reusing Electronic Health Records Data for Clinical Research: Results from the EHR4CR European Project

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Abstract

Background: The new technological platform developed by the Electronic Health Records for Clinical Research (EHR4CR) European research project (2011-2016) has been specially designed to enable the trustworthy reuse of health data contained in hospital-based electronic health records for enhancing and speeding up clinical research scenarios. In particular, protocol feasibility assessments, patient identification for recruitment, and clinical data exchange for study conduct, in accordance with data privacy, ethical and legal requirements. The objective of our study was to assess the financial impact of adopting these advanced solutions compared to current practices, from the perspective of the primary sponsors of clinical trials in Europe.

Methods: Considering a scalable implementation of EHR4CR solutions in up to 5-10% of Phase II, III and IV clinical trials to be commercially sponsored in Europe over 5 years, two potential market sizes were defined. The first has a European initial scope (i.e., for European clinical trials only), and the second has a European subsequent broader scope (also including European arms of global studies). Based on expert opinions, the EHR4CR initial scope target market was estimated to be 30% of the broader scope. Direct costs to clinical research sponsors were estimated under current practices, and with the EHR4CR platform. Uncertainty was managed using 100,000 Monte Carlo simulations.

Results: Compared to current practices, the potential average 5-year savings with EHR4CR solutions for Phase II, III and IV commercially sponsored clinical trials in Europe were estimated at €175.5 m for the European initial scope market, and at €585.3 m for the European broader scope market. These results were confirmed by robust probabilistic sensitivity analyses.

Conclusions: Compared to current practices, EHR4CR solutions appear cost-saving for primary sponsors of clinical trials. These results suggest that the potential for savings would increase with a broader adoption of EHR4CR solutions in Europe, and beyond.

Keywords: Financial impact; Budget impact; Clinical trials; Clinical research; Electronic health records

Introduction

Innovative medicines introduced into the market are the results of demanding and costly research and development (R&D) efforts of the biopharmaceutical industry. By the time a new medicinal product reaches the market, an average of 12-13 years will have elapsed since the first synthesis of the new active substance [1]. Today, the cost of bringing to market a new chemical or biological entity is estimated between €142 million and 1.75 billion [2,3]. In 2012, research-based pharmaceutical industry invested an estimated €30,500 million in R&D in Europe [1]. Nonetheless, Europe is facing increasing competition from emerging economies which contribute to the gradual migration of research activities from Europe to these fast-growing markets [1].

Notably, bringing a new drug to market requires generating evidence of clinical efficacy and safety in order to gain regulatory approval. But also, and increasingly, evidence of comparative effectiveness and cost-effectiveness, including from real-world contexts [4]. Thus, the demand for clinical trials is growing in complexity and labor intensity. In parallel, current clinical research practices are facing significant challenges. In particular, clinical trial protocols would benefit from more precise feasibility assessments prior to launching clinical studies. This would contribute to reducing or avoiding multiple and costly protocol amendments downstream, as well as the number of failed trials. Patient identification is also slow and demanding due to the increasing complexity of study protocols. It is estimated that almost 50% of all trial delays are caused by participant recruitment problems. Moreover, studies recruiting on time are reportedly extremely low across markets: 18% in Europe, 17% in Asia-Pacific, 15% in Latin America, and 7% in the US [5]. In addition, clinical data entry

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in different data capture systems is still being achieved manually by different individuals and sites, leading to potential duplications, errors and again, significant delays. Recent studies have shown that over 40% of clinical trial data are entered into the patient's health record, the clinical trial data capture system, and, possibly, a third paper copy. It is also estimated that over 70% of data are duplicated between electronic health records (EHR) and clinical trial systems [5]. All these factors contribute to slower than expected patient enrolment, significant study delays, and increasing costs. Hence, reusing health data contained in EHRs promises to enhance protocol feasibility assessments, patient identification for recruitment, and electronic clinical data exchange, contributing to improving current practices and reducing the operational costs of clinical study conduct.

In response to this growing demand for more clinical evidence, the biopharmaceutical industry must therefore enhance its drug development processes and transform pharmaceutical R&D frameworks for value-based innovations [6,7]. Such reengineering involves improving the design of study protocols, speeding up patient recruitment, optimizing the conduct of clinical trials, and curbing clinical research costs. This transformation is also expected to boost and attract more R&D investments in Europe [1].

The EHR4CR (Electronic Health Records for Clinical Research) European project consists of one of the largest public-private research partnership funded by the European Commission and by the European Federation of Pharmaceutical Industries and Associations (EFPIA) in the frame of the Innovative Medicines Initiative (IMI) joint actions (http://www.ehr4cr.eu/). This vast multidisciplinary research initiative has developed an innovative technological platform that enables the trustworthy reuse of health data contained in hospital-based EHR to enhance and speed up clinical research practices [5,8-10]. Specially, this new platform has been designed to enhance and speed up the following clinical research scenarios, namely:

- **Scenario 1**: Protocol feasibility assessments;
- **Scenario 2**: Patient identification for recruitment;
- **Scenario 3**: Clinical study conduct enabled by electronic data exchange between EHRs and e-Clinical Research Forms (eCRF) systems, including for the reporting of serious adverse events (SAE).

The R&D efforts and technological advancements developed by the EHR4CR multidisciplinary research consortium have been described in previous publications [5,8-10]. In summary, a reference architecture was defined to serve as a technical specification for the construction of a scalable interoperable platform to enable the reuse of hospital-based EHR data for clinical research. Specific tools and services have been developed to ensure optimal interoperability between varying and disparate data sources (e.g. EHR and Electronic Data Capture Systems), allowing for the consistent interpretation of data available from those sources by the EHR4CR end-user services. After having been successfully tested in many hospitals and clinical research sites across Europe, the EHR4CR innovative platform is now ready to be implemented as a common set of components and services that will allow the integration of the lifecycle of clinical studies with heterogeneous clinical systems. This innovative platform will facilitate data extraction and aggregation, workflow interactions, privacy protection, information security, in compliance with ethical, legal and regulatory requirements. All these advancements will help speed up the protocol feasibility refinement process with rapid feedback on population numbers and their geographic distribution. They will also assist in identifying suitable patients via their nominated care providers, speed up and improve the accuracy of patient recruitment and trial execution, and enable more complete and real time safety monitoring [8-10]. By supporting distributed querying, the EHR4CR platform will improve and accelerate the conduct of clinical trials, enabling more efficient study conduct through reusing high quality electronic health data [11]. Importantly, EHR4CR solutions will be certified and delivered by accredited service providers. Certification and accreditation services will be provided by the newly founded European Institute for Innovation through Health Data (*i-HD*) (http://www.i-hd.eu/), which will also promote the benefits and governance of the research uses of health data, help regulate this emerging ecosystem, stimulate and coordinate new R&D opportunities.

Additionally, in order to ensure that value will be optimised in a sustainable manner for all stakeholders involved, a sound business model has been developed by the EHR4CR project. The objective was to define the most suitable organizational framework that will best contribute to creating, delivering, and optimizing value from implementing these innovative solutions in a multi-stakeholder ecosystem. The EHR4CR solutions having been successfully piloted and tested, they are now ready for implementation across Europe. They will first be provided by InSite, the first EHR4CR service platform in Europe (https://www.insiteplatform.com).

Nonetheless, as for any new health technology entering the health sector, the use of EHR4CR solutions will need to be budgeted for by the main sponsors of clinical trials, namely pharmaceutical industry. The objective of this study was thus to assess the financial impact of adopting EHR4CR solutions compared to clinical research current practices, from the perspective of pharmaceutical industry as primary sponsors of clinical trials in Europe, and globally. For this purpose, a budget impact analysis (BIA) was developed to take into account the estimated operational direct costs for clinical trials sponsors for conducting defined clinical research scenarios under current conditions, and under EHR4CR conditions, applied to Phase II, III and IV commercially sponsored clinical trials to be conducted in Europe over 5 years.

Considering that the EHR4CR platform will displace clinical research direct costs incurred under current conditions, the cost difference between the two situations represents the estimated financial impact of adopting EHR4CR solutions compared to existing practices at a European level.

Because this analysis was conducted using a 5-year horizon, the theoretical modelling framework used the most recent published retrospective data available at time of model development, as well as carefully estimated projections relevant to the number of commercially sponsored clinical trials to be conducted in Europe over 5 years, and projected rates of adoption of EHR4CR solutions for each of the clinical scenarios defined. Then, as described in the following methodology, extensive probabilistic sensitivity analyses were conducted to manage uncertainty and to confirm the robustness of the results.

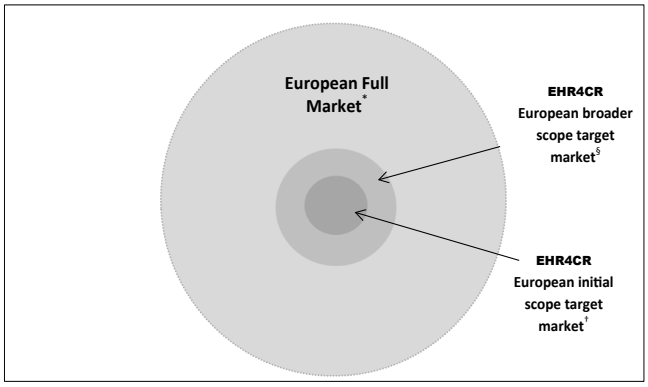
Materials and Methods

This study was conducted in accordance with BIA good practices [12]. The key elements of a BIA include defining the current standards, target market and size, the expected uptake of a new technology, and the related direct costs (including direct acquisition costs of the new technology based on the expected use and price per unit) compared to current practices. Our BIA model was developed to reflect the anticipated market uptake of the EHR4CR innovative solutions, considering the projected use and costs of this new alternative over

a 5 year horizon, compared to current practices. Hence, our model estimated the financial impact for the primary sponsors of clinical trials (pharmaceutical industry) in Europe of adopting EHR4CR solutions compared to existing practices. This approach has involved the development of a computing modelling framework specially designed to capture the shifts in direct costs for pharmaceutical industry caused by the EHR4CR intervention. This was achieved by first defining the clinical research targeted markets, the anticipated market uptake of EHR4CR solutions, the direct costs under current practices and under EHR4CR conditions, accounting appropriately from the perspective of the primary sponsors and budget holders of clinical trials.

Using best practices, the EHR4CR BIA model structure was developed and validated by a multidisciplinary scientific panel composed of two expert health economists, six senior clinical research scientists (representing leading R&D pharmaceutical companies involved in the EHR4CR European research project), and two academic partners who also provided expert opinions (refer to authorship). As our study did not involve any human participants, patients, or samples, but rather focused on developing a BIA model and advanced mathematical calculations, seeking approval by an ethics committee was not deemed necessary.

This BIA model was defined considering a scalable implementation of EHR4CR solutions for conducting Phase II, III and IV commercially sponsored clinical trials in Europe over 5 years. The size of the EHR4CR target markets were defined considering 2 potential scopes: i) A European initial scope (initially for European clinical studies only), and ii) A European subsequent broader scope (then also including European arms of global studies). These two market sizes were defined to reflect the projected gradual uptake of EHR4CR solutions. Given the widespread use of EHRs systems in Europe, the EHR4CR BIA broader scope target market considers the condition of a mature market where EHR4CR solutions could be implemented in up to 5-10% of all Phase II, III, and IV commercially sponsored clinical trials to be conducted across therapeutic areas over 5 years. This broader scope thus reflects that EHR4CR solutions would be used for conducting both Europe-only clinical trials, as well as European arms of global studies. However, considering potential introductory factors, the EHR4CR BIA also defined a more conservative initial "sub-market" to reflect that EHR4CR solutions would likely be initially implemented for clinical trials strictly conducted in Europe. For this purpose, and as validated by the multidisciplinary expert panel, the EHR4CR European initial scope target market was defined as corresponding to 30% of the European broader scope target market. The EHR4CR target markets are illustrated in Figure 1.



*: Defined as Phase II, III, IV commercially funded clinical trials in Europe over 5 years

§: EHR4CR broader scope target market estimated to capture 5-10% of the full European market

†: EHR4CR initial scope target market estimated to be 30% of the EHR4CR broader scope target market

Figure 1: European and EHR4CR target markets.

Data sources

This study was conducted in accordance with BIA good practices [12]. Published data available at the time of model development were used to populate our model. Because our model uses a 5-year horizon and a European scope, informed assumptions were also generated by senior clinical research scientists (representing six leading R&D pharmaceutical companies) in order to project 5-year estimates. As described below, the most recent published retrospective number of clinical trials commercially sponsored in Europe available at the time of model development was used as baseline. The estimated adoption rates of EHR4CR solutions per clinical research scenario used individually, in combination or in sequence were also defined compared to current practices. Based on early pilot studies, the estimated percentages in the reduction of operational direct costs for clinical trials sponsors were determined as minimum-maximum values for each clinical research scenario compared to existing conditions. All quantitative assumptions were carefully assessed and derived by designated clinical research experts of each participating pharmaceutical company, and expressed as minimum-maximum value ranges in order to reflect the potential variability of internal practices, as well potential slight differences across companies. Academic expert opinions were also sought, providing supplemental face validity with participating academic partners for all parameters and data used. The BIA model was developed and populated by highly experienced senior health economists who have also conducted a thorough quality assurance of the model structure, computations, and outputs. In order to manage uncertainty and to take into account all possible values across the minimum-maximum ranges provided for all parameters, using best practices, extensive probabilistic sensitivity analyses (100,000 Monte Carlo simulations) were carried out for confirming the robustness of the results. All these steps have contributed to further validating the methodological approach, calculations, and results.

Estimated number of clinical trials

The estimated number of Phase II, III, and IV commercially sponsored clinical trials was derived using the publically available European Medicines Agency (EMA) European Clinical Trials (CT) Database (EudraCT) [13]. The EudraCT 2012 statistics were used as baseline (i.e., 1,218 commercially sponsored Phase II, III and IV clinical trials in 2012). In order to forecast the expected number of Phase II, III and IV commercially sponsored clinical trials to be conducted in Europe over the next 5 years, participating pharmaceutical partners provided company-specific forecasts defined as minimum-maximum 5-year values. These values were computed using uniform distribution shapes, and then integrated into the EHR4CR BIA simulation modelling framework. The estimated numbers of Phase II, III and IV commercially sponsored clinical trials over 5 years in Europe, and for the EHR4CR target markets defined, are provided in Table 1.

For validation purposes, the EudraCT 2013-2014 dataset was again consulted in November 2014. The 2013-2014 EudraCT estimates confirmed that the projected ranges defined by participating pharmaceutical industry clinical research experts were fully accurate for that period, validating and further reinforcing our confidence in the 5-year forecasts.

Market Definition	European Market*	EHR4CR European Broader Scope Target Market§	EHR4CR European Initial Scope Target Market†
5-year estimates of Phase II, III, and IV commercially sponsored CTs	4900-9285	245-929	74-279

CT: Clinical Trials
*: Based on EudraCT (2012 baseline) and 5-year forecasts from participating clinical research scientists
§: Corresponding to 5-10% of European Market estimates
†: Corresponding to 30% of EHR4CR European Broader Scope Target Market

Table 1: 5-year estimates-Phase II, III and IV commercially sponsored clinical trials in Europe, and per EHR4CR target market (minimum-maximum values).

Costing Data

Our analysis focused on clinical research direct costs to the pharmaceutical industry as primary sponsors of clinical trials. In order to calculate the estimated cost of Phase II, III, and IV commercially sponsored clinical trials, the BIA used the estimated number of patients per clinical trial phase, as well as average per-patient costs estimates. As described in Table 2, the number of patients per clinical trial phase was defined using minimum and maximum values, as estimated by participating senior clinical research scientists (2014).

These estimates were combined with the average worldwide per-patient cost estimates for Phase II, III and IV clinical trial phases across therapeutic areas, namely: €28,123 (Phase II), €37,199 (Phase III), and €13,315 (Phase IV), based on a EUR/USD conversion rate of 0.78135 (October 2014). These values were generated from processing queries during the first quarter of 2013 on the Cutting Edge database (http://www.cuttingedgeinfo.com). These average worldwide per-patient cost estimates include costs related to patient recruitment, data provider fees, technology, site retention, data cleaning, statistical analysis, reports, and patient retention.

Hence, the estimated direct costs to clinical trial sponsors under current conditions were derived considering the estimated number of Phase II, III and IV commercially sponsored clinical trials to be conducted over 5 years, the estimated number of patients per clinical trial phase, and the average worldwide per-patient cost estimates for each.

In order to estimate the costs under EHR4CR conditions, the BIA forecasted the potential use of EHR4CR solutions by pharmaceutical industry. For this purpose, and as described in Table 3, the participating expert clinical scientists first defined a mix of five potential EHR4CR deployment strategies, and for each, a projected 5-year implementation rate by pharmaceutical industry relevant to upcoming Phase II, III and IV commercially sponsored clinical trials.

The potential deployment strategies included EHR4CR Scenario 1 (protocol feasibility assessment), EHR4CR Scenario 2 (patient identification for recruitment), and EHR4CR Scenario 3 (clinical study conduct and SAE reporting), either used individually, in combination or in sequence for the same clinical trial workflow, as follows:

- Strategy 1: EHR4CR Scenario 1;
- Strategy 2: EHR4CR Scenario 2;
- Strategy 3: EHR4CR Scenarios 1+2;
- Strategy 4: EHR4CR Scenario 3;
- Strategy 5: EHR4CR Scenarios 1+2+3.

Then, based on the forecasted implementation rate of EHR4CR solutions (across all commercially sponsored clinical trials within our scope), the direct costs to clinical trial sponsors under EHR4CR conditions were calculated. These costs considered the potential cost savings for each EHR4CR scenario, as well as the potential service providers' fees relevant to each EHR4CR scenario. In order to estimate the potential operational cost reductions with EHR4CR solutions compared to current practices, percentage estimates were derived for each EHR4CR scenario based on EHR4CR highly conclusive pilot testing. Furthermore, participating senior clinical research scientists also carefully assessed and independently defined the estimated operational cost reductions based on their company-specific practices and internal data. Taking into account potential introductory factors for adopting EHR-enabled solutions (e.g. potential transition costs), the cost reduction assumptions were deemed conservative, varying from 1-5% for EHR4CR Scenario 1, from 1-10% for EHR4CR Scenario 2, and from 2-6% for EHR4CR Scenario 3, as determined considering the operational costs of current conditions. Importantly, these cost reduction estimates were quite consistent albeit defined independently. The EHR4CR operational cost reduction assumptions are summarized in Table 4.

In order to also include the service providers' fees for EHR4CR solutions, given that our study was conducted prior to the commercialization phase of the platform, the EHR4CR service providers' fees were estimated using a robust willingness-to-pay (WTP) approach conducted with participating senior clinical research scientists. The potential fees for service relevant to EHR4CR Scenario 1, 2, and 3 were derived as minimum and maximum values on a per clinical trial basis (Table 5). The WTP minimum and maximum values were derived by applying marginal increasing percentages to

Clinical Trial Phase	Estimated number of patients
Phase II	100-250
Phase III	500-2000
Phase IV	250-1000

Source: Estimates defined by participating senior clinical research scientists (2014)

Table 2: Estimated number of patients per clinical trial phase (minimum-maximum values).

EHR4CR Strategy	EHR4CR Scenarios	Estimated use rate (%)
Strategy 1	Scenario 1	55
Strategy 2	Scenario 2	30
Strategy 3	Scenarios 1+2	10
Strategy 4	Scenario 3	4
Strategy 5	Scenarios 1+2+3	1

Source: Senior clinical research scientists (2014)

Table 3: EHR4CR potential deployment strategies and 5-year estimated implementation rate by the pharmaceutical industry.

Expert #	EHR4CR Scenario 1*	EHR4CR Scenario 2§	EHR4CR Scenario 3†
1	1-3%	5-10%	3-6%
2	1-2%	2-4%	2-4%
3	1-3%	1-3%	3-5%
4	2-5%	5-8%	2-5%
5	1-2%	2-4%	2-5%

*: Protocol feasibility assessments
§: Patient identification for recruitment
†: Clinical study conduct and SAE reporting

Table 4: Estimated percentages (minimum-maximum) of operational direct costs reduction for clinical trial sponsors using EHR4CR clinical research scenarios.

EHR4CR Scenarios	EHR4CR potential fee for service
Scenario 1	50-200K€ per clinical trial
Scenario 2	75-250K€ per clinical trial
Scenario 3	125-500K€ per clinical trial

Source: Participating clinical research scientists, 2012

Table 5: Estimated willingness-to-pay ranges for EHR4CR fees.

the estimated average per-patient costs for conducting Phase II, III and IV commercially sponsored clinical trials across therapeutic areas (and which senior clinical research scientists considered acceptable), and by considering the estimated minimum and maximum number of patients defined for each clinical trial phase.

In order to take into account all potential values across the ranges provided, for each parameter, estimates were computed by the BIA model using a uniform distribution shape between the minimum and maximum values provided. The cost reduction estimates used a triangular distribution centered on the mean. The uncertainty of EHR4CR market uptake and costs was managed by conducting extensive probabilistic sensitivity analyses, namely 100,000 Monte Carlo simulations across all distribution ranges provided, thus increasing the robustness of the results.

Results and Discussion

The estimated average 5-year costs for conducting Phase II, III, and IV commercially sponsored clinical trials in Europe under current practices, and with EHR4CR solutions, and the estimated 5-year savings per target market, are summarized in Table 6.

Overall, the average 5-year costs for conducting Phase II, III, and IV commercially sponsored clinical trials in Europe were estimated at €188.6 billion (Median = 168.5; SD = 120.8) under current clinical research practices.

For the EHR4CR European broader scope target market (corresponding to 5-10% of the European full market), the average 5-year costs for conducting Phase II, III, and IV commercially sponsored clinical trials in Europe were estimated at €15.6 billion (Median = 13.0; SD = 11.2) under current practices, and at €15.0 billion (Median = 12.5; SD = 10.8) under EHR4CR conditions, representing a mean difference of €585.3 million (Median 388.3; SD = 654.4) in potential savings with EHR4CR-enabled solutions.

For the EHR4CR European initial scope target market (corresponding to 30% of the EHR4CR European broader scope target market), the average 5-year costs for conducting Phase II, III, and IV commercially sponsored clinical trials in Europe were estimated at €4.6 billion € (Median = 3.9; SD = 3.3) under current practices, and at €4.5 billion € (Median = 3.7; SD = 3.2) under EHR4CR conditions, representing a mean difference of €175.5 million (Median 116.5; SD =196.3) in potential savings with EHR4CR-enabled solutions.

Considering that current clinical research processes are increasingly labor intensive and time-consuming, these results are most encouraging. In view of escalating R&D costs [1,2], the biopharmaceutical industry is exploring new ways to enhance R&D platforms and to reduce costs. By enabling the reuse of EHR health data for clinical research, the EHR4CR innovative platform provides a new powerful tool to increase the efficiency of clinical research processes [5,8-11]. Importantly, by using advanced interoperable electronic data exchange systems, the EHR4CR platform performs protocol feasibility assessment in a seamless manner, simultaneously in multiple countries, across various hospitals, in a matter of minutes rather than the days or weeks under current conditions. The EHR4CR platform also enables the identification of eligible patients in relation to the clinical trials' inclusion and exclusion criteria in order to ensure their timely recruitment, as well as efficient clinical data exchange for facilitating clinical trial execution and SAE reporting. Accordingly, and as reported by Kalra et al., EHR4CR solutions are expected to deliver important benefits [5], such as improved clinical study planning, reduced number of protocol amendments (the cost of one protocol amendment being estimated at more than €400,000 (USD 450,000), with Phase III trials exceeding on average 3.5 amendments per trial [14, 15]), reduced administrative burden, better patient and investigational site targeting, faster patient recruitment, seamless study conduct, reduction in clinical research actual person-time and costs, reduced clinical trial cycle time, etc.

A recent cost-benefit assessment (CBA) conducted by Beresniak et al. has assessed the value of the EHR4CR platform compared to current practices for conducting Phase II and III clinical trials in oncology (as the reference case) [11]. This study has established that the EHR4CR platform provides significant added value to clinical trial sponsors for enabling the trustworthy reuse of EHR hospital-based clinical data for clinical research, in compliance with regulatory, legal, ethical and data privacy protection requirements. While a CBA typically assesses the monetary value of new technologies compared to current standards, a BIA estimates the financial impact on primary budget holders for adopting new alternatives. For this purpose, a BIA often use a time horizon between 1 to 5 years, with results presented for each budget period after the new intervention is adopted. As BIAs are increasingly required to assist funding decisions, they can be freestanding or part of a more comprehensive economic assessment, along with a CBA [12].

Albeit not company-specific, our study reflects the upcoming implementation of EHR4CR solutions based on validated market uptake assumptions and specific data inputs of interest to pharmaceutical industry in Europe, as main sponsors of clinical trials. To address the context of commercially sponsored clinical trials in Europe, the EHR4CR BIA provides synthetic information which incorporates direct costing estimates pertinent to this setting.

The results of this BIA show that EHR4CR solutions appear cost-saving compared to current practices for conducting Phase II, III and IV commercially sponsored clinical trials in Europe. The average 5-year savings for the EHR4CR European initial scope target market (i.e., for European clinical trials only) being estimated at €175.5 m, and

Market Size	**European Market**	**EHR4CR European Broader Scope Target Market (5-10% of European Market)**		**EHR4CR European Initial Scope Target Market (30% of European Broader Market)**	
Conditions	**Current Practices**	**Current Practices**	**EHR4CR***	**Current Practices**	**EHR4CR***
Estimated 5-year Mean Costs (€)	188.6B (Median: 168.5 SD: 120.8)	15.6B (Median: 13.0 SD: 11.2)	15.0B (Median 12.5 SD: 10.8)	4.6B (Median 3.9 SD: 3.3)	4.5B (Median 3.7 SD: 3.2)
Estimated 5-year Mean Savings (€)		585.3m (Median: 388.3 SD: 654.4)		175.5m (Median: 116.5 SD: 196.3)	

B=Billion
m=Million
SD: Standard Deviation
*: Includes EHR4CR estimated fees

Table 6: Estimated 5-year costs for conducting Phase II, III and IV commercially sponsored clinical trials under current practices and with EHR4CR-enabled solutions, and estimated 5-year savings.

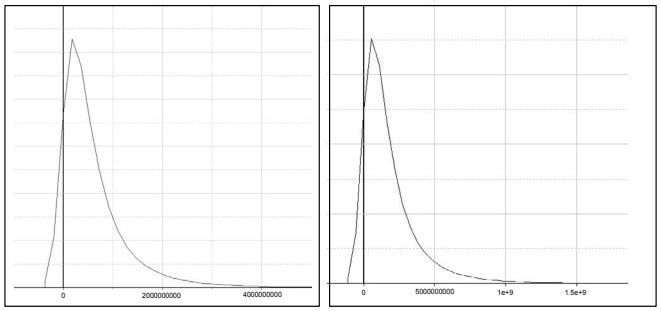
at €585.3 m for the EHR4CR European broader scope target market (also including European arms of global studies), these results suggest that the estimated cost savings would increase with a scalable market uptake of EHR4CR solutions in Europe, and beyond.

Importantly, our study shows that EHR4CR solutions appear cost-saving notwithstanding very conservative cost reduction assumptions (between 1-10% across EHR4CR scenarios compared to existing clinical research processes), as well as the inclusion of EHR4CR service providers' fees. In addition, for the purpose of the EHR4CR BIA, Phase IV trials were defined as well controlled post-registration clinical trials, targeting special populations, or comparing a new intervention with current treatments (standard of care). Hence, the Phase IV trials considered in our analysis exclude non-interventional observational studies for assessing comparative effectiveness in real-word contexts. But given an increasing demand from regulatory authorities, health technology assessors and payers for comparative effectiveness, safety and cost-effectiveness real-world evidence, it is expected that observational studies conducted in real-world conditions will also benefit from EHR4CR-enabled solutions in the future.

As our analysis uses advanced modelling, it relies on published estimates, as well as on clinical research scientists' and academic expert opinions. Nonetheless, most underlying assumptions were strongly converging, although generated independently by different experts. In particular, BIAs typically carries two types of uncertainty: parameter uncertainty in the input values used, and structural uncertainty introduced by the assumptions made in framing the BIA [16]. Examples of parameter uncertainty include estimates for current and new interventions. Structural uncertainty includes changes in expected intervention patterns with the availability of the new intervention and restrictions for use. Given there are limited data for many of the parameters, much of the parameter uncertainty of BIAs typically cannot be meaningfully quantified and thus standard approaches such as one-way and probabilistic sensitivity analyses cannot be carried out fully. Moreover, much of the uncertainty is structural and not easily parameterized. Thus, specific analyses are often undertaken by changing selected input parameter values and structural assumptions to produce plausible alternative situations [12]. Given that the EHR4CR BIA used expert assumptions and estimates expressed as minimum-maximum ranges, in order to manage uncertainty, it has been possible to carry out advanced mathematical simulations and extensive probabilistic sensitivity analyses using 100,000 Monte Carlo simulations [17]. Monte Carlo simulations consist of using random numbers to screen potential values across distribution shapes, also establishing a frequency distribution of results parameters.

Hence, our study results suggest that EHR4CR solutions appear cost-saving compared to existing clinical research processes. As illustrated in Figure 2, the shape of the cost-saving distribution curves is narrow with a positive median (peak), confirming a high probability for cost savings for the two EHR4CR target markets defined. Accordingly, our findings suggest that compared to the costs of current practices, the implementation of EHR4CR solutions could generate substantial savings for conducting Phase II, III, and IV commercially sponsored clinical trials in Europe, across therapeutic areas. These results were achieved despite conservative cost reduction assumptions and the inclusion of EHR4CR service providers' estimated fees.

As the EHR4CR BIA model was developed prior to launching the EHR4CR platform, and considering that different EHR4CR service providers will likely introduce competitive pricing schemes in the future (i.e., bundling of services, rebates, discounts, etc.), our BIA used



European broader scope market | European initial scope market

Figure 2: Shape of the distribution curves of the expected savings for using EHR4CR solutions in the European broader scope market (left) and the European initial scope market (right), compared to current practices.

the minimum and maximum values of potential applicable EHR4CR service providers' fees (defined as WTP ranges by participating experts) computed using a uniform distribution shape. Accordingly, the advanced simulations carried out have considered all potential values across the ranges provided so not to overestimate or underestimate the financial impact for pharmaceutical industry, as the main sponsor of clinical trials.

Notwithstanding the limitations of a theoretical model, our study provides useful evidence and guidance to assist decisions from clinical research decision makers in Europe. Considering that our analysis estimates the 5-year budgetary impact at a European macro level of the scalable adoption of EHR4CR solutions for Phase II, III and IV clinical trials across therapeutic areas, our model could also be adapted to a particular clinical trial workflow or study setting, in order to assist decisions at a clinical team level. By forecasting the budget impact of implementing EHR4CR solutions according to the unique considerations of a given pharmaceutical company, our model could generate highly specific results taking into account particular corporate situations, budget planning periods, clinical research portfolios, implementation rates, and established fees of service providers.

Lastly, it is worth noting that this BIA does not include the substantial value that EHR4CR solutions are expected to deliver from enhancing and speeding up the overall efficiency of clinical research processes. As mentioned above, these financial benefits have been assessed in the context of a CBA, establishing the added value of EHR4CR solutions versus current practices [11].

Conclusions

Using the perspective of the European pharmaceutical industry as primary sponsors of clinical trials, and assuming a conservative 5-year EHR4CR market uptake of up to 5-10% across Phase II, III, and IV commercially sponsored clinical trials conducted in Europe, the results of our study suggest that EHR4CR solutions appear cost-saving compared to current practices. These findings also suggest that more savings would be realized with a broader deployment of EHR4CR solutions in Europe, as well as globally.

As this study uses advanced modelling at a European level, further adaptations of this model are warranted at a company level in order to determine the estimated budget impact of adopting EHR4CR solutions compared to current practices, considering company-specific clinical research portfolios, use of EHR4CR solutions, operational costs, and budget planning periods.

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