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Review

Bridging the gap between the randomised clinical trial world and the real world by combination of population-based registry and electronic health record data: A case study in haemato-oncology

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Abstract Randomised clinical trials (RCTs) are considered the basis of evidence-based medicine. It is recognised more and more that application of RCT results in daily practice of clinical decision-making is limited because the RCT world does not correspond with the clinical real world. Recent strategies aiming at substitution of RCT databases by improved population-based registries (PBRs) or by improved electronic health record (EHR) systems to provide significant data for clinical science are discussed. A novel approach exemplified by the HemoBase haemato-oncology project is presented. In this approach, a PBR is combined with an advanced EHR, providing high-quality data for observational studies and support of best practice development. This PBR + EHR approach opens a perspective on randomised registry trials.

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1. Introduction

Clinical science contributes to evidence-based medicine (EBM) being considered the basis for medical decision-making, which in individual cases can be fine-tuned by shared decision-making. EBM justifies the superiority and effectiveness of the provided health care [1]. Over the years, the original idea of EBM was narrowed down to evidence supplied by randomised clinical trials (RCTs). However, a well-known problem in daily clinical practice is the gap between the RCT data and facts and the individual patient features representing the real world of medicine. Specifically, patients' age and the complexities of comorbidities are increasing, making it more and more difficult to justify clinical decisions based on RCT outcomes.

An approach in solving this problem is to expand the RCT world. Common obstacles are inconsistent or unspecific signs and symptoms, low incidence, variable disease phases and precursor lesions, heterogeneity in comorbidity and socioeconomic status, high costs of an RCT and so on. Owing to these practical factors, complicated by ethical aspects, the possibilities of an RCT world expansion are limited.

With respect to these shortcomings of EBM and RCT, much attention has recently been drawn to the potential contribution of cancer registries (CRs) or population-based registries (PBRs) [2]. In this article, we review several aspects of RCT, CR, PBR and electronic health records (EHRs). Subsequently, we will discuss the perspective of merging PBR and EHR as a potentially powerful tool for clinical research. HemoBase, a domain-specific PBR/EHR in haemato-oncology in Friesland, a province in the northern part of the Netherlands, is proposed as a paradigm.

2. Randomised clinical trials, cancer and population-based registries

2.1. RCT

RCTs are the most powerful instruments to investigate the evidence of new therapies while eliminating selection bias and confounding by carefully selecting patients and using strict methodology. RCTs are focused on a specific research question, with a well-defined hypothesis to be tested, and all the types of data necessary to answer the question(s) are collected in a predefined manner, using electronic case report forms. However, the results are often not representative of the real-world patients with comorbidities and/or advanced age, making the RCT knowledge less valuable or in need of extrapolation before it can be applied to clinical practice. A meta-study by Cherubini *et al.* [3] showed that more than 40% of the trials have an upper age limit. Furthermore, in more than 90%, the presence of at least one comorbidity may already lead to exclusion of the patient. In the real world of medicine, most of the patients are older and have more than one comorbidity.

This dilemma is framed as the inferential gap: clinicians are required to fill in where they lack knowledge or where no knowledge yet exists [4,5]. Especially when treating the elderly, the inferential gap may be large.

2.2. CR and PBR

CRs and PBRs have their roots in public health rather than in clinical medicine. Already at the beginning of the 20th century, regional- or domain-(tumour) specific observational registries were started to gain insight into cancer epidemics and risk or environmental factors [6]. The successes of the observational approaches, for example, determination of the etiological roles of smoking, hypertension or infected water are well known. From the 1940s onwards and especially into the 1970s, this resulted in an increase in developing CRs and PBRs.

The design of a CR or PBR is not based on a rigid scientific methodology as RCT design is. Basically, data on new patients and some specific outcomes distributed in time and geographic locus are collected. The SEER database is a well-known example [7,8]. Past decades have shown a tendency to broaden the purposes in domain or scope of the registry. In addition, from the 1990s onward, momentum has risen, linking regional databases to national databases, and national databases to international databases. These developments have increased the power of observational research. A serious drawback is still the immense efforts needed to achieve high-quality data, such as in standardisation, reclassification or adjudication of critical data.

Especially in Europe, many regional- or domain-specific CRs were developed. In sum, approximately 160 CRs and PBRs are active [9,10]. Well-known registries in haemato-oncology, for example, had their start-up in Burgundy (France), South Netherlands, Sweden, England and Scotland [11–15]. The expansion of CRs and PBRs resulted in national and international cooperative projects such as the Belgian and Netherlands Cancer Registry (NCR) and projects such as the European Network of Cancer Registries (ENCRs), Eurocare-5 and Eurocourse [6,9,12,16]. A common denominator in the evolution of CRs and PBRs is that they started as quantitative registries of basic data regarding incidence, prevalence and overall survival. Subsequently, processes developed for adding qualitative data of tumour characteristics and patient care. Linkage of CRs and PBRs resulted in large observational databases with potential power to address clinically relevant research questions [10,17]. An interesting possibility is the precise linking of PBR data with RCT data to address specific questions. Recently, this was published for Hodgkin's lymphoma in a paper that addressed the potential difference between the real world and the RCT world [18]. Another

interesting development is demonstrated by the SHIELD project, in which observational PBR data of haemato-oncological orphan diseases of the elderly were enriched with clinical data by a collaborative program, using a web-based registry in the United Kingdom and Germany [19].

Recently, the RegisTree® model (Fig. 1) is proposed to describe the evolution of CRs and PBRs [20]. The biological metaphor of the growing tree illustrates the functional development of CRs and PBRs. Development of CRs is not guided by a scientific methodology but by contingent local circumstances. The hospital, outpatient clinic and laboratory archives function as the roots of a CR. The trunk pillars represent classifications, validity checks, storage, data and back-office processing, linkages and privacy adherence. The branches stand for the 5 research domains from a public health perspective (aetiology and primary prevention, screening and secondary prevention) and from a patient care perspective (quality of care processes, prognosis, quality of life). The leaves symbolise research groups, research questions, interim results and so on providing energy for CR development. Finally, the revenues e.g. articles, reports, dissertations, policy reports, internet publications and so on are represented by the coloured fruits. Accidental environmental factors or adaptive capacities of the program owners will define the characteristics and features of a specific CR or PBR. The RegisTree® model is a tool to analyse complex CR or PBR systems and can provide a roadmap for adjustment.

It can be observed that lately the goal of basic quantitative cancer registries is now transforming toward qualitative cancer surveillance data. These cancer surveillance registries contain detailed information on frequency, aetiology, quality of care, quality of life and prognosis. The development of the Dutch NCR, supplemented by data of the Population-based HAematological Registry for Observational Studies [21,22], and now referred to as the NCR + database, is such an example.

In addition, the RegisTree® model gives an opportunity to assess the internal validity of linked PBRs by representing the relationships between the multiple medico-administrative processes that reflect the clinical realities of the day. External validity is evaluated by the judgement of patient selection and the methodology of data handling as described by the PBR guidelines.

2.3. RCT versus PBR?

Although the concept of an RCT functions as a solid basis for clinical science, there is growing anticipation that PBR data can have a complementary role. PBR systems collect data of unselected patients, of all ages, irrespective of confounding diseases or other patient characteristics. As such, PBR data represent the clinical real world. So the question is whether PBR data can bridge the gap between the artificial RCT world and the clinical real world of patients? A recent study claimed that PBR data could answer questions similar to RCT data, thereby reducing costs [23]. In this study, statistical methods are developed for effectiveness studies based on observational databases. A hypothetical RCT was emulated on the data of an observational database, using the same inclusion and exclusion criteria as an RCT would have done. Despite strong confounding by indication, a potential beneficial effect of statin therapy was found based on the observational data, in line with RCT results. Another example of successful application of PBR data is the exploration of cost effectiveness of new, expensive drugs [21].

In bridging the gap between the RCT and the real world, one strategy is to invest in upgrading PBR systems by adding data fields. However, many challenges remain in this strategy. Drawbacks are that by default the designed data fields will be lagging behind clinical practice, and information is collected by data managers, who are not professionals involved in the care processes. Data have to be validated to ensure high quality and, last but not least, the data accrual and registration will be cost-inefficient. Complete and structured data capture is important to affirm research endpoints. Some of these problems may be tackled by the use of EHRs as a source of real-world data. The next section explores this.

3. Electronic health records

3.1. The evolution of EHR systems

There is an overwhelming amount of literature on the development and applicability of EHR systems, a full review of which is beyond the scope of this article. For our purpose, it suffices to summarise that the development of EHRs can be described in terms of increasing complexity and functionality. Determinants to be analysed are, for example, digitalisation of patient data (laboratory, symptoms, diagnostic data and so on), using either descriptive text or discrete data. Other crucial determinants of an EHR are workflow processes such as order management, administration of outpatient clinic visits, patient portals, multidisciplinary consultation, medical decision support systems and so on. Within this Darwinian approach, EHRs can be classified as generations on an evolutionary scale of increasing complexity and functionality. In the context of EHRs, two consequences of the Darwinian metaphor are important to realise. First, systems with a certain level of complexity on a particular feature cannot be linked to systems with different complexity, whether at higher or lower levels of this feature. Another consequence is that the recognition of generations of EHR systems implies that a certain level of low complexity cannot be upgraded simply to a high and advanced level of functionality.

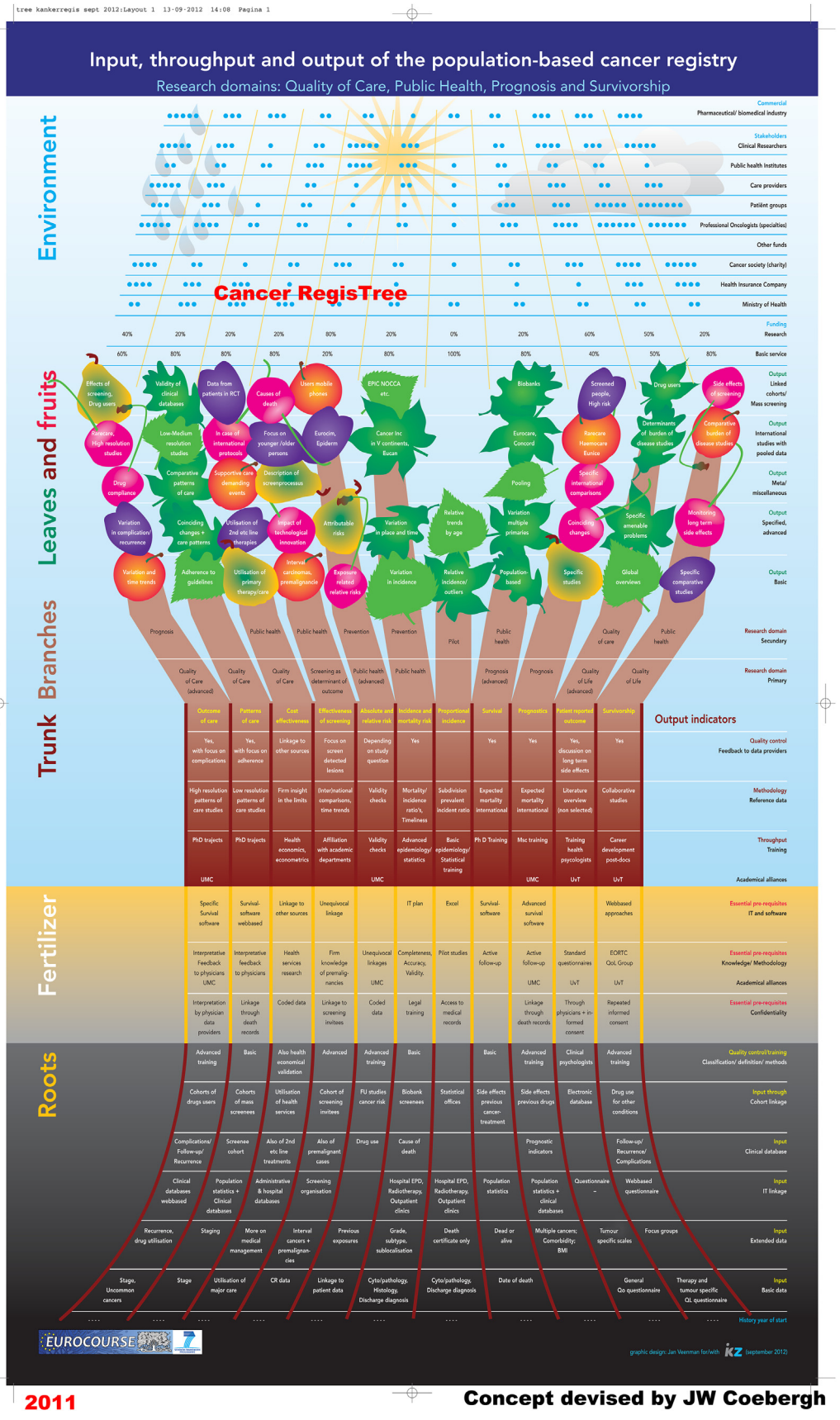

Fig. 1. RegisTree®: structural and process description of population-based cancer registry. RegisTree®: cancer registries are rooted in clinical, pathology, laboratory, ambulatory, general practitioner and nursing home archives. The trunk pillars symbolise back-office

Previously, the claim was made that EHR systems may provide more complete real-world representations. Intuitively, higher generations of EHR are more promising for this goal than lower generations. The two mentioned consequences, however, have practical consequences for the application of EHRs to bridge the gap of the RCT world and the real world. It may be impossible to pool data from different hospitals or policlinics, or it may be impossible to add a sophisticated EHR module suitable for real-world representation to an earlier-generation EHR. The direct collection of data at the source by medical professionals is a potential strong point of the EHR approach.

3.2. HemoBase: a domain-specific, high-level EHR

In the early years of the 21st century, the Haematology Workgroup Friesland (WHF) in the north of the Netherlands started to develop a patient management system to support multi-centre clinical patient conferences and multidisciplinary scientific meetings regarding haemato-oncology care suppliers. This resulted in the development of a web-based application that was coined HemoBase. In current terminology, HemoBase is a domain-specific, regional EHR system for haemato-oncology superposed over a general EHR with workflow functionality of the care processes (Fig. 2). HemoBase is a web-based system containing the specific haemato-oncological data of the four hospitals in Friesland, the central clinical chemistry and pathology laboratories and the radiotherapy institute. As such, HemoBase can be designated as a PBR for haemato-oncology (pop. 660,000). The key feature of HemoBase is the representation of the clinical process, that is, the patient's journey, into the database. Due to the key concept of an integrative diagnosis and the registry of discrete data irrespective of clinical or ambulatory processes, the database is suitable for scientific research purposes [24–28]. The validity of the data is secured by the multidisciplinary consultations. The clinical conferences provide the opportunity to check the completeness and the quality of the registered data. As the medical professionals enter and use up-to-date data and classifications, the HemoBase user forms can equal the CRF of an RCT.

3.3. Future perspective: PBR + EHR = best practice

In the traditional view, progress in medicine is achieved by basic or translational science theories that are subsequently tested in controlled experiments eliminating confounding parameters, the RCT. It is argued that the RCT world differs from the real world of clinical practice, which limits its value for daily practice. As a strategy to bridge this inferential gap, EHR is proposed to develop into knowledge databases that can perform as local mini-RCTs [4]. However, in practice, this is not simple, and many challenges remain, among others, that collected information needs to be validated to ensure high-quality and complete data and that structured data capture is important to affirm research endpoints. Other limitations are the heterogeneity of data systems, the lack of data security and the lack of knowledge of these systems [29,30].

The information collected by RCTs and EHR is often very similar, but the use of data from EHRs for prospective clinical research is still limited because of insufficient scientific relevance or robustness. Recently, the viewpoint of fusing RCT with big (EHR) data in a randomised, embedded, multifactorial, adaptive platform (REMAP) trial was proposed [31]. Alternatively, the so-called randomised registry trial (RRT), fusing RCT and PBR data, was suggested [2]. These trials use big data but retain the random assignment of patients in study groups to investigate a causal link.

The above discussed characteristics of RCTs, CRs or PBRs and EHRs are summarised in Table 1. An alternative strategy, proposed here, is to combine PBR with an advanced domain-specific EHR. The argument developed in this review is that part of the gap between the scientifically robust RCT world and the daily, fuzzy real world can be bridged by high-level (domain-specific) EHR modules operating like PBRs. This concept can be expanded to other fields such as solid oncology, cardiology or chronic diseases such as immune thrombocytopenic purpura. [The national registry of the Dutch Haematology Foundation for ITP is based on the HemoBase concept.] In 2010, Kanas *et al.* [32] elaborated on the criteria of an EHR to be fulfilled for use in oncology research; HemoBase meets these criteria.

This will lead towards multi-institutional EHR systems that will serve as a valuable data source for PBRs. This approach will secure the use of data fields in line with the clinical state of the art and secure the robustness of the data as they are filled in by care professionals, that is, prospective data accrual at the source, which will support the internal validity of the data. By adding patient portal functions, it is possible to obtain quality-of-life and patient-reported outcome measurement data, which are of utmost importance for the ageing patient population, comorbidity and cost-effective evaluation [33].

The regional HemoBase haemato-oncology registry is a paradigm of this approach; it facilitates the multidisciplinary consultation and secures high-quality data collection necessary for transparency, evaluation of therapy results and cost-effectiveness. In this sense, EHR

processes, classifications, storage and data processing. The branches represent the research domains in public health and patient care. The leaves represent factors providing energy for improvement of the registries. The coloured fruits symbolise the valuable output of the registries [20, appendix A]. Reprinted with permission of the publisher.

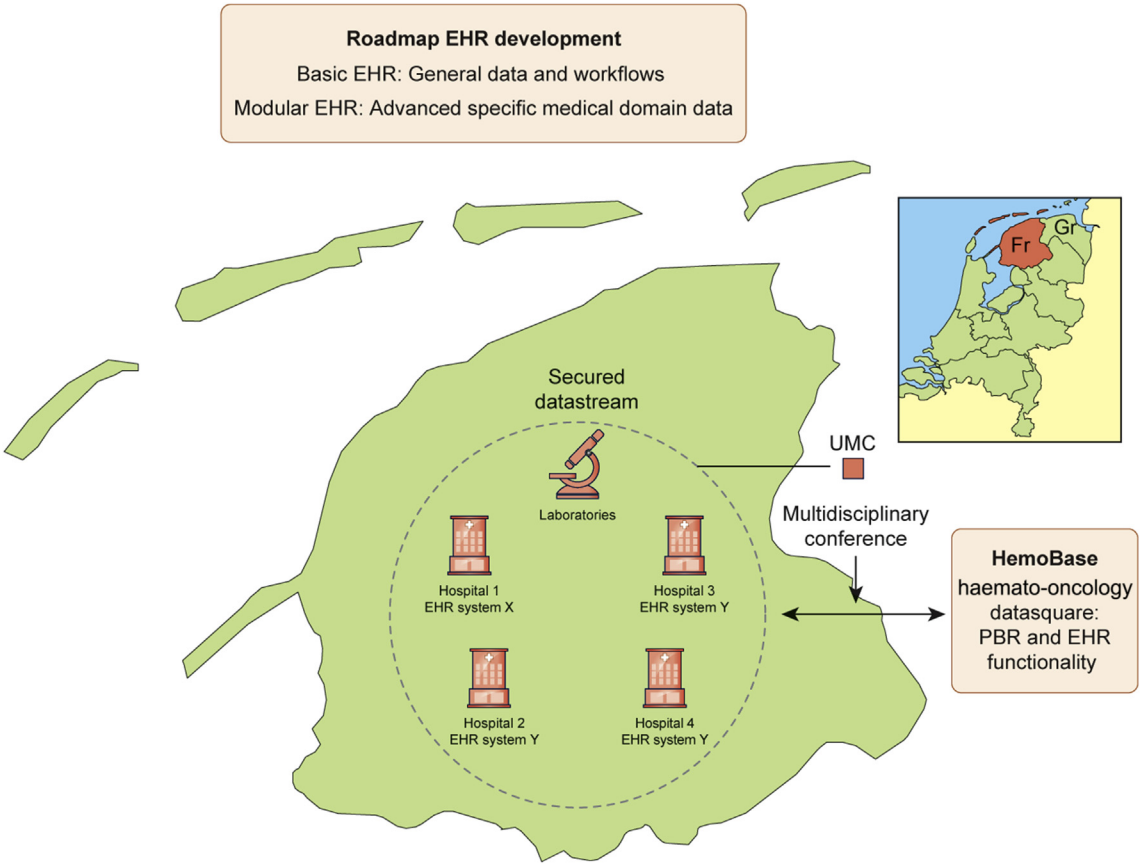

Fig. 2. HemoBase model of PBR + EHR. The graphic displays the HemoBase infrastructure in Friesland (Fr) province of the Netherlands (inset: map of the Netherlands). The 4 hospitals employ 2 types of EHR systems, in addition clinical and laboratory haemato-oncology care providers use HemoBase for registration of diagnosis, staging, prognosis and specifically multidisciplinary patient conferences. The UMC of the province Groningen (Gr) delivers molecular and genetic data and participates in multidisciplinary conferences. The HemoBase datastream is secured by the Health IT network of the 3 northern provinces. The HemoBase cumulative hospital and laboratory data (advanced EHR functionality) constitute a PBR of haemato-oncology in Friesland. Inset: roadmap for future EHR development: modular integration of high level medical domain data (e.g. haemato-oncology, breast cancer, auto-immune diseases, transplant follow up etc.) with basic EHR functions (general patient administration, pharmacy, finance etc.). This integration of advanced medical domain-specific functionality in EHR systems will make high level data input more efficient and cost effective. EHR, electronic health record; PBR population-based registry; UMC, university medical centre.

plus PBR contributes to a best practice. To expand the HemoBase strategy further into clinical practice, some challenges remain. It will be necessary to link the domain-specific, high-level systems to the general workflow EHRs (Fig. 2). As stated earlier, a higher-level EHR such as HemoBase cannot be linked to a lower generation of EHR. First, a representation of pathways of care (patient journeys) is a necessary condition, which means that the EHR system supports a prospective model of disease follow-up demonstrated, for example, by a time line (HemoBase). Second, the EHR system should collect data of the complete clinical patient journey, including multidisciplinary consultation sessions and ambulatory data. Third, all the data must be discrete and coded according to validated classifications.

At the moment, to the best of our knowledge, there is no such EHR yet, although pre-stages certainly are under construction. As in Europe, the concept of a comprehensive pathway of care is well established; in our opinion, there is a realistic opportunity to implement this in current advanced EHR systems. The goal of the WHF is to link HemoBase to such an advanced general EHR system. Furthermore, as discussed earlier, in Europe, a unique infrastructure of regional, national and international connected CRs and PBRs is established. The evolutionary direction of these PBRs is from cancer registry towards cancer surveillance. The proposed linking of high-level EHRs to PBRs can function as a successful adaptation of EHR and PBR evolution, serving the patient journey and clinical science. The high-level EHR systems will provide prospective clinical data from professional sources to be used in a PBR context. This combined strategy will have a positive influence on the internal and external validity of the evidence used for medical decision-making as EBM was meant originally [1]. For clinical science purposes, it is

Table 1
RCT, CR, PBR and EHR characteristics.

	RCT	CR or PBR	EHR
Function	Scientific testing of new therapies	Data accrual for medical and public health policy purposes	Prospective data accrual for patient care and a warehouse for management purposes
Scope	A well-defined hypothesis to be tested	Data on new patients and some specific outcomes distributed in time and geographic locus	Defined by medical help questions
Patient domain	Selective and specified by the research methodology	Referral to or access to specialised care; population in general (screening)	All patients visiting a clinic or outpatient care facility
Data form	Specific case report form	PBR-specific form	Multiple flexible forms situation dependent
Selection bias	Results from methodology	By (non)referral to specialised care and data form limitations	None, all patients are included (mixture of incident and prevalent patients)
Data collection and validity	By data managers and warranted by monitoring and data review	By data managers, immense efforts needed to achieve high quality and validated data	During care process by medical and laboratory professionals; validation secured by multidisciplinary conferences
Costs	High investment per research question	Expansion of scope is cost inefficient	Minor investment per research question
Stakeholders	Clinical researchers and fund suppliers	Public health, clinical researchers and policy makers	Patients, clinicians and hospital management
Critical points	Inferential gap, results are not applicable to all patients in daily practice	Insufficiency of data fields (qualitatively and quantitatively)	Lack of representation of clinical process (integrative diagnosis); Practical difficulties in linkage of different systems and hospitals

CR cancer registry, EHR electronic health record, PBR population based registry, RCT randomized clinical trial.
The table summarizes the data characteristics of RCT, CR, PBR and EHR in relation to the reasoning here presented.

proposed that this combination of PBR and EHR functionality will facilitate so-called RRT research.

Conflict of interest statement

None declared.

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References

[1] Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. BMJ 1996 Jan 13;312(7023):71–2.
[2] Lauer MS, D'Agostino RBS. The randomized registry trial–the next disruptive technology in clinical research? N Engl J Med 2013 Oct 24;369(17):1579–81.
[3] Cherubini A, Pierri F, Gasperini B, Zengarini E, Cerenzia A, Bonifacio E, et al. Are ongoing trials on hematologic malignancies still excluding older subjects? Haematologica 2013 Jul;98(7):997–1000.
[4] Stewart WF, Shah NR, Selna MJ, Paulus RA, Walker JM. Bridging the inferential gap: the electronic health record and clinical evidence. Health Aff (Millwood) 2007 Mar-Apr;26(2):w181–91.
[5] Perlin JB, Kupersmith J. Information technology and the inferential gap. Health Aff (Millwood) 2007 Mar-Apr;26(2):w192–4.
[6] Coebergh JW, van den Hurk C, Rosso S, Comber H, Storm H, Zanetti R, et al. EUROCOURSE lessons learned from and for population-based cancer registries in europe and their programme owners: improving performance by research programming for public health and clinical evaluation. Eur J Cancer 2015 Jun;51(9):997–1017.
[7] Wu SG, Li H, Tang LY, Sun JY, Zhang WW, Li FY, et al. The effect of distant metastases sites on survival in de novo stage-IV breast cancer: a SEER database analysis. Tumour Biol 2017 Jun;39(6). http://dx.doi.org/10.1177/1010428317705082.
[8] Lau CSM, Zywot A, Mahendraraj K, Chamberlain RS. Gallbladder carcinoma in the United States: a population based clinical outcomes study involving 22,343 patients from the surveillance, epidemiology, and end result database (1973-2013). HPB Surg 2017;2017:1532835.
[9] Siesling S, Louwman WJ, Kwast A, van den Hurk C, O'Callaghan M, Rosso S, et al. Uses of cancer registries for public health and clinical research in europe: results of the european network of cancer registries survey among 161 population-based cancer registries during 2010-2012. Eur J Cancer 2015 Jun;51(9):1039–49.
[10] Sant M, Minicozzi P, Mounier M, Anderson LA, Brenner H, Holleczek B, et al. Survival for haematological malignancies in europe between 1997 and 2008 by region and age: results of EUROCARE-5, a population-based study. Lancet Oncol 2014 Aug;15(9):931–42.
[11] Dandoit M, Mounier M, Guy J, Petrella T, Girard S, Casasnovas RO, et al. The heterogeneity of changes in incidence and survival among lymphoid malignancies in a 30-year French population-based registry. Leuk Lymphoma 2015 Apr;56(4):1050–7.
[12] Dickhoff C, Dahele M, Smit EF, Paul MA, Senan S, Hartemink KJ, et al. Patterns of care and outcomes for stage IIIB non-small cell lung cancer in the TNM-7 era: results from The Netherlands cancer registry. Lung Cancer 2017 Aug;110:14–8.

[13] van Spronsen DJ, Post PN, Crommelin MA, Breed WP, Coebergh JW. Modest decline in late mortality following hodgkin's disease in the southeastern Netherlands since 1972. Ann Hematol 1998 May;76(5):205–9.
[14] Blimark C, Holmberg E, Mellqvist UH, Landgren O, Bjorkholm M, Hultcrantz M, et al. Multiple myeloma and infections: a population-based study on 9253 multiple myeloma patients. Haematologica 2015 Jan;100(1):107–13.
[15] Jones GL, Taylor PR, Windebank KP, Hoye NA, Lucraft H, Wood K, et al. Outcome of a risk-related therapeutic strategy used prospectively in a population-based study of hodgkin's lymphoma in adolescents. Br J Cancer 2007 Jul 2;97(1):29–36.
[16] Dal Maso L, Tavilla A, Pacini F, Serraino D, van Dijk BAC, Chirlaque MD, et al. Survival of 86,690 patients with thyroid cancer: a population-based study in 29 european countries from EUROCARE-5. Eur J Cancer 2017 May;77:140–52.
[17] Gavin A, Rous B, Marcos-Gragera R, Middleton R, Steliarova-Foucher E, Maynadie M, et al. Towards optimal clinical and epidemiological registration of haematological malignancies: guidelines for recording progressions, transformations and multiple diagnoses. Eur J Cancer 2015 Jun;51(9):1109–22.
[18] Liu L, Giusti F, Schaapveld M, Aleman B, Lugtenburg P, Meijnders P, et al. Survival differences between patients with hodgkin lymphoma treated inside and outside clinical trials. A study based on the EORTC-Netherlands cancer registry linked data with 20 years of follow-up. Br J Haematol 2017 Jan;176(1):65–75.
[19] Proctor SJ, Wilkinson J. A web-based study concept designed to progress clinical research for 'orphan' disease areas in haematological oncology in the elderly: the SHIELD programme. Crit Rev Oncol Hematol 2007 Jan;61(1):79–83.
[20] Coebergh JW, van den Hurk C, Louwman M, Comber H, Rosso S, Zanetti R, et al. EUROCOURSE recipe for cancer surveillance by visible population-based cancer RegisTrees in europe: from roots to fruits. Eur J Cancer 2015 Jun;51(9):1050–63.
[21] Blommestein HM, Franken MG, Uyl-de Groot CA. A practical guide for using registry data to inform decisions about the cost effectiveness of new cancer drugs: lessons learned from the PHAROS registry. Pharmacoeconomics 2015 Jun;33(6):551–60.
[22] Oerlemans S, Issa DE, van den Broek EC, Nijziel MR, Coebergh JW, Huijgens PC, et al. Health-related quality of life and persistent symptoms in relation to (R-)CHOP14, (R-)CHOP21, and other therapies among patients with diffuse large B-cell lymphoma: results of the population-based PHAROS-registry. Ann Hematol 2014 Oct;93(10):1705–15.
[23] Danaei G, Rodriguez LA, Cantero OF, Logan R, Hernan MA. Observational data for comparative effectiveness research: an emulation of randomised trials of statins and primary prevention of coronary heart disease. Stat Methods Med Res 2013 Feb;22(1):70–96.
[24] Boslooper K, Kibbelaar R, Storm H, Veeger NJ, Hovenga S, Woolthuis G, et al. Treatment with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone is beneficial but toxic in very elderly patients with diffuse large B-cell lymphoma: a population-based cohort study on treatment, toxicity and outcome. Leuk Lymphoma 2014 Mar;55(3):526–32.
[25] Wieringa A, Boslooper K, Hoogendoorn M, Joosten P, Beerden T, Storm H, et al. Comorbidity is an independent prognostic factor in patients with advanced-stage diffuse large B-cell lymphoma treated with R-CHOP: a population-based cohort study. Br J Haematol 2014 May;165(4):489–96.
[26] Boslooper K, Hoogendoorn M, van Roon EN, Kibbelaar RE, Storm H, Hovenga S, et al. No outcome disparities in patients with diffuse large B-cell lymphoma and a low socioeconomic status. Cancer Epidemiol 2017 Jun;48:110–6.
[27] Oortgiesen BE, van Roon EN, Joosten P, Kibbelaar RE, Storm H, Hovenga S, et al. The role of initial clinical presentation, comorbidity and treatment in multiple myeloma patients on survival: a detailed population-based cohort study. Eur J Clin Pharmacol 2017 Jun;73(6):771–8.
[28] de Vries JC, Oortgiesen B, Hemmelder MH, van Roon E, Kibbelaar RE, Veeger N, et al. Restoration of renal function in patients with newly diagnosed multiple myeloma is not associated with improved survival: a population-based study. Leuk Lymphoma 2017 Sep;58(9):1–9.
[29] Cowie MR, Blomster JI, Curtis LH, Duclaux S, Ford I, Fritz F, et al. Electronic health records to facilitate clinical research. Clin Res Cardiol 2017 Jan;106(1):1–9.
[30] Cooke CR, Iwashyna TJ. Using existing data to address important clinical questions in critical care. Crit Care Med 2013 Mar;41(3):886–96.
[31] Angus DC. Fusing randomized trials with big data: the key to self-learning health care systems? JAMA 2015 Aug 25;314(8):767–8.
[32] Kanas G, Morimoto L, Mowat F, O'Malley C, Fryzek J, Nordyke R. Use of electronic medical records in oncology outcomes research. Clin Outcomes Res 2010;2:1–14.
[33] Denis F, Lethrosne C, Pourel N, Molinier O, Pointreau Y, Domont J, et al. Randomized trial comparing a web-mediated follow-up with routine surveillance in lung cancer patients. J Natl Cancer Inst 2017 Sep 1;109(9). http://dx.doi.org/10.1093/jnci/djx029.