CURRENT USE AND COSTS OF ELECTRONIC HEALTH RECORDS FOR CLINICAL TRIAL RESEARCH: A DESCRIPTIVE STUDY

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ABSTRACT

Background: Electronic Health Records (EHRs) may support randomized clinical trials (RCTs). We aimed to describe the current use and costs of EHRs in RCTs with a focus on recruitment and outcome assessment.

Methods: This descriptive study is based on a PubMed search for RCTs published since 2000 that evaluated any medical intervention while utilizing EHRs. Cost information was obtained from RCT investigators using EHR infrastructures for recruitment or outcome measurement but not exploring EHR technology itself.

Results: We included 189 RCTs. Most were carried out in North America [153 of 189, (81%)] and published recently [median 2012; interquartile range (IQR) 2009 to 2014]. Seventeen RCTs (9%) including a median of 732 patients [IQR 73 to 2513] explored interventions not related to EHRs, including quality improvements, screening programs, or collaborative care and disease management interventions. Here EHRs were used for recruitment [14 of 17;(82%)] or outcome measurement [15 of 17;(88%)]. Overall, the majority of studies measured the outcome using EHRs [158 of 189; (84%)], including many of the most patient-relevant clinical endpoints, from unscheduled hospitalizations to mortality. The per-patient costs varied from 44 to 2000 United States Dollars (USD), and total RCT costs from 67'750 to 5'026'000 USD. The other 172 of 189 RCTs evaluated EHR or EHR-modifications as modality of the intervention.

Interpretation:

RCTs are frequently and increasingly conducted using EHRs, but mainly as part of the intervention. Some RCTs successfully used EHRs to support recruitment and outcome assessment with possible cost savings once the data infrastructure is established.

BACKGROUND

Randomized clinical trials (RCTs) are the standard for evaluating benefits and harms of medical treatments. However, they are often time consuming and expensive to conduct and some trials rely on strictly standardized research settings that may limit the generalizability of their results(1). Electronic health records (EHR), or electronic databases containing patient level variables that are gathered during routine medical

care (Appendix 1, Box), provide great potential for implementing large scale and pragmatic trials(2, 3). RCTs could be directly integrated in routine care offering almost perfect generalizability of their results(4). Recently, the Patient-Centered Outcomes Research Institute (PCORI) has awarded 332 million United States Dollars (USD) to 28 pragmatic clinical studies, many of them utilizing EHR infrastructures and many of them integrated in routine care(5).

Great debate of the potential barriers and limitations of EHR use in clinical research persists, and further details on these obstacles have been discussed elsewhere(3, 6). Briefly, the two largest direct advantages of using routinely collected data (RCD) for clinical trials may be the facilitation of patient recruitment and of outcome assessment. Randomization of treatment may occur directly from the EHR during the patient's visit, maximizing recruitment rates(7). Recruiting patients through the EHR would allow to pre-screen for eligibility before approaching the potential participant and thus allowing to tailor the efforts towards the appropriate sample; furthermore, rapid consecutive enrollment would favor recruitments through automatic screening and selection of participants through the EHR database(8). This could substantially boost trials requiring large sample sizes or slow recruiting trials. Yet, the ability to assess outcomes without having to measure or collect them could be the most appealing resource-sparing advantage of EHRs in RCTs. Even when funds are not at issue, just the decrease in logistical difficulties themselves, particularly in large RCTs, could be worth extracting routinely collected EHR data. Thus, EHR may have an important role in the potential of implementing large scale and pragmatic trials(2, 3). This offers entirely new perspectives on evaluating health care interventions that favor the development of learning healthcare systems(7).

Nonetheless, the cost associated with implementing the EHR/EMR infrastructure in the first place may be substantial(9). While one could argue that using EHRs for research purposes might lead to more affordable trials, there is no systematic overview of empirical cost estimates per individual trial participant in EHR-supported RCTs.

We conducted a systematic descriptive survey of the use of EHRs in RCTs to determine how EHRs are implemented in clinical research settings and to describe specifically how this technology is used to support recruitment and outcome assessment. We aimed to determine their frequency of use and describe possible applications of the EHR

technology in current practice, focusing on trials that were supported by the EHR rather than evaluating the EHR itself.

METHODS

We performed a descriptive study assessing the current use of EHR technology in RCTs. We included any RCT in humans, addressing any health-related topic, published in English since January 2000, that utilized EHR for any purpose, including the recruitment of participants, intervention delivery, or outcome assessment(10). Focusing on modern technology we did not include older trials. There were no other eligibility criteria.

Definitions for EHR and related data vary(10-12). Our working definitions are shown in, Appendix 1, Box. Briefly, we considered EHRs an archive of health-related data in digital form, collected during routine clinical care for each individual patient, stored and exchanged securely, and accessible by multiple authorized users in a network of care providers(11). The EHR infrastructure used in eligible RCTs must have already existed and data just been obtained through a query of the EHR-database (i.e. no data specifically fabricated for the experiment would be considered routinely collected, for example when the trial was about the novel implementation of an EHR vs. no such implementation). There is no protocol published for this descriptive study.

Literature search

We queried PubMed (last search on 13 September 2017) for English articles, published since 1 January 2000 using keywords such as “electronic health record”, “electronic medical record”, “health information exchange“, “patient health record”, ”e-health” using an established RCT filter(13) (Appendix 2). Our search integrated the search strategy for EHRs provided by the U.S. National Library of Medicine(14), and was developed with the support of an information specialist (HE). Two reviewers (KAM and HE or AL) screened titles and abstracts. We obtained any article deemed pertinent by at least one reviewer as full text. One reviewer (KAM) evaluated full texts and determined eligibility, another reviewer confirmed all exclusions (LGH).

Data extraction

Eligible RCTs were classified based on the way in which the EHRs were utilized: (a) for patient recruitment in any form, (b) outcome assessment in any form, (c) for the trial

intervention itself, or (d) other possible purposes. For patient recruitment, we considered any effort of identifying trial participants based on certain characteristics, which was done through an EHR query, as well as any randomization of consecutive patients done through the EHR. For outcome assessment, we considered any trial in which any of the outcomes was obtained by querying or manually checking the EHR document (thus, where the endpoint was routinely found within the EHR).

We then sub-classified included RCTs into, (1) EHR-supported trials, where the EHR was used as research tool for conducting the trial (e.g. when patients with certain conditions are identified as enhanced recruitment strategy or adverse event outcomes are queried through a hospital) and into, (2) EHR-evaluating trials, in which using an EHR or an EHR-modification was evaluated as part of the randomly allocated intervention (i.e. software alteration or addition, e.g. a randomized implementation of a drug interaction alert system in a hospital's EHR ordering system). Furthermore, we extracted the RCT's research question, other study characteristics (sample size, country of origin, and unit of randomization), and whether the trials included order entry systems (CPOE/CDS, see Appendix 1, Box), telehealth or personal health records (PHRs).

For EHR-supported trials, we additionally determined the trial settings and more specific EHR utilizations (type of EHR and application in the trial, such as the type of alerts it would display in decision support systems). Furthermore, we extracted whether an advanced algorithm for patient identification/recruitment, or other purpose was developed. We also recorded if the recruitment was done prospectively (e.g. by advertisement and invitation, not through EHR), concurrently (i.e. in the point-of-care setting, through EHR), or retrospectively (i.e. screening a patient list, may be through EHR or not); and whether RCD were the only outcome source or if a hybrid approach was utilized. A hybrid approach could be that (1) some outcomes were based on RCD alone and other outcomes were entirely actively collected or (2) some outcomes were measured based on RCD and this measurement was supplemented by active data collection (e.g. when reported by patients outside an EHR network), or if a relevant amount (more than 10% of the total RCD source) was manually checked for validation. We specifically recorded the primary outcome of the trial and if it was measured using routinely collected EHR data alone, when it was measured (duration of follow-up), and any information on missing data or loss to follow-up. Furthermore, we extracted, for each

trial, whether blinding and allocation concealment measures were performed. We searched the full-texts for keywords, such as “placebo”, “blind”, “label” and “mask” to identify such statements, and then proceeded with extracting the statement when reported. One reviewer (KM) extracted all data. We aimed to provide a general overview on potential issues of bias in the EHR-supported studies. One reviewer (KAM and BS) used the Cochrane risk of bias tool, a second reviewer verified the assessments (KAM, HE, BS or LGH). Any disagreement was resolved by discussion.

Trial costs

We contacted the authors of included EHR-supported trials, requested cost information through a standardized email and extracted any cost information reported in the publications. We aimed to obtain a cost estimate which would allow comparison with traditional trials. Therefore, we were not interested in costs of EHR-evaluating trials.

We explained to the authors that the costs of the trial could have been divided in three major ways(15): (1) Cost of the project/trial development and preparation (e.g. for insurance, travelling, infrastructure, consulting, sample size calculation, database set up, etc.), (2) Cost of enrollment, treatment and follow up (e.g. per-patient costs, salary costs, patient reimbursement costs, materials and/or drugs costs; etc.) and (3) Cost after last patient out (data cleaning costs, analysis costs, publications costs; etc.).

We aimed for only a raw cost estimate and accepted any information we could. We converted cost values to USD where applicable, based on the exchange rate on 1 November 2017(16). We sent the data presented here to all trial authors for confirmation.

Statistical analysis

Results are reported descriptively using proportions and medians with interquartile ranges if not otherwise stated. Since our study was exploratory, we did not use any statistical tests.

RESULTS

After screening 1680 titles and abstracts, 394 potentially relevant articles were obtained as full texts and 189 EHR-RCTs were eligible (Figure 1).

All RCTs

Of the 189 RCTs, 17 were supported by an EHR (EHR-supported trials; 9%) while the majority [172; (91%)] utilized EHRs as modality of intervention (EHR-evaluating).

The vast majority of both EHR-supported and EHR-evaluating trials originated from North America [13 of 17; (76%) and 140 of 172; (81%), respectively] and were published recently [median 2012; (IQR 2009 to 2014)]. EHR-supported trials were cluster-randomized in 3 of 17 of trials (18%), while the EHR-evaluating trials were cluster randomized in 61 of 172 of trials (35%). There were no placebo controlled trials in our sample, and the majority of trials did not report the level of blinding [101 of 189; (53%)]; blinded outcome assessment was the most frequent type of blinding reported (19%), followed by open label (14%), single-blinding (10%) and double-blinding (4 %)(Table 1).

RCTs supported by EHRs

The interventions and settings varied among the 17 EHR-supported trials(17-33) (Table 3). Five trials (29%) utilized the EHR of a U.S. Veteran's Affairs or affiliated facility. Most trials evaluated quality improvement interventions which often involved clinician education and feedback initiatives [8 of 17; (47%)], screening programs [4 of 17; (24%)], and collaborative care and disease management interventions integrated in primary care settings [3 of 17; (18%)]. Almost half of the studies took place in primary care clinics [8 of 17; (47%)], in healthcare networks [5 of 17; (29%)] and in hospitals [3 of 17 (18%)]. One trial was performed entirely within a pharmacy EMR (6%).

Supported outcome measurement

Of the 17 EHR-supported trials, 15 measured outcomes using the EHR (88%) (Table 1). The EHR-assessed outcomes were typically screening uptake (e.g. women seeking a Pap-test after receiving an automated call from the EHR prompting cervical cancer screening) [6 of 15; (40%)], clinical outcomes [4 of 15; (27%)], drug adherence [2 of 15; (13%)], or guideline concordant care measures [2 of 15; (13%)]. In 7 out of 15 trials (47%), the RCD source was the only source of outcome data in the entire trial, while in the remaining 8

(53%) a hybrid approach was applied with some outcome data being actively collected. In 4 of these 8 cases(18, 19, 27, 30), the primary outcome was fully extracted from an EHR but additional outcomes were actively collected while in 3 cases(20, 21, 32), the primary outcome was actively collected but additional outcomes were EHR-based. In one case, the primary outcome was collected through the EHR but verified with actively collected data(22). Overall, 12 of 15 of the trials (80%) relied on EHR for the primary outcome assessment. The trial duration was on median 10 months (IQR 5 to 12); 10 of 17 trials (59%) reported the number of missing data or patients lost to follow-up, but none reported on the quality of the data.

Supported recruitment

Of the 17 EHR-supported trials, 14 (82%) used the EHR as tool for patient recruitment (Table 1). One(29) of them reported a prospective approach, while the remaining 13 used the EHR retrospectively (i.e. they reported merely using a manual check or simple retrospective query of eligible patients via EHR); additionally, only one(17) reported using a complex querying system (another one(26) appeared to but did not report it specifically). The other 3 of the 17 trials used a (traditional) prospective recruitment approach without EHR (18%).

Costs

We contacted 13 of the 17 corresponding authors from the EHR-supported trials. Emails were undeliverable to 3 addresses, for which we were also unable to find an alternative contact online and we were never able to reach the authors. We obtained information of trial costs for 4 (17, 23, 26, 29) of the 17 trials and, additionally, intervention cost data from one trial(33) (24% response rate).

Cost information came from one Australian (17) and 4 U.S. trials(23, 26, 29, 33) (2 within the Veterans Affairs network(26, 33)). The costs varied from 67'750 USD to 5'026'000 USD for total trial costs (median 86'753 USD) and from 44 USD to 2000 USD for per-patient costs (median 315 USD) (Table 3). Overall trial costs were derived from funding budgets in three cases while one author stated that the overall costs were 2000 USD per patient. In the trial(17) which leveraged the EHR database through automated data extraction, the per-patient costs was 44 USD. In the 2 cases(23, 29) where the extraction of study data from the EHR source was still done manually, the per-patient costs varied

from 560 to 2000 USD. We have no information in this regard for one trial(26). The trial which presented only the costs of the intervention (extracting data from EHR to give a feedback to health–care providers) reported costs of 44 USD per patient when the data was extracted manually and a sensitivity analysis indicated that these costs could decrease to only 9 USD if the data were extracted automatically(33).

Risk of Bias

Three trials had no indication for high risk of bias in any of the assessed domains (Appendix 4). There were no indications for high risk of bias related to randomization or allocation concealment in any of the trials. Most trials were open-label or assessed an intervention that was not disguisable from the participants/providers, which may indicate a high risk of bias. Relevant to EHRs-trials, risk for attrition bias was generally low (missing outcome data for not more than 10% of patients), and in four trials, all data was reported for all patients.

RCTs using EHR for intervention

Of the 172 EHR-evaluating trials (references in Appendix 2), 143 measured outcomes using the EHR (83%), and 91 (53%) used the EHR as tool for patient recruitment (Table 1). Computerized decision support systems such as CPOE or CDS (definitions in Appendix 1, Box) were evaluated in 75% (128 of 172) of the trials. Personal health records were evaluated in 15% (26 of 172) of the trials. Telemonitoring tethered vital sign measuring devices connected to the EHR were evaluated in 8% (14 of 172) of the trials and very few [4 of 172; (2%] evaluated electronic patient reported outcomes (Table 1).

INTERPRETATION

The majority of trials using EHR explored the EHR technology itself. However, we identified 17 trials that investigated an EHR-unrelated intervention and were supported by using EHR for patient recruitment or for outcome assessment. Most of them were published recently, indicating a rapid development in this field.

There is, to our knowledge, no similar study describing the current use of EHR in clinical trials. However, the potential of registry-based trials for comparative effectiveness research and the current state of using registries for RCTs, in particular for outcome ascertainment, has been reviewed recently(8, 34). Interestingly, while the settings and implementation were similar to those identified in our sample, registry trials are most frequently performed in Scandinavian countries(34), and EHR trials predominantly in North America. Registry trials also often collect their primary outcome data using routine data (82%), similarly to EHR trials (80%), indicating confidence in the reliability of this data(34). Information about data quality and validity was rarely reported for registry-based trials (11%)(34) as well as in our sample of EHR-supported RCTs (where it was not reported by any of the trials), indicating similar reporting problems as in observational RCD research(35). This may be expected given the current lack of a standardized reporting guideline for RCD-RCTs but also highlights a substantial transparency problem.

The overwhelming majority of trials in our sample were measuring an outcome with EHRs [158 of 189; 84%], including many of the most patient-relevant clinical endpoints, from unscheduled hospitalizations to mortality. But there were also less pragmatic and more exploratory, mechanistic(36, 37) outcomes which help to understand pathophysiological processes (for example one study even utilized EHR-extracted lipid levels during a lipid-lowering agent trial(38)). We also identified the, to our knowledge, first trial that used routinely collected data in a pre-licensing setting in the context of drug approval (the Salford lung study(32)).

The identified EHR-supported trials were quite heterogeneous concerning their targeted populations and outcomes measured, with a few exceptions. For example, over a third of this subsample was comprised of Veteran's Affairs trials, all of which utilized EHR for outcome and patient identification. This is likely due to the fact the VA has had a long

established EHR system, and its widespread network allows for ease in designing and implementing these types of trials.

Another interesting finding that relates to the EHR-evaluating trials in our sample is the high proportion, approximately one third, of trials using cluster-randomization. This indicates that EHR-based trials mostly evaluate interventions not on at the patient-level but more at a system-level, as when aiming to redirect physician behavior, etc. This introduces the risk of contamination between the randomized units (e.g. physicians) and thus requires a cluster design to be implemented.

Other than by its affordability, the great theoretical value of integrating EHR in clinical trials lies in its potential for patient recruitment. For example, D'Avolio et al ("Implementation of the Department of Veterans Affairs' first point-of-care clinical trial.") reports on a VA pilot study(39) that in addition to those identified in our sample shows how convenient it can be to identify patients based on specific characteristics (the EHR database is "scanned" and a list of possibly eligible patients results), and even to recruit them, by sending an automatic electronic message to their clinician. Even with a smaller response rate, when the contacted patients are in the order of thousands, this could lead to greater recruitment capacity; which could be of substantial value particularly in those RCTs where difficult recruitment is already suspected during planning. We identified that almost half of the EHR-supported trials that used EHR for recruitment made use of more sophisticated techniques such as the proposed mechanisms of data-mining. While there are trials that recruited patients by screening the EHR without specifying the use of a particular algorithm addition, most EHRs will require some programming to identify specific traits in the system that go beyond the basic EHR abilities (i.e., typing a diabetes ICD-10-CM code in a search window and obtain a list of patients, which can be done manually). More advanced EHR add-ons, which can screen for multiple variables at multiple levels contemporary and continuously (i.e. screening the system every two hours or instantly during care for the whole time of the trial) do require planning and validation. An example of such EHR screening tool is one developed and used in the Bereznicki 2008 trial, where this "data-mining tool" scrutinized the pharmacy EMR based on a specified protocol (history of asthma medication being dispensed more frequently than guideline customs, such as patient refilling its rescue inhaler more often than expected) which flagged patients with poorly controlled asthma. These patients were

then contacted, received educational material for self-management, and were prompted to contact their care providers. This example shows how using an EHR for patient identification and recruitment can be efficiently done yet that it requires significant planning and software development. We provide a general framework with the various potential applications and challenges of using RCD in different trial conduct phases elsewhere(3, 6).

The author-reported costs could support the assumption that using RCD for RCT may promote cost reduction as long as the outcome data source is already established and not a financial responsibility of the research endeavor. In the three trials(17, 26, 33) in which the EHR infrastructure was well established and merely redirected for use in these trials, the costs per patient (median 44 USD) were much lower than often reported costs in traditional trials(40). The costs of the two trials(23, 29) in which the infrastructure was less integrated (such as actively screening the EHR for assessing the clinical endpoint), remained more similar to those of traditional RCTs (median 1280 USD per patient). The recently published overview of registry trials by Li et al. (8) found similar trial cost patterns (i.e. a reduction of costs when the outcome data did not require manual collection but leveraged the registry infrastructure instead).

Limitations

Some limitations of our study merit closer attention. Firstly, we did not aim for a complete sample of all published EHR-based trials and we searched PubMed only, but we aimed for a systematic, comprehensible and reproducible survey of the current literature. We used a highly sensitive search algorithm and implemented specific EHR search filters provided by the U.S. National Library of Medicine. Nonetheless, we assume that we overlooked several pertinent publications that did not indicate in their keywords, title or abstract the application of EHRs. This may have engendered an overrepresentation of EHRs used for interventions in our sample and especially the observed disproportion of EHR-evaluating and EHR-supported trials needs to be interpreted with caution.

Secondly, searching for English articles indexed in PubMed alone may have created regional bias, with a potential overrepresentation of Anglo-American studies. This could explain the high proportion of studies from the USA. Nonetheless, substantial legislative and financial efforts have been placed in North America, encouraging the acquisition and

employment of EHR technology, which may be more likely the reason for this critical imbalance.

Thirdly, the trials were highly diverse showing the various fields of EHR application, but we would need more data to further evaluate individual details and explore, for example, the ethical constraints associated with no-consent point-of-care trials(41, 42).

Fourthly, only one reviewer (KAM) assessed the full-text eligibility and completed several parts of the data extraction, which could have introduced some error in the selection of the trials. Nonetheless, we feel that the identified trials still provide an overview of the mode of utilization of EHR trials.

Fifthly, we did not test any hypothesis regarding the effect of using EHR in trials, nor did we assess the impact of using EHR on endpoint ascertainment. While we extracted a few characteristics that can point to the methodological quality of the studies, including an evaluation of major domains of risk of bias, we did not evaluate the treatment effects reported in the EHR trials, but merely offered a description of their use.

Finally, we obtained only a few rough cost estimates without details, not allowing us to deduce any cost patterns; however, it provides first estimates to shed some light in this area.

Conclusions

We conclude that EHRs are a novel and valuable addition to clinical research. There are numerous examples of how EHR successfully implemented in clinical research settings supported recruitment and outcome measurement in randomized trials. They may be associated with lower research costs, overall allowing the conduct of more or larger RCTs. Altogether, these are very promising developments towards more randomized real-world evidence.

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Data sharing

No additional data available.

Declaration of competing interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf and declare no financial relationships with any organization that might have an interest in the submitted work in the previous three years.

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They have no other relationships or activities that could appear to have influenced the submitted work. All other authors declare to have no relationships or activities that could appear to have influenced the submitted work

Contributors

LGH conceived the study. KAM, HE and AL screened titles, abstracts and full-text publications. KAM extracted the data. KAM and LGH analysed the data. All authors interpreted the results. KAM and LGH wrote the first draft and all authors made revisions on the manuscript. All authors read and approved the final version of the paper. KAM and LGH are the guarantors.

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Transparency declaration

The Corresponding Author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Ethical approval

Not required, this article does not contain any personal medical information about any identifiable living individuals.

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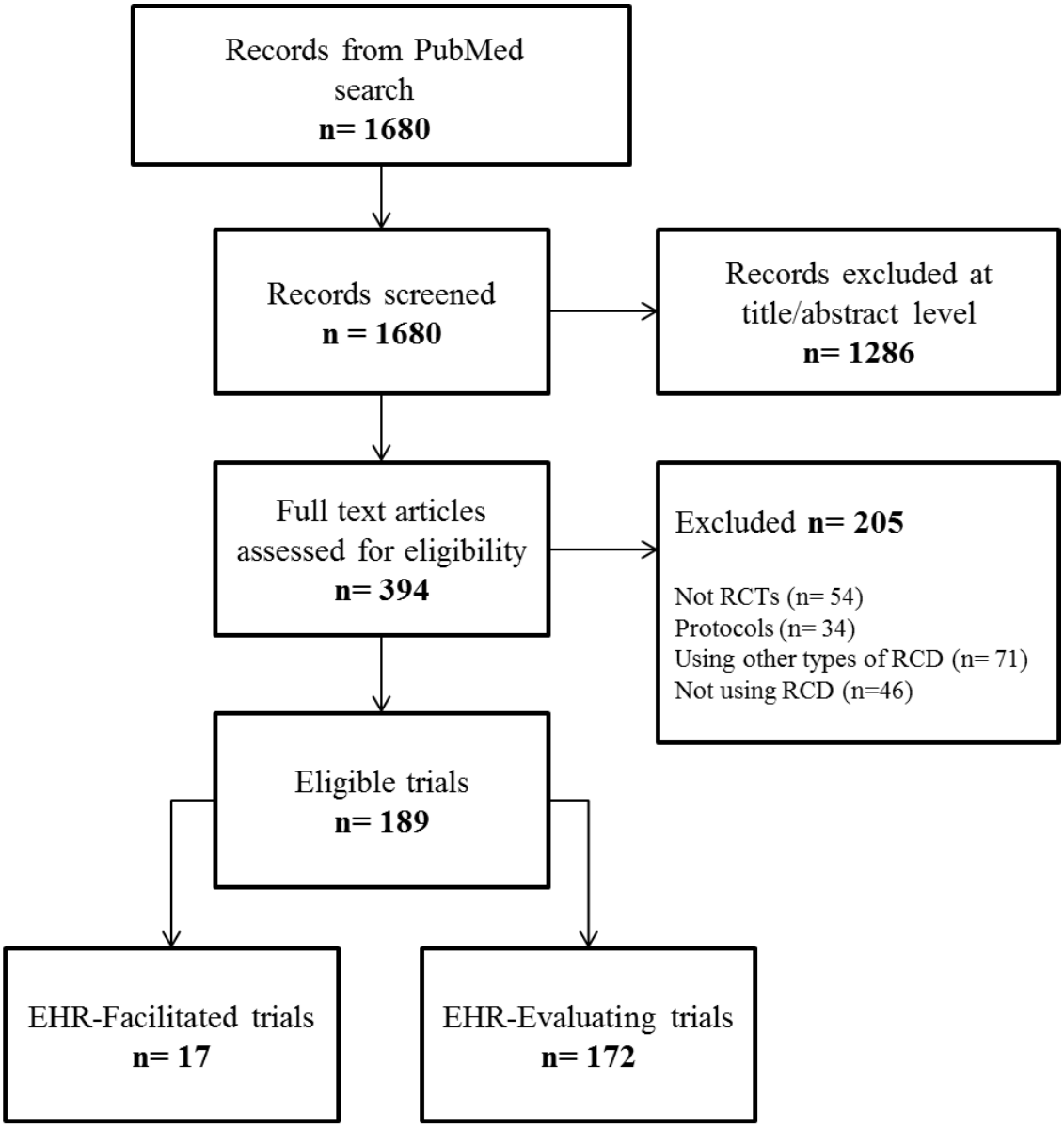
575

FIGURES

Figure 1: Flow-chart:



EHR: Electronic health records; RCD: Routinely collected data; RCT: Randomized controlled trial

TABLES

Table 1: Characteristics of all RCTs using Electronic Health Records

	EHR trials, overall		EHR-evaluating trials		EHR-supported trials	
	N	%	N	%	N	%

Total	189	(100%)	172	(100%)	17	(100%)
EHR for intervention	172	(91%)	172	(100%)	-	-
▪ Computerized decision or physician order entering system (CPOE/CDS)	128	(68%)	128	(75%)	-	-
▪ Telehealth	14	(7%)	14	(8%)	-	-
▪ Personal health record (PHR)	26	(14%)	26	(15%)	-	-
▪ Electronic patient reported outcomes (ePRO)	4	(2%)	4	(2%)	-	-
EHR for outcome measurement	158	(84%)	143	(83%)	15	(88%)
EHR for patient recruitment	105	(55%)	91	(53%)	14	(82%)
Country						
▪ North America	153	(81%)	140	(81%)	13	(76%)
▪ UK	9	(5%)	7	(4%)	2	(12%)
▪ Continental Europe	15	(8%)	14	(8%)	1	(6%)
▪ Other*	12	(6%)	11	(7%)	1	(6%)
Cluster-RCT	64	(34%)	61	(35%)	3	(18%)
Unit of randomization:						
▪ Clinicians	49	(26%)	46	(27%)	3	(18%)
▪ Patients	76	(40%)	65	(38%)	11	(65%)
▪ Pharmacies	1	(<1%)	1	(<1%)	0	(0%)
▪ Practice/Clinic	54	(28%)	51	(29%)	3	(18%)
▪ Unit/Floor	9	(5%)	9	(5%)	0	(0%)
Publication year	2012 (2009 - 2014)		2012 (2009 - 2014)		2013 (2010 - 2013)	
Sample size**:						
▪ Total	89 (24 -732)		80 (22 - 513)		732 (73-2513)	
▪ Cluster-RCT excluded	239 (57 - 1187)		254 (60 – 1187)		900 (111 - 3075)	
▪ Cluster-RCTs only	24 (12 - 47)		24 (12 - 52)		18 (12-24)	
Blinding:						
▪ Open label	27	(14%)	23	(13%)	4	(24%)
▪ Single blinded	19	(10%)	18	(11%)	1	(6%)
▪ Double blinded	7	(4%)	6	(3%)	1	(6%)
▪ Outcome assessment blinded	35	(19%)	30	(17%)	5	(29%)
▪ Not reported	101	(53%)	95	(55%)	6	(35%)
Placebo use	0	(0%)	0	(0%)	0	(0%)

*Other: includes China, Japan, Taiwan, Iran, India, Pakistan, Lebanon, Australia and Kenya.
**Data are medians and IQR if not stated otherwise.
Abbreviations: EHR, Electronic health record; RCT, Randomized clinical trial.

Table 2: Characteristics of EHR-supported trials

Trial **Year**	**Country** **Sample size**	**EHR use for Recruitment** **Type**	**EHR use for Outcome assessment** **Extent of RCD use***	**Patient population/ Indication**	**Intervention and Control****	**Primary Outcome** **Follow-up (FU)** **Missing data**	**Setting**
Bereznicki, Peterson, et al.(17) 2008	Australia 1551 patients	Yes Retrospective	Yes EHR alone	Uncontrolled asthma	Intervention: Contact by community pharmacist, plus educational material and referral to GP for asthma management	Ratio of dispensed preventer and reliever medication FU: 6 months Missing data: NR	Community pharmacy network
Corson, Doak, et al(18) 2011 (SEACAP)	USA 42 care givers randomized (365 patients)	No Prospective	Yes Hybrid; Primary outcome EHR alone	Musculoskeletal pain	Intervention: Patient and clinician education, symptom monitoring and feedback to clinicians	Guideline–concordant care FU: 12 months Missing data: NR	Primary care clinics associated with VA medical center and a urban hospital
de Jong, Visser, et al(19) 2013	Netherlands 73 general practitioner trainees randomized (No. of patients not reported)	Yes Retrospective	Yes Hybrid; Primary outcome EHR alone	Skin and psychosocial conditions	Steering patient mix of general practitioner trainees	Trainees exposure to specific field (patient mix); knowledge and self-efficacy FU: 6 months Missing data: 5%-10%	Practice network with GP training program
Fu, van Ryn, et al.(20) 2014	USA 6400 patients	Yes Retrospective	Yes Hybrid; Primary outcome active data	Current smokers	Proactive outreach plus choice of smoking cessation services	6-month prolonged smoking, abstinence at 1 year FU: 12 months	Veteran's Affair medical center

			collection alone			Missing data: 48.3% (but 0% for EHR outcome)	
Galbreath, Krasuski, et al.(21) 2004	USA 1069 patients	Yes Retrospective	Yes Hybrid; Primary outcome active data collection alone	Symptomatic congestive heart failure	Congestive heart failure management program (plus at-home scale)	All-cause mortality and healthcare utilization FU: NR, time to event Missing data: NR	Various healthcare networks and Medicare/-aid participants
Gerber, Prasad, et al.(22) 2013	USA 18 practices, 170 caregivers randomized (185212 patients)	Yes Retrospective	Yes Hybrid; Primary outcome hybrid	Clinical practice groups with primary care pediatricians (Children with acute respiratory tract infections)	Antibiotic stewardship program	Change in broad spectrum antibiotics prescribed for bacterial infections or change in antibiotic prescribed for viral infections FU: 12 months Missing data: 5% of caregivers	Pediatric primary care network
Green, Wang, et al.(23) 2013	USA 4675 patients	Yes Retrospective	Yes EHR alone	Prevention of colorectal cancer	Automated Interventions, vs Assisted care vs Navigated care, vs Usual care	Receiving any colorectal cancer test and being current for colorectal cancer testing in years 1 and 2. FU: 24 months Missing data: 0.2%	Primary care practice network

Hoffman, Steel, et al.(24) 2010	USA 404 patients	Yes Retrospective	No Active data collection alone	Prevention of colorectal cancer	Fecal Immunochemical test (vs Guaiac-based occult blood test)	Screening adherence FU: 3 months Missing data: NR	VA network (primary care clinics and laboratory)
Israel, Farley, et al.(25) 2013	USA 732 patients	Yes Retrospective	No Active data collection alone	Inpatient adults with at least one of several cardiovascular disease diagnoses in EHR	Minimal intervention (medication reconciliation) or enhanced intervention (minimal intervention plus pharmacist) follow-up usual care	Rate of underutilization of cardiovascular drugs FU: 3 months Missing data: NR	University hospital (orthopedic, internal medicine, family medicine and cardiology wards)
McCarren, Furmaga, et al.(26) 2013	USA 12 practices randomized (220 patients)	Yes Retrospective	Yes EHR alone	Heart failure and guideline nonconcordant beta-blocker prescription	Information to pharmacy about prescription non-concordance	Guideline concordant prescriptions FU: 6 months Missing data: 0%	VHA facilities and pharmacies
Phillips, Rothstein, et al.(28) 2011	USA 3895 patients	Yes Retrospective	Yes EHR alone	Prevention of breast cancer	Quality improvement patient navigation	Adherence to biennial mammography FU: 9 months Missing data: NR	Hospital-based internal medicine practices
Piazza, Anderson, et al.(29) 2013	USA 2513 patients	Yes Retrospective	Yes EHR alone	Hospitalized medical service's patients at risk for venous thromboembolism and planned discharge within 48 hours	Alert for physician	Symptomatic deep vein thrombosis or pulmonary embolism FU: 3 months Missing data: <0.1%	Inpatient medical unit

Qureshi, Armstrong, et al.(30) 2012	UK 24 caregivers randomized (748 patients)	No Prospective	Yes Hybrid; Primary outcome EHR alone	Adult primary care patients no previously diagnosed cardiovascular risk	Family history questionnaire (in addition to Framingham risk score)	Proportion of identified participants with high cardiovascular risk scores FU: NA Missing data: 1.7%	Family practices in research network
Skinner, Halm, et al.(31) 2015	USA 1032 patients	Yes Retrospective	Yes EHR alone	Prevention of colorectal cancer	Tablet-based Cancer Risk Intake System (CRIS) assessment prior to an appointment (tailored and non-tailored) and control group	Received risk-appropriate colorectal cancer testing and any type of colorectal cancer testing FU: 12 months Missing data: 0%	Family practices affiliated with a university medical center
Stewart, Perkins, et al.(27) 2014	USA 235 patients	Yes Retrospective	Yes Hybrid; Primary outcome EHR alone	Dysthymia or major depressive disorder	Collaborative care program with psychotherapy and antidepressant drugs	Cardiovascular events FU: 96 months (8 years) Missing data: 0%	Academic group practice
Vestbo, et al.(32) 2016 (Salford Lung Study)	UK 2802 patients	No Prospective	Yes Hybrid; Primary outcome active data collection alone	COPD and regular maintenance inhaler therapy	Once a day inhaled fluticasone furoate 100 µg and vilanterol 25 µg	Moderate or severe COPD exacerbations FU: 12 months Missing data: 24.8%	Healthcare network in (and around) Salford, hospitals, GPs, pharmacies

Wolf, Fitzner, et al.(33) 2005	USA 113 health-care provider (randomized) 1290 patients	Yes Retrospective	Yes EHR alone	Prevention of colorectal cancer	Education session plus performance feedback	Completion of colorectal cancer screening FU: NA Missing data: NR	VA primary care clinics

*The extent of RCD use can be: EHR alone (all of the RCT's outcomes are routinely collected), Hybrid (either the primary outcome or other outcomes are entirely routinely collected and some outcome in the RCT is also entirely actively collected, or some outcomes are routinely collected and supplemented by active data collections) and Active data collection alone (all of the outcomes are actively collected, no RCD).
**All comparisons are "usual care" unless otherwise specified.
[1]University of Texas Health Science Center at San Antonio, in partnership with Wilford Hall Medical Center, Brooke Army Medical Center, South Texas Veterans Health Care System, TRICARE Region 6, and University Health System.
Abbreviations: COPD, chronic obstructive pulmonary disease; EHR, electronic health record; EMR, electronic medical record; GP, general practitioner; QOL, quality of life; RMDQ, Roland Morris Disability Questionnaire; VA, Veterans Affairs; VHA, Veterans Health Administration.

Table 3: Costs of EHR-supported trials

EHR trial Author, Year	EHR use for	EHR source pre-existing	Intervention integrated during routine care (no additional staff needed)	Total trial cost in US$	N patients	Per patient cost in US$
Automatic data extraction from EHR source						
Bereznicki, Peterson, et al. 2008	Recruitment (retrospective) Outcome assessment (all with EHR alone)	Yes	Yes	67750[1]	1551	44
Manual data extraction from EHR source						
Green, Wang, et al. 2013	Recruitment (retrospective) Outcome assessment (all with EHR alone)	Yes	No	2800000[2]	5000	560
Piazza, Anderson, et al. 2013	Recruitment (retrospective) Outcome assessment (all with EHR alone)	unclear	No	5026000[3]	2513	2‘000
Wolf, Fitzner, et al. 2005	Recruitment (retrospective) Outcome assessment (all with EHR alone)	Yes	Yes	86753[4]	1978	44
Unclear if data extraction from EHR source was automatic or manual						
McCarren, Furmaga, et al. 2013	Recruitment (retrospective) Outcome assessment (all with EHR alone)	Yes	Yes	69300[5]	220	315

[1]Total received funding; including USD 42157 for staff costs for the duration of the project, USD 6132 for a consultant programmer (for software development), USD 15330 for pharmacy payments and USD 6132 for non-salary costs such as printing, postage, travel, and others.
[2]Total received funding.
[3]The study costs were USD 2000 per patient and included costs of the trial startup and close out.
[4]Total cost of the colorectal cancer screening promotional effort (intervention only).
[5]Total received funding. “Most of the [working] time was donated”

APPENDICES

Appendix 1: Box - Definitions, types and applications of Electronic Health Records (EHRs)

EHR type	*Definition*
Electronic Health Record (EHR)	EHRs are electronic platforms that contain health-related data collected during medical care in practices, clinics and other medical settings from various sources, connected to form a network of patient clinical data. EHRs can also incorporate software that allow straightforward physician ordering practice (CPOEs), even including safety features; or that guide them through clinical decision making with up-to-date guidelines (CDS).
Electronic Medical Record (EMR)	EMR are routinely collected data sources that contain standard medical and clinical data gathered during medical care in an individual location of a practice, clinic or other medical setting. When the data is shared among different locations and units it becomes a network and it is considered an EHR (i.e. a primary care practice with electronic chart system that cannot be accessed by any other entity is an EMR, a hospital system where laboratory data, affiliated clinic charts, etc., are all accessed under one platform, is an EHR).
EHR applications	*Definition*
Personal Health Records (PHR)	PHRs are electronic platforms (often online interfaces such as web pages) that securely store patient's health information and allow patients to actively engage in their own health. Often, they can add information to a PHR, can exchange it with health providers, see test results, make appointments, or receive educational information. We consider PHR only those platforms that are tethered to an EHR, where information can be exchanged in both directions (otherwise if the patient is simply adding data but not viewing any of his/her data, we consider it ePRO).
Clinical Decision Support System (CDSS)	A CDSS is an application that supports health providers in performing health care by mining data of an EHR or EMR and providing guideline specific recommendations. CDSS systems can often identify errors or missing data and display alerts or messages through the EHR.
Computerized Physician Order Entry (CPOE) system	CPOE systems are electronic ordering technology where physician orders can be entered and processed in a computerized way, often mimicking the workflow found in clinical settings. CPOEs can be more advanced and identify ordering mistakes, display preferred treatments by individual patient EHR query, or even set up blocks with medication interaction orders.
Telehealth	Telehealth is the use of telecommunication technologies (telemonitoring) to improve the provision of care. This allows for care to be provided at a distance and therefore to maintain clinical contact with patients at home without requiring the same amount of resources to be dispensed. Examples of telehealth are blood glucose monitoring machines tethered to an EHR that integrate blood glucose levels taken by the patient at home into the EHR automatically (and can send an alert in the EHR interface to the clinician if the values are out of a predefined range and action must be taken); and increasingly mobile health data collected by wearable devices.
Electronic Patient Reported Outcomes (ePRO)	ePROs are health related information recorded by the patient themselves in electronic form, often through a web page or application. While ePROs have often been utilized in clinical trials, we also consider ePROs any data that have been collected by the patients themselves and tethered to an EHR or PHR. An example would be a patient pain diary, in which a pain score and information are inputted

	daily on a webpage or via a smartphone app and these data are added to an EHR; where the clinician can monitor it and consult it during a visit.
These definitions are our own working definitions used for this project and have been adapted from HealthIT.gov(10) **and CMS.gov**(12)**.**	

Appendix 2: Search strategy

Search	Query
#12	(#11 AND #10)
#11	((health information exchange [tw] OR hie [tw] OR rhio [tw] OR regional health information organization [tw] OR hl7 [tw] OR health level seven [tw] OR unified medical language system [majr] OR umls [tw] OR loinc [tw] OR rxnorm [tw] OR snomed [tw] OR icd9 cm [ti] OR icd 9 cm [ti] OR icd10 [ti] OR icd 10 [ti] OR metathesaurus [tw] OR patient card [tw] OR patient cards [tw] OR health card [tw] OR health cards [tw] OR electronic health data [tw] OR personal health data [tw] OR personal health record [tw] OR personal health records [tw] OR Health Records, Personal [Majr] OR Health Record, Personal [Majr] OR ehealth [tw] OR e-health [tw] OR medical informatics application [mh] OR medical informatics applications [mh] OR medical records system, computerized [mh] OR medical records systems, computerized [mh] OR computerized patient medical records [tw] OR automated medical record system [tw] OR automated medical record systems [tw] OR automated medical records system [tw] OR automated medical records systems [tw] OR computerized medical record [tw] OR computerized medical records [tw] OR computerized patient records [tw] OR computerized patient record [tw] OR computerized patient medical record [tw] OR electronic health record [tw] OR electronic health records [tw] OR Electronic Health Record [Majr] OR Electronic Health Records [Majr] OR electronic patient record [tw] OR electronic patient records [tw] OR electronic medical record [tw] OR electronic medical records [tw] OR electronic healthcare records [tw] OR electronic healthcare record [tw] OR electronic health care record [tw] OR electronic health care records [tw] OR archives [majr] OR ehr [tw] OR ehrs [tw] OR phr [tw] OR phrs [tw] OR emr [tw] OR emr[tw] OR Health Information Systems [Majr]) AND (medical record [ti] OR medical records [mh] OR medical records [ti] OR patient record [ti] OR patient records [ti] OR patient health record [ti] OR patient health records [ti] OR patient identification system [mh] OR patient identification systems [mh] OR Patient Outcome Assessment[Majr] OR Patient Discharge Summaries[Majr] OR healthcare record [ti] OR healthcare records [ti] OR health care record [ti] OR health care records [ti] OR health record [ti] OR health records [ti] OR hospital information system [tw] OR hospital information systems [tw] OR umae [ti] OR attitude to computers [mh] OR medical informatics [ti])) OR ((medical records systems, computerized [majr] OR medical records systems, computerized [mh] OR computerized patient medical record [tw] OR computerized patient medical records [tw] OR automated medical record system [tw] OR automated medical record systems [tw] OR automated medical records system [tw] OR automated medical records systems [tw] OR computerized medical record [tw] OR computerized medical records [tw] OR computerized patient records [tw] OR computerized patient record [tw] OR electronic health record [tw] OR electronic health records [tw] OR electronic patient record [tw] OR electronic patient records [tw] OR electronic medical record [tw] OR electronic medical records [tw] OR electronic healthcare records [tw] OR electronic healthcare record [tw] OR electronic health care record [tw] OR electronic health care records [tw] OR unified medical language system [majr] OR unified medical language system [tw] OR umls [tw] OR loinc [tw] OR rxnorm [tw] OR snomed [tw] OR icd9 cm [ti] OR icd 9 cm [ti] OR icd10 [ti] OR icd 10 [ti] OR Metathesaurus [tw] OR ehr [tw] OR ehrs [tw] OR phr [tw] OR phrs [tw] OR emr [tw] OR emrs [tw] OR meaningful use [tiab] OR meaningful use [tw]OR Meaningful Use [Majr]) AND (j ahima [ta] OR j am med inform assoc [ta] OR amia annu symp proc [ta] OR health data manag [ta] OR int j med inform [ta] OR yearb med inform [ta] OR telemed j e health [ta] OR stud health technol inform [ta]))
#10	(#8 NOT #9)
#9	(((animals [mh] NOT humans [mh])))
#8	((#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7))
#7	trial [ti]
#6	randomly [tiab]
#5	clinical trials as topic [mesh: noexp]

#4	placebo [tiab]
#3	randomized [tiab]
#2	controlled clinical trial [pt]
#1	randomized controlled trial [pt]

Interface: PubMed; Filters: English and date from 2000/01/01
Date of last search: 13 September 2017

Appendix 3: References of all included EHR-Evaluating RCTs

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Appendix 4: Risk of Bias assessment

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data (>10%)	Selective outcome reporting[2]
Bereznicki, Peterson, et al.	?	-	-	-	?	n/a
Corson, Doak, et al.	?	?	+	-	?	n/a
de Jong, Visser, et al.	-	?	+	?	-	n/a
Fu, van Ryn, et al.	?	?	+	-	+[1]	n/a
Galbreath, Krasuski, et al.	?	?	+	+	?	n/a
Gerber, Prasad, et al.	?	-	+	?	-	n/a
Green, Wang, et al.	-	-	+	-	-	n/a
Hoffman, Steel, et al.	-	?	?	?	?	n/a
Israel, Farley, et al.	-	?	-	-	?	n/a
McCarren, Furmaga, et al.	-	?	+	+	-	n/a
Phillips, Rothstein, et al.	?	?	+	?	?	n/a
Piazza, Anderson, et al.	-	-	+	?	-	n/a
Qureshi, Armstrong, et al.	-	-	+	?	-	n/a
Skinner, Halm, et al.	?	?	+	?	-	n/a
Stewart, Perkins, et al.	-	-	+	-	-	n/a
Vestbo, Leather, et al.	-	-	+	?	+	n/a
Wolf, Fitzner, et al.	?	?	+	?	?	n/a

-: Low risk of bias; **?**: Unclear risk of bias; **+**: High risk of bias

[1]EHR-based outcome data completeness (secondary study outcome) was perfect (0% missing data).

[2]Since only the publication identified in our literature search was assessed (there was no systematic protocol search and no searching for further manuscripts related to that study), the "selective outcome reporting" item was not considered.